FORMATION AND REACTIONS OF 1,2-ADDUCTS FROM *IPSO*-NITRATION OF TOLUENE DERIVATIVES

by

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ABSTRACT

Nucleophilic trapping by acetate anion of **ipso**-Wheland intermediates (W_i^{Me}) formed in the nitration of 4-X-toluenes (X=Br, Cl, OMe, NHCOMe) and 2-X-4-methylanisoles (X=Br, Cl, NO_2), yielded (Z)-3-X-6-methyl-6-nitrocyclohexa-2,4-dienyl and (Z)-4-X-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetates respectively. Both (E)- and (Z)-diastereomers of 2-nitro-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetates were also formed in the nitration of the corresponding anisole. Similar nitration of 3-X-4-methylanisole (X=Cl, NO_2) yielded 3-X-4-methyl-4-nitrocyclohexa-2,4-dienones. The observed order of reactivity of these substrates in nitration and the regioselectivity of the nucleophilic trapping can be explained in terms of the electronic and steric effects of the substituents. The isomer proportions obtained in the nitration agree with those predicted on the basis of the principle of additivity of substituent effects and are discussed in Chapter II of this dissertation.

Several 1-Y-5-X-2-methyl-6-nitrocyclohexa-2,4-dienes (Y=OAc, Cl, OH, OMe; X=Cl, Br, $NHCOCH_3$, OMe) were prepared from 1-Y-3-X-6-methyl-6-nitrocyclohexa-2,4-dienes under neutral conditions by a thermally induced [1,5]-nitro shift. The reaction has contributions from both a radical chain process, leading to epimerization, and a stereospecific [1,5]-sigmatropic shift. The former process was suppressed by radical traps. Effects of substituents on the mechanism of these reactions are discussed in chapter III.

Under acidic conditions (Chapter IV) the dienes revert to the W_i^{Me}, but with decreasing acidity, reactions via other intermediates become important for those dienes which do not contain a methoxy substituent. The fate of the W_i^{Me} is dependent on the substituents and also on the nucleophilicity of the reaction media. The W_i^{Me} from dienes bearing a methoxy group react via the encounter pair, at high acidities, or are trapped by nucleophiles to yield 1,4-adducts which ultimately collapse to cresols via dienones. The extent of denitration via leakage from the encounter pair increases when deactivating substituents (NO_2>Cl) are present on the ring. A 1,2-nitro shift in the W_i^{Me} from dienes (X=Cl, Br) under strongly acidic conditions was observed, but with decrease in acidity aromatization via nitrous acid elimination from the dienes and reactions via rearranged dienes becomes important.

Several (Z)-1-Y-3-X-6-methyl-6-nitrocyclohexa-2,4-dienes (Y=Cl, Br, OMe; X=Cl, Br) and 1-Y-2-X-1-methoxy -4-methyl-4-nitro-cyclohexa-2,5-dienes (Y=CN, OMe; X=H, Cl, NO_2) were prepared by nucleophilic trapping of W_i^{Me}, regenerated from the ipso-adducts. Similar reactions with other nucleophiles under milder conditions are discussed in Chapter V.

The 1,2-adducts formed by nucleophilic trapping were shown to be (Z)-diastereomers by a combination of X-ray crystallography and NMR studies. This stereoselectivity on diene formation (approach of nucleophiles anti to the methyl group on the adjacent carbon) is unique and can be rationalized in terms of steric approach control of the incoming nucleophile. 1,4-Dienes are not formed stereoselectively.

Examiners:

(A. Fisher)

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To my mother.

CHAPTER I: INTRODUCTION

1.1 Opening Remarks

Faraday, in 1825, recorded the first known reaction leading to the nitration of benzene[1]. Since then electrophilic aromatic nitration has received wide attention and is now regarded as one of the better understood organic reactions. Studies of the mechanism of nitration have contributed significantly to the elucidation of the fundamental principles of organic chemistry. Nitration has also matured into an extremely valuable synthetic transformation, now used in laboratories and industries around the world.

In recognizing the main generalizations regarding orientation in electrophilic substitution i.e. ortho/para- or meta-directing, and its connection with activation, Holleman[2] utilized extensive data related to nitration. Ingold and his coworkers exploited the data of orientation and rate of nitration in elaborating their original ideas of the electronic theory of the course of organic reactions[3]. Nitration has also been used as a model reaction for the development of reactivity indices[4], theories related to the perturbations leading to the transition states[5], in the construction of qualitative potential energy surfaces[6] and in studying heteroaromatic reactivity[7]. On the synthetic front the use of nitroaromatics as intermediates in the synthesis of plastics, pharmaceuticals, dyestuffs, explosives and insecticides is well known[8].

Over the years a multitude of nitrating agents has been investigated. Nitric acid, metal nitrates, alkyl nitrates, mixed anhydrides or nitrate esters have been used as nitrating agents in aqueous media or organic solvents. Catalysis, in the form of sulfuric

acid, Lewis acids like boron trifluoride, or other organic acids, is often required, although nitric acid itself and even dilute nitric acid is capable of nitrating reactive substrates. Acetic anhydride is particularly a good solvent for aromatic compounds and reaction in it occurs readily under mild conditions. Thus mixtures of nitric acid and acetic anhydride have been widely used as potent nitrating agents. Solid super acids have been used as catalysts. Transfer nitrating agents such as N-nitropyrazole, nitro- and nitrito-onium salts are recent additions[9] in nitration chemistry and have paved the way for development of new polymeric nitrating agents[10]. The products obtained and the mechanism of nitration vary on changing the nitrating agent.

It is important to distinguish these mechanisms on basis of the actual nitrating agent. They are

1. An ionic mechanism with nitronium ion;
2. An electron transfer mechanism involving radical cation-radical pair;
3. A radical mechanism with nitrogen dioxide;
4. Nitration via nitrosation.

In several cases it has been established that nitration has proceeded via two or more of these mechanisms in parallel.

1.2 The Ionic Mechanism of Nitration with Nitronium Ion

1.2.1 Evidence for the Nitronium Ion (NO_2^+) as the Electrophile in the Ionic Mechanism:

The state of nitric acid in different media has been studied extensively in order to determine the exact nature of the electrophile involved in nitration. Evidence from Raman spectroscopy[11], cryoscopic

measurements[12], ultraviolet spectroscopy[13], and conductometric measurements[14] of concentrated solutions of nitric acid in sulfuric acid clearly indicate the formation of nitronium ion. In most organic solvents kinetic evidence indicates that nitronium ion is formed and is effective as the nitrating agent.

Ingold and Benford[15] showed that the nitration of benzene homologs in nitromethane with excess nitric acid proceeded at a constant rate, independent of the concentration of aromatic compound. For halogenobenzenes the dependence was between zeroth and first order and completely first order in aromatic for di- and tri-halogenobenzenes. Similar kinetic phenomena were obtained in acetic acid, in acetonitrile[16], in carbon tetrachloride[17] and in sulpholan[18], thus denying the solvent any specific role in the rate determining step. Variation in the reaction conditions did not alter the ratio of o-, p- and m- products thus indicating that the same electrophile is involved in all these processes. The same product ratios were obtained by Olah and Kuhn[19] using nitronium salts as nitrating agents. These results implicated the nitronium ion as the active nitrating species.

1.2.2 The Stepwise Mechanism in Nitration with NO_2^+:

The accepted stepwise mechanism[20] involved in nitration can be represented as:

$$H^+ + HNO_3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} NO_2^+ + H_2O \qquad (1)$$

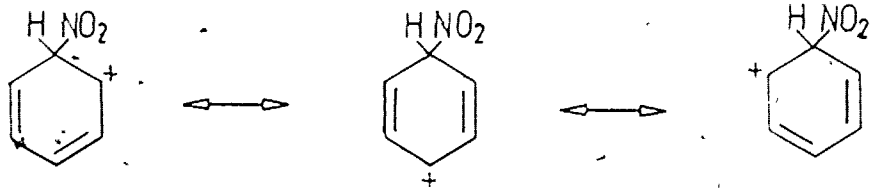
$$ArH + NO_2^+ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \overline{ArHNO_2}^+ \quad \text{Encounter pair} \qquad (2)$$

$$\overline{ArH\ NO_2}^+ \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} W \quad \text{(Wheland intermediate)} \qquad (3)$$

$$W \xrightarrow{k_4} ArNO_2 + H^+ \qquad (4)$$

Scheme 1.1

The Wheland intermediate (also known as arenium cation, benzonium cation, cyclohexadienyl cation, σ complex, Pfitzer complex) has the general structure 1 (Scheme 1.2)



1a 1b 1c

Scheme 1.2

Using the steady state concept the rate expression of the overall process can be shown to be

$$\text{Rate} = \frac{k_1\ k_2\ k_3\ k_4\ [ArH]\ [HNO_3]}{k_{-1}\left((k_{-2}+k_3)(k_{-3}+k_4) - k_3k_{-3}\right) + k_2\ k_3\ k_4[ArH]} \qquad (1)$$

Depending on the substrate and the reaction conditions any of the above four stages can be the slowest. For substances more reactive

than benzene, formation of the nitronium ion becomes rate determining and the reaction exhibits zeroth order dependence on the aromatic substrate, as observed in the nitration of benzene homologs in nitromethane and other inert organic solvents[15]. Nitration of anthracene with nitronium tetrafluoroborate in acetonitrile is a specific example where the proton elimination step (step 4) is rate determining and a kinetic isotope effect (k_H/k_D = 6.1 ±0.6) near to the theoretical limit is observed[21]. Steric reasons have been suggested for this.

The classical mechanism of nitration, established on the basis of extensive contributions of Ingold[3] and of Melander[22], did not distinguish between steps (2) and (3) (Scheme 1.1). The overall process was denoted by a single stage representing the slow uptake of nitronium ion via an S_E2 mechanism. This picture, generalized to electrophilic substitution, provided the basis of Brown's selectivity-reactivity principle[23], which proposes that loss of substrate selectivity should be accompanied by loss of positional selectivity in competitive processes, both of which depend on the reactivity of the electrophile.

Olah and his co-workers[24] proposed the formation of a π-adduct as an intermediate in a rate determining step preceding Wheland intermediate formation to explain the results. They observed, in competetive studies of the reactivity of toluene compared to that of benzene in the nitration with nitronium salts under their conditions, the substrate selectivity, i.e. rate of nitration of toluene / rate of nitration of benzene (k_T/k_B), decreased dramatically from the values observed in the nitration with nitric acid, without the loss of positional selectivity in toluene[24]. They proposed that substrate selectivity was lost in the formation of a π-adduct in the first step, which collapsed to a Wheland intermediate in the following step, with

retention of positional selectivity which was determined in the latter step.

Schofield and his co-workers observed a similar breakdown of the selectivity-reactivity principle in the nitration of benzene homologs with mixed acid and proposed a rate determining encounter pair formation with the onset of diffusion control[25] with the more highly reactive substrates. No structure for this encounter pair was proposed. Similar rate limiting encounter controlled reactions were recognized in nitration of reactive substrates with aqueous nitric acid, acetic anhydride, methanesulfonic acid, nitromethane, perchloric acid, phosphoric acid, sulpholan and trifluoroacetic acid[26]. From the calculated rate constants for encounter in these solvents and the measured values of k_M/k_B (Mesitylene = M) the values of k_B have been evaluated (mesitylene reacts at the encounter rate). These values have the expected degree of constancy for the range of solvents studied. Whether or not the formation of the encounter pair is rate determining in a particular case depends upon the reactivity of the substrate and the viscosity of the reaction medium. There have been objections to the suggestion by Olah that the encounter pair is a π-adduct[27]. A plot by Rys[28] of relative rates for the nitration of benzene homologs with nitronium salts against the stabilities of the π-adducts had a correlation coefficient of only 0.91. The loss of substrate selectivity observed by Olah has been shown to be due to incomplete mixing and the low values observed for k_T/k_B result from macroscopic diffusion control[29]. On the other hand Kochi and Fukuzumi[30] have observed transient charge transfer bands on mixing electrophiles with various aromatics, indicating the formation of charge transfer complexes. With m-toluonitrile and nitronium fluoroborate, a band at 400nm is reported. Such charge transfer complexes are presumably π-complexes in

the sense used by Olah. However there is no evidence that these are the species formed as the encounter pair in the encounter controlled nitrations.

Formation of the proposed encounter pair prior to the Wheland intermediate explains the discrepancy of the observed results with the selectivity-reactivity principle but does not explain the high positional selectivity observed.

Positional selectivities in pseudocumene were explained by Schofield on the basis of a non-interacting encounter pair[31] with a rate constant of diffusion apart in the order of $10^{9} - 10^{8}$ s^{-1}. The upper limit of the rate constant for collapse of the Wheland intermediate would be comparable to the magnitude of a vibration frequency i.e. 10^{12} to 10^{13} s^{-1}. Thus, there could be a positional selectivity of up to 100 in a non-interacting encounter pair. The extension of this argument to the nitration of durene has, however, led to some contradictory predictions. Schofield and his coworkers[32] have applied Holleman's product rule to the partial rate factors for the nitration of toluene to show that the ratio of the reactivities of C-1 and C-3 of durene is 1:2.7. They also claim that positional selectivity in durene should persist but be small and thus justify (the compatibility of) the experimental value of 1:3.6 on the basis of a non-interacting encounter pair. On the basis of the proposal that the rate of collapse to Wheland intermediate at C-5 and C-6 of pseudocumene is 10^{11} and 10^{12} s^{-1}, Perrin[33] argued that C-1 and C-3 of durene should collapse to Wheland intermediates at a rate of 10^{13} s^{-1}, which is the theoretical maximum. Thus both C-1 and C-3 should react at the same rate. However intramolecular selectivity persists in durene and also in pentamethylbenzene. From these observations which, according to Perrin, necessitate an interacting encounter pair, Perrin[33] proposed an

encounter controlled electron transfer followed by radical pair collapse to the Wheland intermediates i.e. the interacting encounter pair consists of the aromatic radical-cation and the nitrogen dioxide radical. Perrin's postulate that all aromatics more reactive than toluene could transfer an electron to the nitronium ion via an exothermic step hence leading to an intermediate of lower energy than the non-interacting encounter pair has been refuted by Eberson[34] and his coworkers. Calculations[34] based on Marcus theory of non-bonded electron transfer show that such processes can be ruled out for aromatics with E^0 lower or equal to perylene [E=-1.3V]. Other evidence put forward by Perrin has also been shown to be due to catalysis by nitrous acid or other N(III) species[35]. Thus for nitration with nitronium ion it is unnecessary to consider radical-cation formation along the reaction pathway for aromatics less reactive than perylene.

At the present time it appears that the positional selectivities that have been observed do not require the postulation of an interacting encounter pair.

1.3 Nitration Proceeding via Electron Transfer:

In this mechanism for nitration an initial step involves the transfer of an electron from the aromatic to the nitrating agent to give a radical pair, followed by coupling of the two radicals. The nitrating agent thus behaves as an oxidant and its identification is important. The fact that nitronium ion cannot act as an oxidant towards aromatics less reactive than perylene has been mentioned above. Ridd and his coworkers[36,37] have suggested that in nitrous acid catalyzed nitration NO^+ can act as the oxidant. In the nitration of N,N-dimethylaniline[36]

with $H^{15}NO_3$ in 85-90% sulfuric acid, and in the nitration of p-nitrophenol[37] in trifluoracetic acid, polarization of ^{15}N nuclei was observed in CIDNP studies. This has been explained by radical pair formation via electron transfer as shown in scheme 1.3:

$$ArXH + NO^+ \longrightarrow ArX^\cdot + H^+ + NO^\cdot$$
$$NO^\cdot + NO_2^+ \longrightarrow NO^+ + NO_2^\cdot$$
$$ArX^\cdot + NO_2^\cdot \longrightarrow ArX^\cdot\ {}^\cdot NO_2 \rightarrow \text{products}$$

$X = N^+Me_2$; O;

Scheme 1.3

There is also evidence that the electron acceptor in nitric acid is NO_2, via an acid catalyzed process. Based on this, an alternative sequence for nitration has been proposed by Ross and his coworkers[38], as shown in scheme 1.4:

$$ArH + {}^\cdot NO_2 + H^+ \longrightarrow ArH^{+\cdot} + HONO$$
$$ArH^{+\cdot} + {}^\cdot NO_2 \longrightarrow ArHNO_2^+$$
$$HONO + HNO_3 \longrightarrow 2NO_2 + H_2O$$

Scheme 1.4

This process qualitatively explains the observed catalysis by acids.

It is also possible to effect nitration by generating an aromatic radical cation. Electrochemical oxidation of naphthalene gives the corresponding radical cation. This forms a radical pair with NO_2, which collapses to the Wheland intermediate. The (α/β) product ratio in

this case is higher than that observed[39] in nitration by NO_2^+. Interestingly aromatic radical cations generated in the gas phase react with NO_2^+ to give a σ-bonded $ArHNO_2^+$ but under the same conditions the reactions with NO_2^+ with neutral aromatics yielded only the corresponding aromatic radical cation and the oxygenated radical cation ($ArHO^{+\cdot}$) via an electron or oxygen transfer[40].

1.4 Nitration via a Radical Mechanism:

Radical mechanisms for nitration with nitrogen dioxide have been proposed[41]. A radical mechanism is important in nitration of paraffinic side chains. Nitration of toluene with nitric acid in the presence of a trace of nitrogen dioxide gave phenyldinitromethane and phenylnitromethane. In the absence of nitrogen dioxide, the only products were nitrotoluenes and phenols. The proposed mechanism is a chain reaction initiated by nitrogen dioxide (scheme 1.5):

$$PhCH_2\text{-}H + {}^{\cdot}NO_2 \longrightarrow {}^{\cdot}PhCH_2 + HNO_2$$

$$HNO_2 \longrightarrow {}^{\cdot}NO + {}^{\cdot}HO$$

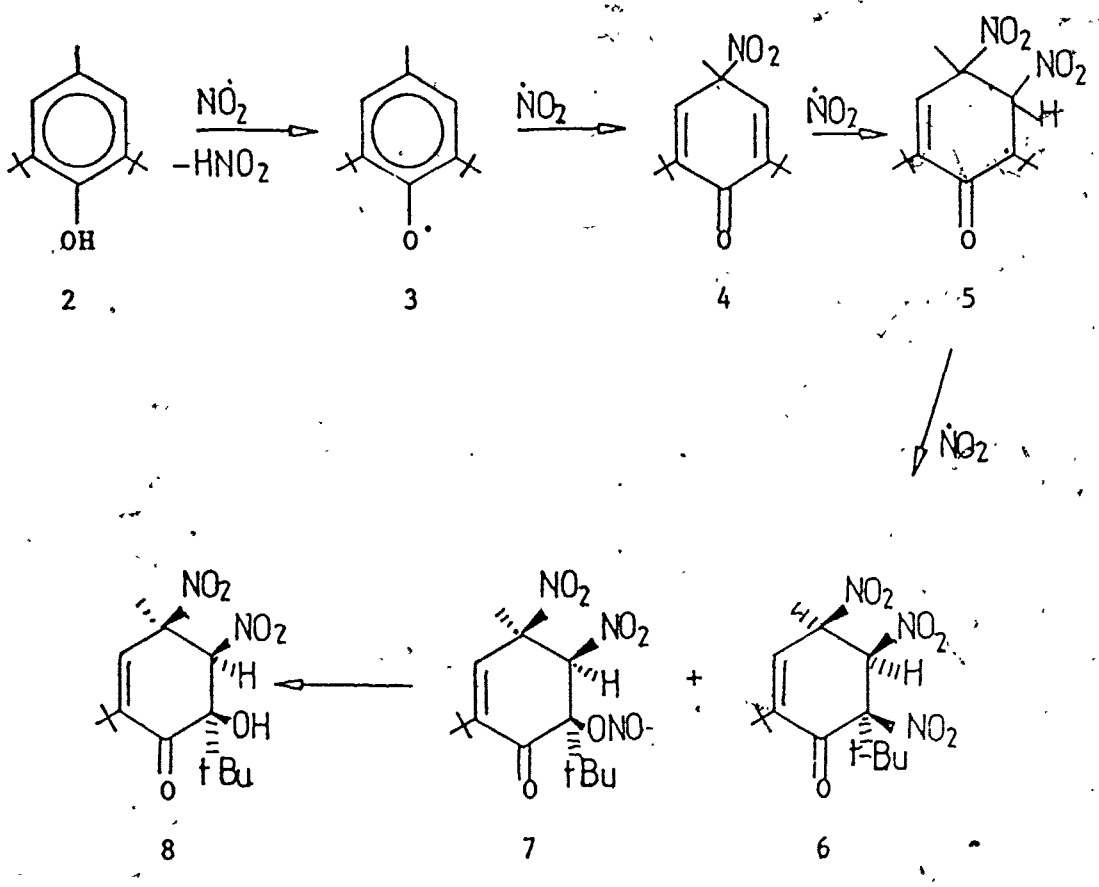
$$NO^{\cdot} + {}^{\cdot}2HNO_3 \longrightarrow 3NO_2^{\cdot} + H_2O$$

$$PhCH_2^{\cdot} + {}^{\cdot}NO_2 \longrightarrow PhCH_2NO_2$$

Scheme 1.5

Hartshorn and his coworkers have studied the nitration of highly substituted phenols with NO_2 in organic solvents. These reactions yield polynitroketones and other oxygenated products[42]. Nitration of 2,6-di-t-butyl-4-methylphenol (2) with NO_2 in cyclohexane gives the trinitroketone (6) and the dihydroxynitroketone (8) in addition

to the 4-nitrodienone 4. A radical mechanism is consistent with these observations (scheme 1.6).



Scheme 1.6

1.5 Nitration via Nitrosation:

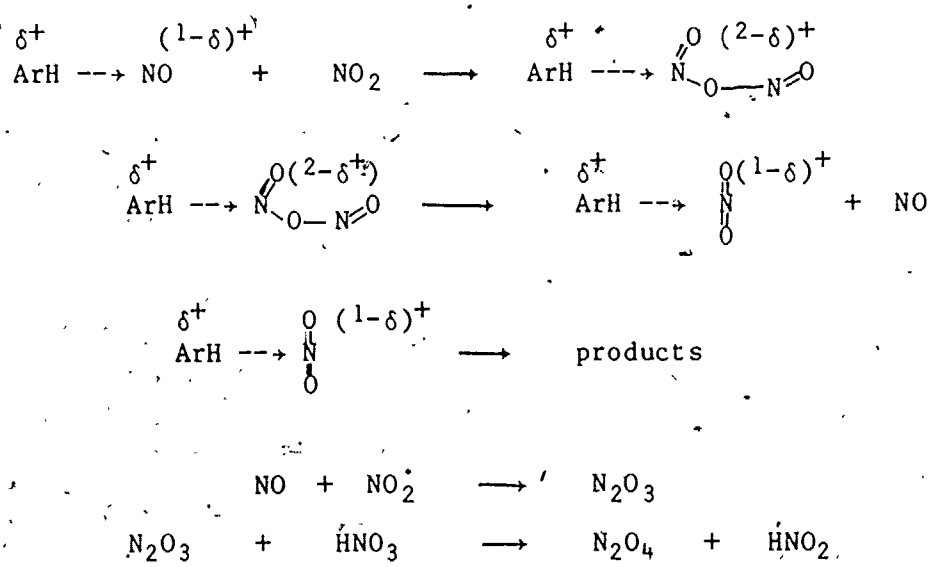
Reactive aromatics like phenols, anisoles and mesitylene can undergo nitrosation followed by oxidation to the nitro compound. This explains the observed catalysis by nitrous acid in nitration with nitric acid. Both nitrosonium ion and dinitrogen tetroxide have been identified as nitrosating agents. In some cases the intermediate

nitroso compounds have been isolated. The mechanism can be written as[43]:

$$ArH + N_2O_4 \longrightarrow ArNO + HNO_3$$
$$ArNO + N_2O_4 \longrightarrow ArNO_2 + N_2O_3$$
$$N_2O_3 + 2HNO_3 \longrightarrow 2N_2O_4 + H_2O$$

Scheme 1.7

There is, in addition to the above reactions, another mode of nitrous acid catalyzed nitration of reactive substrates, which appears in the nitration of pentamethylbenzene with nitronium ion. This leads to the formation of nitropentamethylbenzene accompanied by a large number (at least ten) of by-products. In this case a π-complex between the nitrosonium ion, present as an impurity in the nitronium salt, and the aromatic is involved[44], as shown in scheme 1.8:



Scheme 1.8

The π-complex has been formed separately by reacting benzene homologs (pentamethylbenzene and durene) with nitrosonium hexafluorophosphate[45]. These, on reaction with dinitrogen tetroxide, give the byproducts observed in nitration. The nitrous acid produced makes the reaction autocatalytic.

1.6 The Mechanism of Nitration in Acetic Anhydride:

The mechanism of nitration in acetic anhydride was originally thought to be different from the classical nitronium ion mechanism. Several distinguishing features of nitration carried out in this solvent were responsible for this belief: (a) abnormally high ortho:para ratios were observed in some cases[46]; (b) a higher concentration of mesitylene required for the (apparent) observation of zeroth order kinetics compared to that required in other media[47]; (c) acetoxylation[48] accompanied nitration.

Measurements of vapour pressure, Raman and IR spectra of mixtures of nitric acid in acetic anhydride have shown that the species present in the mixture depend on the proportions of nitric acid and acetic anhydride. The equilibria (1) and (2) (scheme 1.9) below are established in mixtures of nitric acid and acetic anhydride containing more than fifty percent nitric acid[49a].

$$Ac_2O + 2HNO_3 \rightleftharpoons N_2O_5 + 2AcOH \quad (1)$$

$$N_2O_5 + Ac_2O \rightleftharpoons 2AcONO_2 \quad (2)$$

Scheme 1.9

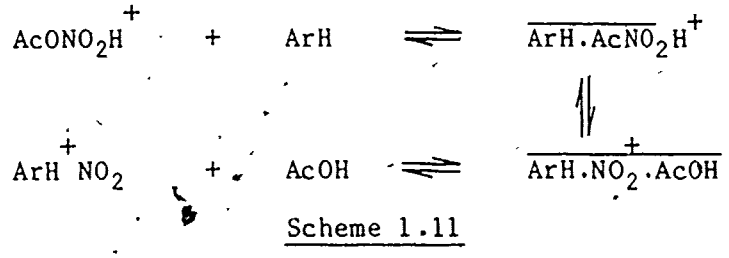
When acetic anhydride is present in large excess the only products are acetyl nitrate and acetic acid formed in the equilibrium

$$Ac_2O + HNO_3 \rightleftharpoons AcONO_2 + AcOH$$

Scheme 1.10

At ordinary temperatures the formation of acetyl nitrate is complete within minutes.

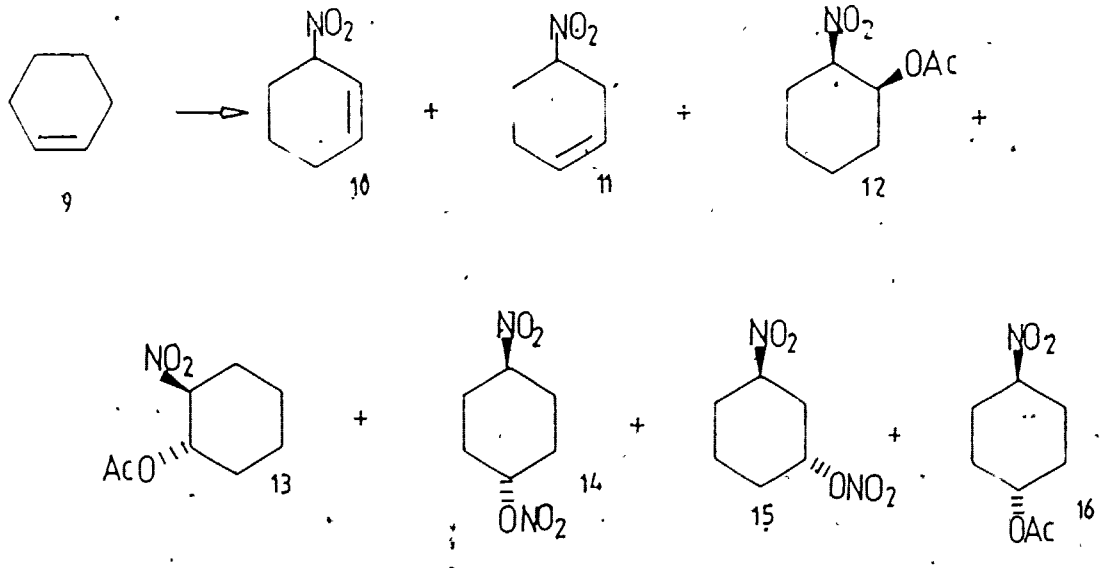
Apparently conclusive evidence regarding the role of nitronium ion as the effective nitrating agent comes from a comparison by Ridd[26b] of the rate of nitration of toluene and mesitylene in acetic anhydride with that in acetic acid. The rate coefficients for the reaction of this electrophile with toluene (k_T) were calculated from the relative rates (k_T/k_M) of nitration of the two hydrocarbons in both solvents with the assumption that the same electrophile is involved in the nitration of both hydrocarbons in the same solvent. The rate coefficients (k_M) for the reaction of mesitylene with the electrophile were calculated on the basis of an encounter controlled reaction for mesitylene in either solvent. The values (k_T) obtained for toluene were almost identical [$k_T(Ac_2O) = 4.0\times10^8$ and $k_T(HOAc) = 3.6\times10^8$] which indicated the electrophile must be identical in both solvents. The electrophile is known to be nitronium ion in acetic acid. An objection to this argument[49] is that the reaction of mesitylene in acetic anhydride is not zeroth order at the encounter rate. It has been proposed that, if nitronium ion is the active electrophile, it is formed from a protonated acetyl nitrate, inside the encounter pair, as shown in scheme 1.11:



Scheme 1.11

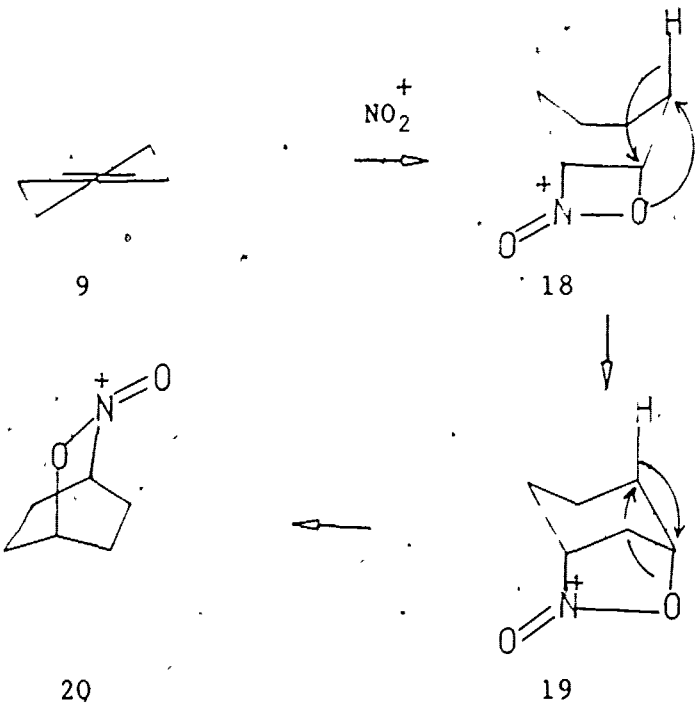
This mechanism could then account for the low half life ($<10^{-10}$ s) of the electrophile and consequently explain why mesitylene, after correcting for medium effect, does not react at the encounter controlled rate at concentrations as high as 0.5 mol dm^{-3}.

Acetyl nitrate also reacts with olefins to yield nitrocyclohexenes, nitroacetates and nitronitrates[50,51]. The products obtained from cyclohexene (9) by Wolfe and his coworkers[51] are shown in scheme 1.12.



Scheme 1.12

It is noteworthy that the products contain no conjugated nitro olefin, which should be the predominant product if the mechanism involved carbocation intermediates. Under the experimental conditions 1-nitrocyclohexene (17) did not isomerize, thus the 3- and 4-nitrocyclohexenes (10) and (11) obtained in the product mixture, were not formed via the 1-nitro isomer 17. The authors interpret these results by an initial cyclic [2+2] addition of nitronium ion, followed by successive rearrangement of the 2-isoxazetidionyl cation 18 to 19 and 20 (Scheme 1.13). Reaction of these isomers would then explain the products observed and also the absence of product 17.



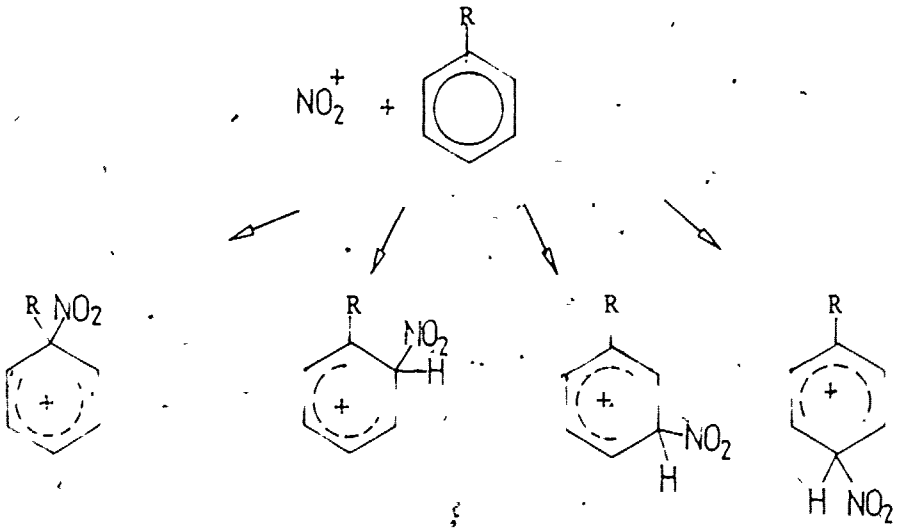
Scheme 1.13

Although the four membered ring is formed at the expense of resonance stabilization of the nitronium ion, it has been shown by

calculations of the C_2H_4-NO_2^+ energy surface to be 240 kJ/mol lower in energy[52] than the acyclic cation, in the gas phase. It is possible however that in solution, the stability could be reversed by external solvation of the acyclic cation. The relevance of such a [2+2] addition is yet to be established in electrophilic aromatic nitration.

1.7 The Wheland Intermediate:

Collapse of an encounter pair leads to the formation of a cyclohexadienyl cation (wheland intermediate). For a mono-substituted benzene there are four possible isomers as shown in scheme 1.14

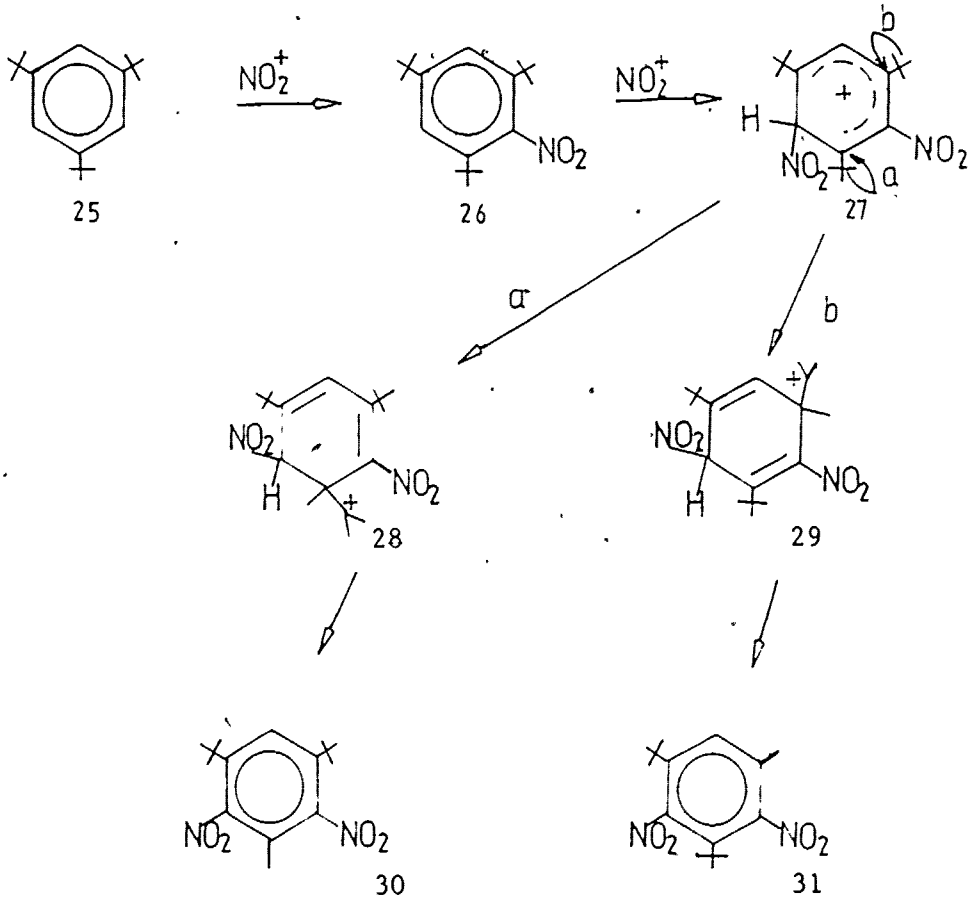


Wi	Wo	Wm	Wp
21	22	23	24

Scheme 1.14

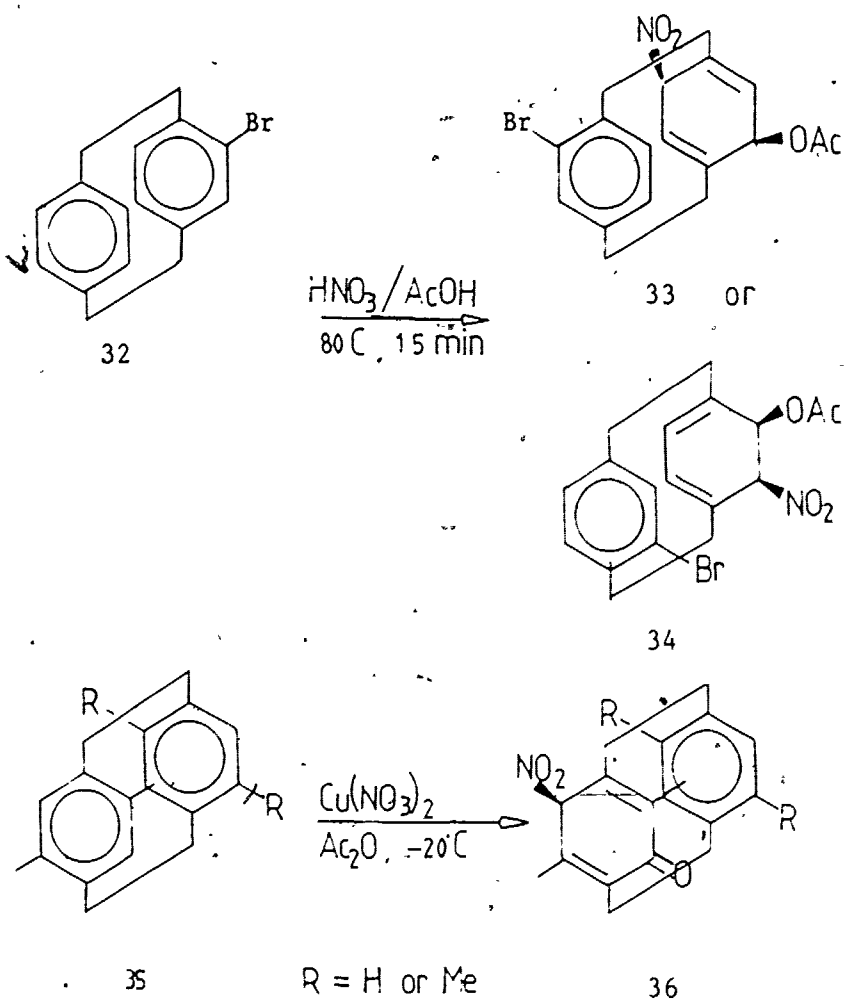
The W_o, W_m and W_p intermediates normally undergo rapid proton loss. In a few instances steric factors slow down this process and secondary reactions are possible. Formation of

1,5-di-t-butyl-3-methyl-2,4-dinitrobenzene (30) and 1,3-di-t-butyl-5-methyl-2,4-dinitrobenzene (31) in the nitration of 1,3,5-tri-t-butyl-2-nitrobenzene (25) has been explained by molecular rearrangement[53] in the long lived Wheland intermediate as shown in scheme 1.15.



Scheme 1.15

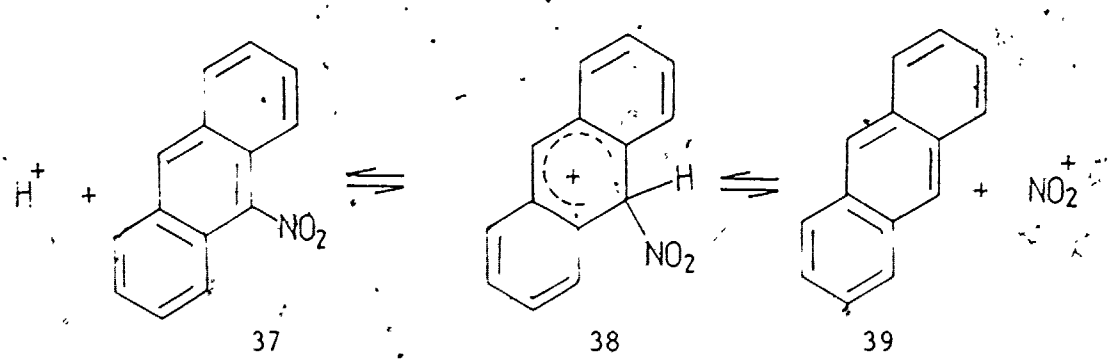
Reich and Cram[54] reported the isolation of an acetyl nitrate adduct (either 33 or 34 (scheme 1.16)) in the nitration of 4-bromo-[2,2]-paracyclophane (32). A cyclohexadienone 36 bearing a secondary nitro group has also been isolated by Horita and his co-workers in the nitration of methyl substituted [2,2]-paracyclophanes 35[55] as shown in scheme 1.16.



Scheme 1.16

In these cases the second aromatic ring sterically hinders deprotonation and hence render the Wheland intermediates long lived. In some exceptional cases the Wheland intermediates have been generated by protonating the nitroaromatics. Protonation of 9-nitroanthracene with sulfuric acid in trichloroacetic acid led to the formation of 81% free nitric acid[56]. Peri interactions between the 9-nitro substituent and the 1- and 8- hydrogens in 37, the product of deprotonation, disfavour proton loss and result in the denitration reaction being

competetive (Scheme 1.17).



37 38 39

Scheme 1.17

The kinetic isotope effect mentioned earlier[21] and that observed by Olah and his coworkers in the nitration of anthracene-d_{10} (k_H/k_D = 2.25)[57] with nitronium hexafluorophosphate also point to the slow proton loss in the Wheland intermediate.

Evidence for the existence of the Wheland intermediates is provided by the linear plot of logarithms of the relative rate constants for nitration of aromatics in acetic anhydride against the protonation equilibrium constants in liquid hydrogen fluoride for the same compounds[58]. This indicated the similarity in the trends for rates of Wheland intermediates formation and the σ-basicities of the corresponding aromatic compounds. Theoretical calculations by Wheland have supported the existence of these intermediates[59]. Spectroscopic studies[60] have now confirmed these structures in the case of **ipso** cations (discussed in the next section).

1.8 Ipso-Wheland Intermediates:

Perrin and Skinner introduced the term **ipso** to denote attack of a reagent at a substituted position[61]. The resultant cation, the **ipso**—Wheland intermediate, W_i^X (X = the original substituent) formed by attack of the nitronium ion is relatively stable and shows a variety of interesting reactions. The understanding of the various factors responsible for its formation and for its ultimate fate is important to an understanding of the overall nitration process. The **ipso**-directive power of a substituent is difficult to measure. A substituent deactivates or activates the ortho/para or meta position by stabilizing or destablizing the respective Wheland intermediate by electron donation or withdrawal. The directing effect depends on various factors which are not necessarily of equal importance for all four positions. On a qualitative basis, inductive effects contribute to all four positions, but become less important with distance. Steric factors influence ortho and **ipso** positions significantly more than meta or para positions. Resonance effects which are significant at ortho and para positions should not be important for the **ipso** position.

A measure of the directing power of a substituent is obtained from partial rate factors[62]. Fischer and his coworkers determined the partial rate factors at the methyl group in toluene (o_f = 44, m_f = 2.1, p_f = 54, i_f = 4.7)[63], and that of other alkyl groups relative to the methyl ($i^{Me} : i^{Et} : i^{iPr} : i^{tBu}$ = 1 : 0.3 : 0.2 : 0)[64]. **Ipso** partial rate factors for halogen substituents have been measured by Perrin[61]. The values above indicate that in alkylbenzenes the

ipso-position is less activated than the ortho or para positions. However in case of disubstituted benzenes the situation can be reversed by the effect of the second substituent. Thus powerful activating substituents ortho or para to the alkyl group can increase the reactivity at the **ipso** position e.g. although only 4% **ipso** attack occurs in toluene, 75% **ipso**-attack occurs in p-xylene. Attempts have been made to quantify these combined effects by using the principle of additivity. However the experimental values do not always agree quantitatively with such predictions[65]. The reactions of the **ipso**-Wheland intermediate can be classified as:-

a) reversal to starting material by the loss of nitro group

b) **ipso**-substitution by loss of the original substituent

c) migration of the nitro group

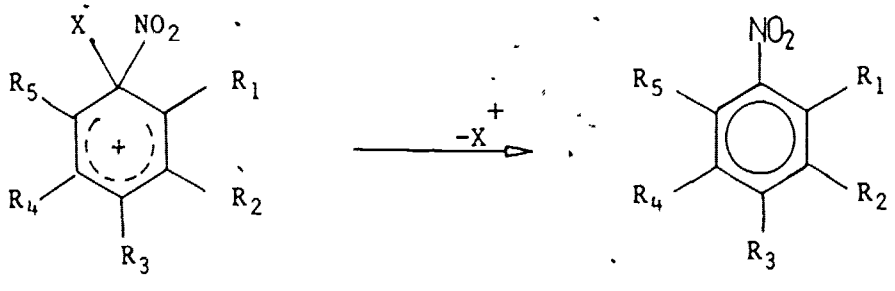
d) migration of the original substituent

e) rearrangement of a substituent ortho- or para- to the **ipso** position

f) capture by a nucleophile.

1.8.1 Ipso Substitution:-

A large number of functional groups which undergo substitution by the nitro group are known. The overall conversion in this case can be represented as in scheme 1.18:

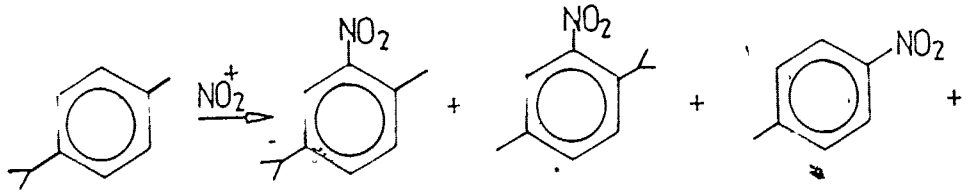


40 41

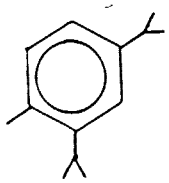
X=CHO, CH_3CO, CO_2H, OMe, iPr, tBu, $ArCH_2$, Br, I, $SiMe_3$, SO_3H

Scheme 1.18

Normally **ipso** substitution occurs only for strongly activated aromatics. The fate of the ejected group has not always been ascertained but in some cases it can serve as electrophile towards a second aromatic molecule. Nitration of p-cymeme (42) with nitronium tetrafluoroborate thus gives 2- and 3-nitro-p-cymene (43) and (44) p-nitrotoluene (45) and diisopropyl toluene (46) as shown in scheme 1.19[66].



42 43 44 45



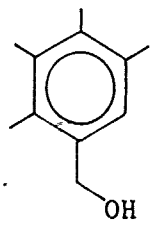
46

Scheme 1.19

1.8.2 Rearrangement of Substituents Ortho- or Para- to the Ipso position:-

Substituents containing an α-hydrogen and situated ortho- or para- to the **ipso** position often undergo loss of a proton, to stabilize the positive charge on the ring. In the case of a hydroxyl group this leads to the formation of a carbonyl group (a dienone) and is discussed separately as internal nucleophilic capture. For alkyl substituents, the intermediate methylene cyclohexadienes react further to yield benzylic compounds. Some examples of such reactions include nitro-oxylation producing nitrates, nitroso-oxylation producing

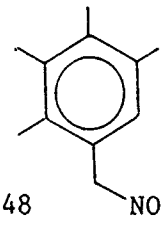
nitrites, nitration to nitromethanes, acetoxylation, arylation, alkoxylation, hydroxylation and oxidation of the side chain. Some examples are shown in scheme 1.20.



Ref 67a

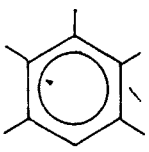
50

Side chain hydroxylation



48 Ref 67a

Nitro-oxylation



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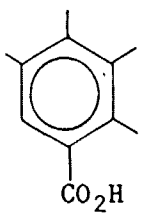
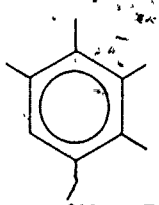


Ref 67c

51

Side chain oxidation



49 Ref 67b

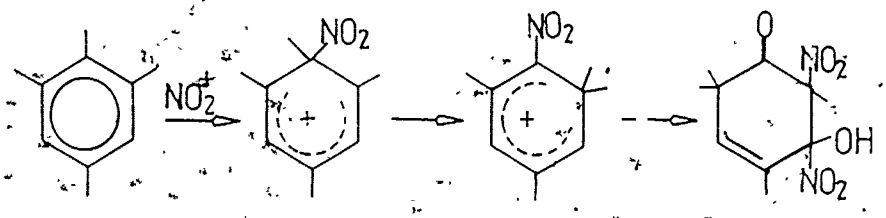
Side chain alkoxylation

Scheme 1.20

These reactions have been studied and reviewed extensively[68]. In some cases intermediate cyclohexadienyl compounds have been isolated and have been shown to yield benzylic compounds.

1.8.3 Migration of the Original Substituents:-

A cyclohexenone derivative, 55, formed in the nitration of iso-durene (52) with nitric acid in dichloromethane[67a] has been explained by a process involving migration of a methyl group in the W_i^{Me} formed by ipso attack of nitronium ion as shown in scheme 1.21. Other examples of alkyl group migration in highly substituted aromatics are also known.



52 53 54 55

Scheme 1.21

1.8.4 Nucleophilic Capture of Ipso-Wheland Intermediates:-

The most convincing evidence regarding the role of ipso-Wheland intermediates has come from the large number of adducts that have been prepared by nucleophilic trapping of W_i^{Me}. Subsequent reactions on these adducts have highlighted the role of these intermediates in the nitration reaction.

The work described in the present thesis is directed towards extending the scope of the ipso-nitration reaction for the prepartion of ipso adducts and the study of the reactions of these adducts. The dissertation has thus been divided into chapters pertaining to the reactions dealing with

a) formation of adducts (Chapter II)

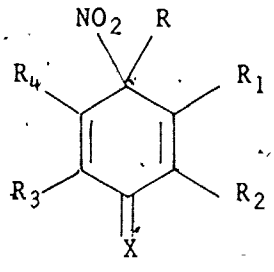
b) reactions of adducts under thermal conditions (Ch. III); in acidic media (Ch. IV); and with nucleophiles in weakly acidic, neutral and basic media (Ch. V).

Included in each chapter is a discussion of previous work described in literature related to that particular topic.

CHAPTER II: FORMATION OF IPSO ADDUCTS:

2.1 Introduction

Ipso Wheland intermediates can be captured by either external or internal nucleophiles. Lone pair bearing susbstituents situated at the ortho or para position, with respect to the ipso position, can lead to intramolecular capture. Dienones and imminium salts are examples of products (Scheme 2.1) obtained from such capture. In the precursor (a phenol or an aniline) the lone pair is conjugated to the ring.



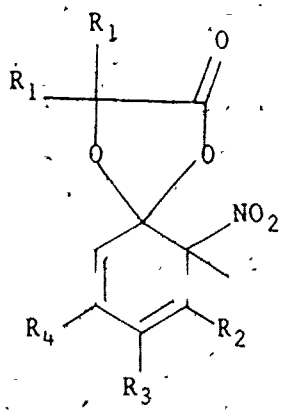
Compound	R	R_1	R_2	R_3	R_4	X	Ref
56	Me	H	H	H	H	O	69
57	Et	H	H	H	H	O	69
58	iPr	H	H	H	H	O	69
59	tBu	H	H	H	H	O	69
60	OMe	OMe	H	H	OMe	O	70
61	CH_2OMe	H	tBu	tBu	H	O	71
62	CH_2CN	H	tBu	tBu	H	O	71
63	Me	H	Me	Me	H	NMe_2^+	72
64	Me	H	NO_2	Me	H	O	73

Scheme 2.1

Dienones are also formed in the nitration of anisoles, but not by direct nucleophilic capture as in the case of phenols. In the

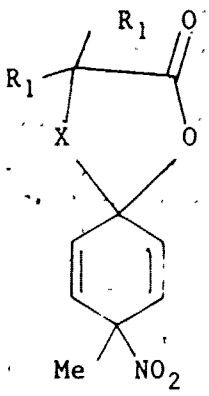
presence of external nucleophiles such as water the initial adduct, a hemiketal, collapses to the dienone. The involvement of attack by water on the ring carbon has been demonstrated by using ^{18}O-labelled water in the nitrating mixture[74]. The labelled oxygen was incorporated in the final dienone. Dienones are also formed in the nitration of cresyl acetates[75].

When the lone pair on the substituent is separated from the ring by a carbon chain, bicyclic spiro-compounds are formed (schemes 2.2 and 2.3). Some of these adducts are interesting in that they behave as protected dienones.



Compound		Ref.
65	$R_1=R_2=R_3=R_4=H$;	76
66	$R_1=Me$; $R_2=R_3=R_4=H$;	76
67	$R_1=Me$; $R_2=R_4=H$; $R_3=NO_2$;	76
68	$R_1=R_2=R_4=Me$; $R_3=H$;	76

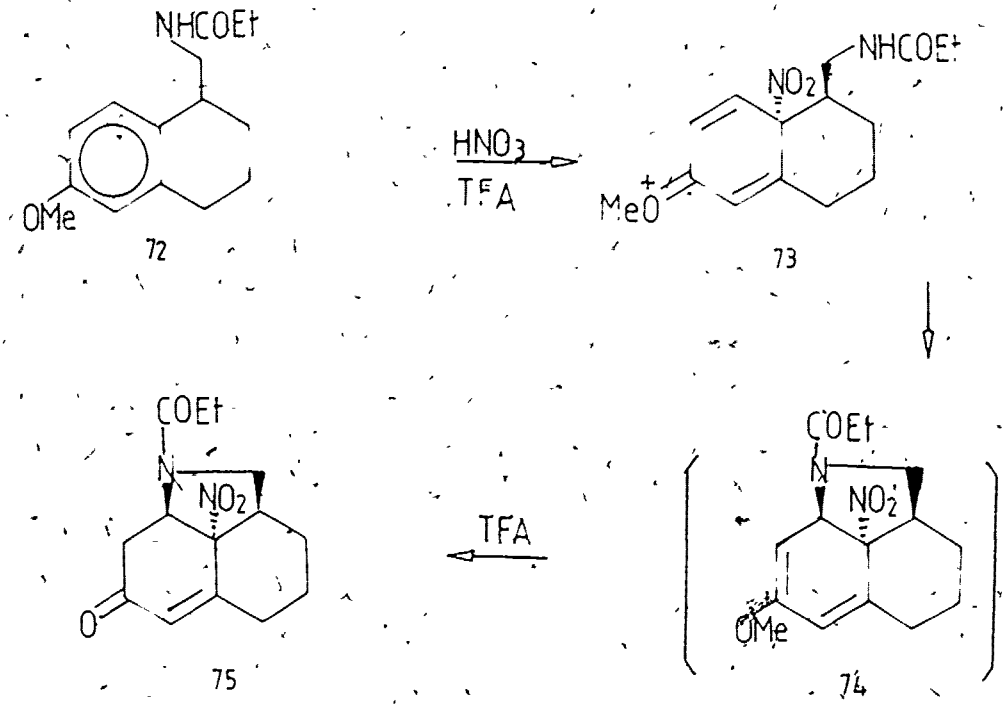
Scheme 2.2



Compound		Ref.
69	$R_1=Me$; X=O	76
70	$X=(CH_2)_2$; $R_1=H$	77
71	$x=(CH_2)_3$; $R_1=H$	77

Scheme 2.3

A recent example of internal nucleophilic trapping of the Wheland intermediate 73 is the formation of a nonaromatic tricyclic adduct 75 in the nitration of the amide 72. The mechanism involved is shown in scheme 2.4

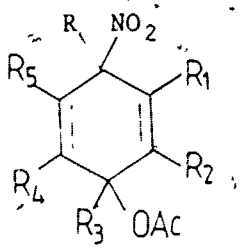


Ref 78 -

Scheme 2.4

Nitration with acetyl nitrate is the most extensively studied condition for the generation of **ipso**-adducts by external nucleophilic capture. The acetic acid present in the reaction mixture can capture the **ipso**-Wheland intermediate thus generating a nitrocyclohexadienyl acetate. Normally a diastereomeric pair of 1,4-adducts is obtained (scheme 2.5 and 2.6) by attack of the nucleophile at the para position with respect to the nitro group leading to non-conjugated dienes. Evidently, in this case, addition

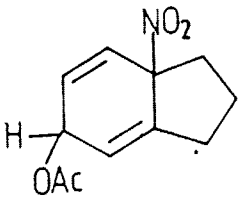
of acetate occurs from either face of the cation. Conjugated dienes formed by 1,2 addition have also been isolated (scheme 2.7), in this case only a single diastereomer has been obtained.



Compound	R	R_1	R_2	R_3	R_4	R_5	Ref
76	Me	H	H	H	H	H	79
77	Me	Me	H	H	H	H	80
78	Me	H	Me	Me	H	H	81
79	Me	Me	H	H	H	Me	81
80	Me	H	H	Me	H	H	82
81	Me	H	H	Et	H	H	64
82	Me	H	H	iPr	H	H	83
83	Me	H	H	tBu	H	H	84
84	Et	H	H	Me	H	H	64
85	Et	H	H	Et	H	H	64
86	Me	Me	H	OMe	H	H	85
87	iPr	Me	H	H	H	H	86
88	Me	Me	CN	H	H	H	87a
89	Me	H	CN	H	H	Me	87a
90	Me	H	COPh	H	H	Me	87c
91	Me	Cl	H	H	H	Me	87b
92	Me	Me	NO_2	H	H	H	65
93	Me	H	NO	H	H	Me	65
94	Cl	Me	H	Me	H	Me	88

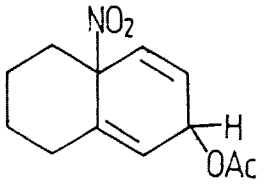
(Examples of 1,4-adducts from monocyclic compounds).

Scheme 2.5



95

Ref 89



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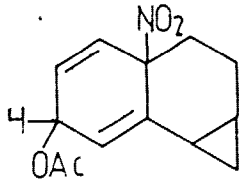

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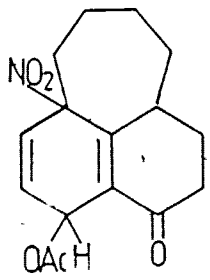
Ref 91



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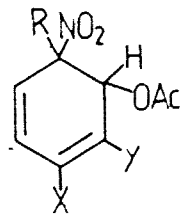
Ref 90

(Examples of 1,4-adducts from polycyclic compounds).

Scheme 2.6



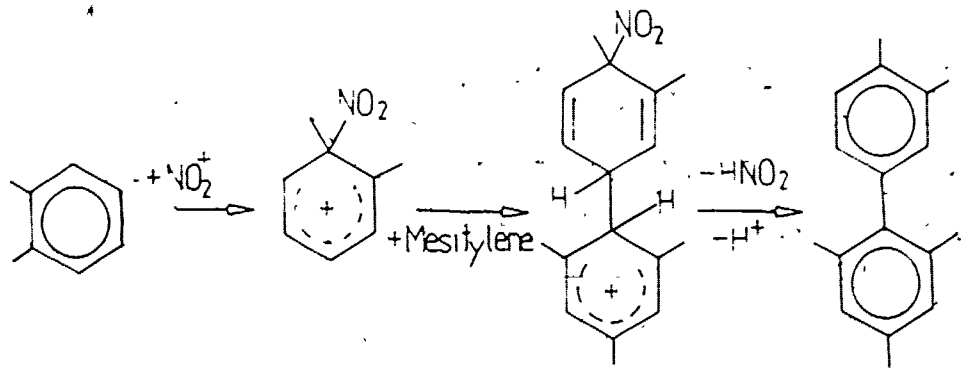
Compound	R	X	Y	Ref
99	Me	F	H	92
100	Me	Cl	H	92
101	Me	Br	H	92
102	Me	OMe	H	92
103	Me	NHCOMe	H	92
104	Me	tBu	H	84
105	Cyclopropyl	OMe	NO_2	93

(Examples of 1,2-adducts)

Scheme 2.7

For most of the substrates studied the possibility of both 1,2- and 1,4-addition exists, but a proper explanation for the predominance of either mode of addition remains elusive.

Ipso-adducts formed by nucleophiles other than acetic acid have also been isolated as shown in scheme 2.8. The formation of biphenyl derivatives accompanying the nitration of aromatics has been explained as involving intermediate **ipso** adducts. A second aromatic acts as a nucleophile[93].



106 107 108 109

Scheme 2.8

The current surge of interest in nitration chemistry is partly due to recognition of the importance of **ipso** attack. The isolation of the adducts, mentioned here, has demonstrated the existence of **ipso**-Wheland intermediates in aromatic nitration. A measure of the minimum extent of **ipso** attack is obtained directly from the amount of adducts detected. It is important to understand the various factors which determine the extent of **ipso** attack, the regioselectivity (1,2- versus 1,4-addition) and the

stereoselectivity that is observed in the nucleophilic trapping of the ipso-Wheland intermediate.

Objectives of the present work:-

The observation by D. L. Fyles[92] that high yields of ipso-adducts are obtained from the nitration of 4-X-toluenes opened a new route to the preparation of cyclohexa-1,3-dienes. In the present work it was the intention (i) to reinvestigate the reactions studied by Fyles and to attempt to determine the stereochemistry of the adducts. (It was also intended to study the reactions of the adducts. This had not been done in the earlier work as is discussed in subsequent chapters.) ii) to attempt to isolate the adduct from 4-acetamidotoluene (4-methylacetanilide), which had not been isolated previously. iii) to extend the investigation of this reaction to di(heteroatom) substituted toluenes as substrates.

The specific substrates investigated were 4-bromotoluene (110), 4-chlorotoluene (111), 4-methylanisole (112), 4-methylacetanilide (113), 2-bromo-4-methylanisole (114), 2-chloro-4-methylanisole (115) 4-methyl-2-nitroanisole (116), 3-chloro-4-methylanisole (117), 4-methyl-3-nitroanisole (118), 2-chloro-4-methylphenol (119) and 3-chloro-4-methylphenol (120).

The reactions of these adducts obtained were also to be investigated and this is discussed in the remaining chapters of this dissertation.

2.2 Results and Discussion.

The **ipso**-adducts were prepared by nitrating the substrate aromatics under conditions which led to optimum yields. The nitration of 4-chlorotoluene (111), 4-bromotoluene (110) and 4-methylanisole (112) were carried out under conditions which had been standardised previously[95] by D. L. Fyles. 4-Acetamidotoluene (113) was nitrated using a slightly modified procedure. The procedures accepted for the nitration of 2-chloro-4-methylanisole (115), 3-chloro-4-methylanisole (117), 2-bromo-4-methylanisole (114), 2-nitro-4-methylanisole (116) and 3-nitro-4-methylanisole (118) were similar and the conditions were determined during the course of this work by carrying out preliminary reactions on a 0.5 mmol scale and following the reactions by ^{1}H-NMR. The dienones which were obtained as by-products in some reactions, were prepared separately by nitrating the corresponding phenols 119 and 120, since this allowed easy separation from the accompanying nitrophenol products by chromatography at low temperatures (-78°C) on a basic alumina column. The nitroaromatics which were formed together with the **ipso** adducts were characterized by either a separate preparation through established routes or by comparison with pure samples of known structure obtained during the subsequent study of the reactions of the adducts. In some cases the nitro derivatives were obtained from commercial sources.

Products obtained in the nitration reactions are listed in figures 2.1 and 2.2 and the reaction conditions and yields of individual reactions are listed in table 2.1. The ^{1}H- and ^{13}C-NMR data of the dienes obtained from nitration is given in tables 2.2 and 2.3 respectively.

Substrate	Temp °C	Time mins	Mol proportion HNO_3	Ac_2O	TFA	Product (percentage)			Total ipso attack
111	-40	60	2	6	1	100(70)	121(17)	122(13)	70
110	-40	90	2	6	1	101(64)	123(28)	124(8)	64
112	-40	30	2	5	0	102(30)	116(70)		30
113	-40	120	5	15	1	103(35)	125(65)		35
115	-40	60	2	5	0	130(49)	134(18)	136(33)	67
119	-45	10	3	5	0	134(42)	137(58)		42
117	-45	38	2	10	0	140(23)	138(26)	139(51)	23
120	-60 to -40	30	1.5	$CDCl_3$	0	140(22)	142(25)	141(53)	22
114	-40	40	2.4	4	0	146(30)	148(27)	147(43)	57
116	-20	30	5	10	1	151(53)	152(5)	153(5)	
							154(25)	155(12)	88
	0	60	3	10	0	151(58)	154(30)	155(12)	88
118	-40	30	5	10	2	157(40)	158(50)	159(~10)	<10

Table 2.1: Summary of conditions for nitration and composition of reaction mixture prior to work up

Figure 2.1: List of Non-Aromatic Products obtained from Nitration

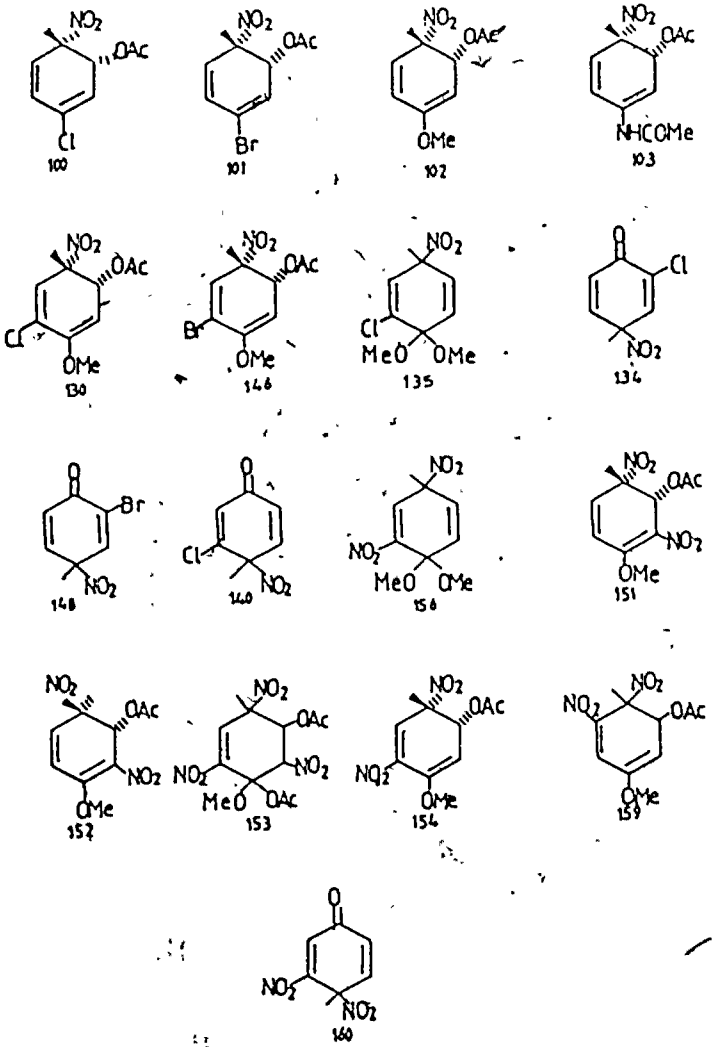


Figure 2.2: List of Aromatic Products obtained from Nitration

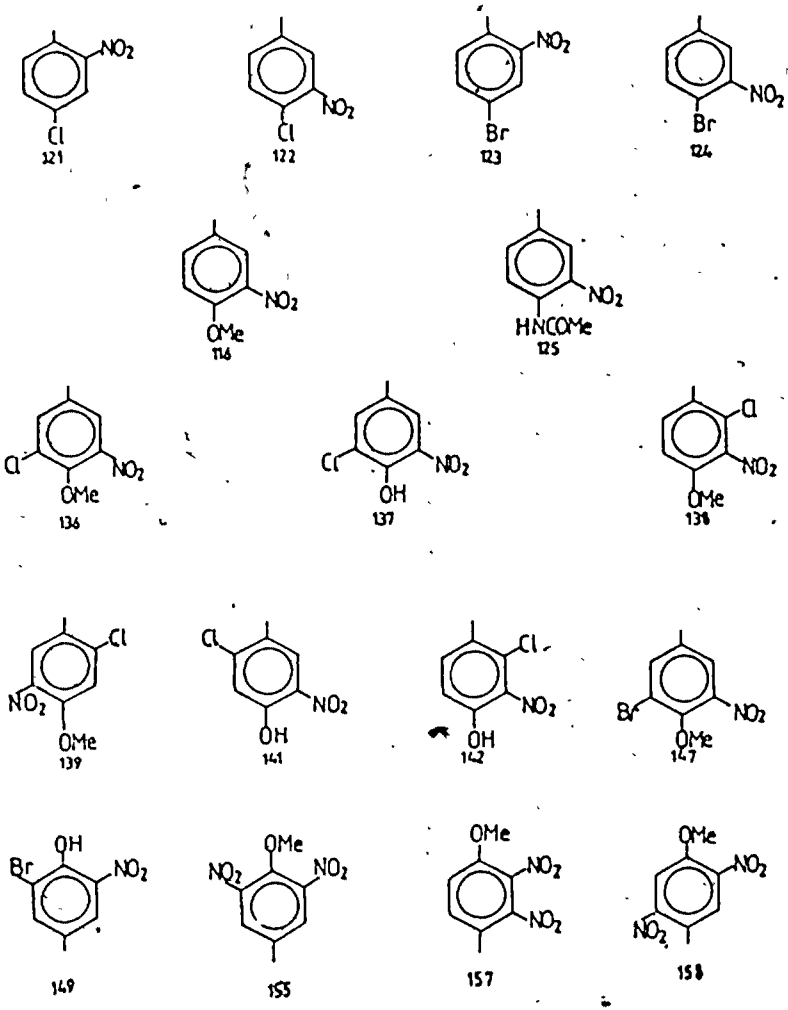


Table 2.2: ^{1}H-NMR data of Dienes obtained from Nitration.

	Chemical Shifts (ppm)							Coupling Constants (Hz)				
#	CH_3	OAc	OMe	1-H	2-H	4-H	5-H	1,2	1,5	2,4	2,5	4,5
100	1.78	1.99	-	5.53	6.12	6.03	6.55	6.13	1.65	1.97	0.61	10.20
101	1.77	1.98	-	5.45	6.37	6.13	6.45	6.15	1.76	1.80	0.55	10.23
102	1.77	1.95	3.60	5.62	4.97	5.93	6.56	6.57	1.52	1.75	-	10.20
103	1.78	1.95	-	5.62	6.49	6.09	6.59	6.55	1.53	1.70	-	10.30
130	1.80	1.97	3.68	5.60	5.12	-	6.73	6.45	1.85	-	-	-
146	1.80	1.98	3.67	5.59	5.09	-	6.99	6.62	1.91	-	-	-
154	1.88	1.99	3.71	5.64	5.27	-	7.29	6.70	2.02	-	-	-
151	1.88	1.97	4.03	7.09	-	6.47	6.51	-	2.06	-	-	10.60
152	1.79	2.10	4.04	7.04	-	6.71	6.36	-	1.60	-	-	10.20

Chemical shifts of other functional groups are included in chapter VII.

Table 2.3: ^{13}C-NMR data of Dienes obtained from Nitrations.

#	CH_3	OAc	OCH_3	C_1	C_2	C_3	C_4	C_5	C_6	CO
100	23.2	20.6	-	70.2	118.1	133.6	126.1	129.4	87.2	169.5
101	23.1	20.6	-	70.4	122.0	122.6	127.8	128.5	86.8	169.0
102	22.6	19.6	53.8	70.8	87.8	155.2	122.7	128.4	87.3	168.8
103	23.3	20.7	-	70.3	102.6	134.3	122.7	129.1	87.7	169.2
	(NHCOMe = 24.5)									170.0
130	23.5	20.7	55.8	71.2	91.1	152.4	127.6	126.2	88.7	169.6
146	23.2	20.7	55.8	71.1	90.5	152.5	117.3	130.4	89.3	169.6
154	22.5	20.6	56.1	70.7	93.5	149.3	145.4	127.3	87.5	169.4
151	22.8	20.4	58.0	70.4	123.7	155.9	117.2	138.3	88.9	168.4
152	21.8	20.5	58.1	68.2	124.3	156.5	122.4	135.6	86.3	169.2

2.2.1 Nitration of 4-X-toluenes:-

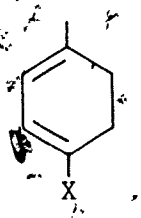
The 4-chlorotoluene (111) was nitrated with acetyl nitrate at -40°C in the presence of trifluoroacetic anhydride. The ^{1}H-NMR spectrum of the reaction mixture indicated the presence of 70% (Z)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (100), 17% 4-chloro-2-nitrotoluene (121) and 13% 4-chloro-3-nitrotoluene (122). After low temperature work up with ammonium hydroxide the composition of the mixture was unchanged and diene 100 was separated by crystallization.

From 4-bromotoluene (110) a mixture of 64% (Z)-3-bromo--6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (101), 28% 4-bromo-2-nitrotoluene (123) and 8% 4-bromo-3-nitrotoluene (124) was obtained. A longer reaction time and excess trifluoroacetic anhydride were needed, as compared with the nitration of 111. Diene 101 was obtained from the mixture by crystallization. Nitration of 4-methoxytoluene (112) in acetic anhydride yielded 30% (Z)-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (102) and 70% of 4-methyl-2-nitroanisole (116). Liquid ammonia work up followed by crystallization gave diene 102 in amount essentially equal to that present in the reaction mixture.

The nitration of 4-acetamidotoluene (113) was carried out by adding the powdered aromatic directly to the nitrating mixture. As reaction proceded a homogeneous solution was obtained. The ^{1}H-NMR spectrum of the reaction mixture indicated the presence of 35% (Z)-3-acetamido-6-methyl-6-nitrocyclohexa-2,5-dienyl acetate (103) and 4-methyl-2-nitroacetanilide (125). After careful work up with ammonium hydroxide at low temperature followed by evaporation

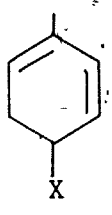
of solvent at -40°C, diene 103 (35%) was obtained in a mixture. Attempts to crystallize the diene from various solvent mixtures failed. The diene was found to be extremely labile and aromatized to 125 over a period of time at -20°C. Pure diene 103 was however obtained by two successive chromatographic separations on a silica column at -78°C. Detailed investigation of the ready aromatization of the diene was carried out subsequently and is discussed in Chapter III.

The structures of the dienes were initially assigned on the basis of spectral information. Elemental analyses were consistent with the addition of acetyl nitrate to the substrate aromatic. Such addition was confirmed by the IR spectra which exhibited strong absorptions around 1750 (for $OCOCH_3$) and 1550 cm^{-1} (for NO_2). The UV spectra (λ_{max} ≈ 265nm) showed that the dienes were conjugated. Isolated double bonds absorb below 253 nm[96]. There are three arrangements of conjugated double bonds which can be derived from addition to a 4-substituted toluene. Using the enumeration of toluene, these may be described a 1,3-diene (126), a 1,5-diene (127) and a 2,4-diene (128), as shown in scheme 2.9



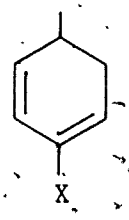
1,3-diene

126



1,5-diene

127



2,4-diene

128

Scheme 2.9

In the 1,3-diene (126) both sp^3 carbon atoms have an attached

hydrogen atom. However the ^{13}C-NMR indicates that there is one sp^3 carbon atom with an attached hydrogen atom (δ_C = 70 ppm, doublet splitting in the gated spectrum J≈150Hz), and one sp^3 carbon atom with no attached hydrogen (δ_C = 87 ppm, singlet in the gated spectrum). Moreover this structure cannot account for the 10Hz splitting of vinylic protons in the ^{1}H-NMR spectra, which points to the presence of adjacent vinylic protons. In the 1,5-diene (127) structure the variable substituent (4-X), is attached to an sp^3 carbon which has no attached hydrogen (after accounting for the addition of $AcONO_2$). However in the ^{13}C-nmr spectra the position of this sp^3 carbon absorption is quite invariant (δ_C≈87.5ppm) which points to a constant substitution pattern at this carbon. Correspondingly the sp^2 carbon which has no attached hydrogen has widely ranging absorption (δ_C 122.6 to 155.2 ppm) consistent with the 4-X-substituent being located at this position. Thus only the 2,4-diene (128) structure is consistent with the position of the absorptions of these two carbon atoms. Finally the nitro group must be located at position 1 because the chemical shift of the quaternary carbon (δ_C=87ppm) is the same as that of the only sp^3 carbon of 4-methyl-4-nitrocyclohexa-2,5-dienone (56) which bears the nitro group and methyl group. The acetate group is thus at position 6. Confirmation of the assigned structure and elucidation of the stereochemistry of the addition was provided in the case of the diene 101 by an X-ray crystal structure determination. Shift reagent studies applied to the two members of a pair of diastereomeric adducts have been used to determine the stereochemistry of some 1,4-adducts[65] but the method could not be applied to the dienes obtained in this work since a pure sample of

the minor diastereomer was not available.

Diene 101 was found to be stable enough to survive for periods at ambient temperature, and amenable to X-ray investigation. The Ortep diagram of the structure obtained is given in Fig. 2.3. Relevant bond lengths and angles are given in tables 2.4 and 2.5. As can be seen from the diagram the diene obtained in the nitration is exclusively (Z)-isomer. Evidently the 1,2-addition of acetyl nitrate (as nitronium acetate) is a cis addition and, by analogy, this would be expected to be generally true for all of the 4-X-toluenes, all of which give only one diastereomer on nitration. The stereoselectivity observed in these reactions is remarkable. The structural features of the dienes and consequent effects on the ^{1}H and ^{13}C-NMR spectra are discussed in chapter III. There it is shown conclusively that the adducts from other 4-X-toluenes have the (Z)-configuration. The relevant mechanistic features leading to such stereoselectivity are discussed in Chapter V.

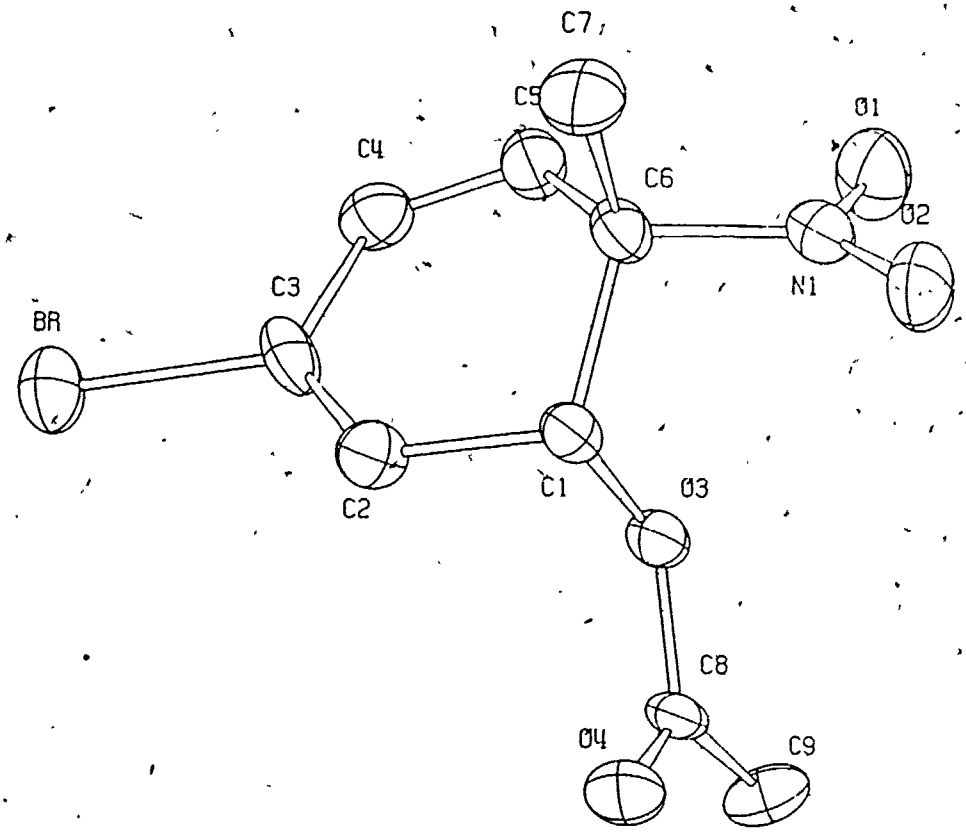


Figure 2.3: Molecular Structure of (Z)-3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (101).

TABLE 2.4

Interatomic Distances (Å) for 101

Atoms	Distance	Atoms	Distance
C(3) -Br	1.909(8)	C(6) -C(1)	1.543(12)
N(1) -O(1)	1.228(8)	C(3) -C(2)	1.302(12)
N(1) -O(2)	1.218(9)	C(4) -C(3)	1.475(13)
C(1) -O(3)	1.455(9)	C(5) -C(4)	1.332(13)
C(8) -O(3)	1.358(10)	C(6) -C(5)	1.492(11)
C(8) -O(4)	1.202(9)	C(7) -C(6)	1.532(12)
C(6) -N(1)	1.520(10)	C(9) -C(8)	1.476(11)
C(2) -C(1)	1.503(11)		

Estimated standard deviations are given in parentheses.

TABLE 2.5

Bond Angles (°) for 101

Atoms	Angle	Atoms	Angle
C(4) -C(3) -Br	115.1(7)	C(2) -C(3) -Br	121.4(7)
C(5) -C(4) -C(3)	118.9(8)	C(3) -C(2) -C(1)	119.7(7)
C(6) -C(5) -C(4)	119.2(8)	C(6) -C(1) -C(2)	109.4(6)
C(5) -C(6) -C(1)	112.8(7)	O(2) -N(1) -O(1)	123.0(8)
C(5) -C(6) -N(1)	109.8(7)	C(1) -C(6) -N(1)	105.8(6)
C(6) -N(1) -O(1)	119.4(8)	C(6) -N(1) -O(2)	117.5(7)
C(6) -C(1) -O(3)	106.6(6)	C(2) -C(1) -O(3)	109.5(6)
C(8) -O(3) -C(1)	116.3(6)	C(4) -C(3) -C(2)	123.4(8)
C(7) -C(6) -N(1)	106.6(7)	O(4) -C(8) -O(3)	121.6(8)
C(7) -C(6) -C(1)	110.3(7)	C(9) -C(8) -O(3)	111.4(8)
C(7) -C(6) -C(5)	111.3(7)	C(9) -C(8) -O(4)	127.0(8)

Estimated standard deviations are given in parentheses.

Other features of the ^{1}H and ^{13}C-NMR spectra of the dienes 100 - 103 are as follows (enumeration now follows that exemplified in 3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (100)). In the ^{1}H-NMR spectra the methyl group resonated at ~δ 1.8 ppm and the acetate methyl protons resonated at ~δ 2.0 ppm. The protons of the methoxy group of diene 102 resonated at δ 3.60 ppm and those of the acetamido group in diene 103 at δ 2.10ppm (CH_3).

The absorptions of the 1 and 2 protons were distinguished from those of the 4 and 5 protons by the 6-Hz coupling of the former as compared with the 10 Hz coupling of the latter. The individual assignment of the absorptions of the 1 and 2 protons was made on the basis that the 1-proton absorption should be essentially invariant in position, and is therefore the absorption at δ ~ 5.5 ppm, whereas the 2-proton absorption should be affected by the variation of the X-substituent, which is vinylic to it and ranges from δ 5.0 to 6.5 ppm. These assignments were confirmed by selective proton decoupling of the 1-H from the C-1 in the ^{13}C-spectra of dienes 101 and 102. The assignments of the 4 and 5 protons were made on the basis of long range coupling constants. The 1-H is coupled to one of 4-H and 5-H (J=1.6Hz) and 2-H is coupled to the other of 4-H and 5-H (J=1.8Hz). The four bond 1,5- and 2,4- couplings should be larger than the five bond 1,4- and 2, 5-couplings and the 4-H and 5-H were assigned to reflect this.

In the dienes 100 and 101 there is in addition a small 2,5-coupling (J=0.6Hz). Decoupling experiments were carried out on diene 101. The 1-H absorption appeared as a doublet of doublets (J=6.2Hz and 1.8Hz). The 2-H absorption appeared as a doublet of

doublet of doublet (J=6.2Hz, 1.8Hz, 0.6Hz). Irradiation of 1-H (5.45 ppm) caused the large coupling in 2-H to disappear, and the smallest coupling disappeared when the 5-H was irradiated (6.45 ppm). The 5-H absorption itself appeared as a doublet of a doublet of a doublet (J=10.2Hz, 1.8Hz, 0.6Hz) which collapsed to a doublet of a doublet (J=10.2Hz and 0.6Hz) when 1-H was irradiated. The 4-H absorption appeared as a doublet of a doublet (J=10.2Hz and 1.8Hz). Similar decoupling experiments were carried out on diene 100. In diene 102 the signal due to 2-H was shifted upfield (δ=4.97ppm) and the five bond coupling between 2-H and 5-H was absent.

The ^{13}C-spectra of these dienes had two peaks due to methyl carbons of which the low field signal (δ_C≈22ppm) was twice the intensity of the other (δ_C≈19ppm). In the single frequency decoupled ^{13}C-spectrum obtained by irradiating the protons on the acetyl methyl group (δ=1.95ppm), the low field signal (δ_C=22ppm) appeared as a quartet whereas the high field signal became a singlet. This allows us to assign the low field signal with higher intensity to the ring methyl and the high field signal as the acetyl methyl. The signal at C-2 was assigned on the basis of the substituent effect of the adjacent 3-X group; in all compounds this was expected to move the peak to higher fields and thus the highest field signal of the peaks attributable to C-2, C-4 and C-5 was assigned to C-2. The observed trend in the shifts of the C-2 and C-3 carbons parallels that reported[97] for mono-substituted olefins (table 2.6). The assignment of C-2 was thus confirmed and that of C-4 and C-5 was made on the basis of single frequency decoupling of the splitting by the protons attached to each carbon in the case of diene 102 and the C-5 proton in other cases. As would be expected the C-4 signal is more affected by the adjacent 3-X substituent (δ_C

122.7 to 127.8ppm) than is the signal of the more remote C-5 (δ_C 128.4 to 129.4ppm) and generally C-5 is at lower field than C-4.

	Reported $C_2=C_1-X$		Observed $X-C_3=C_2$	
X	C_1	C_2	C_3	C_2
H	123.3	123.3	-	-
Br	115.5	122.0	122.6	122.0
Cl	126.0	117.3	133.6	118.1
OMe	153.2	84.1	155.2	87.8

Table 2.6: Comparison of ^{13}C-chemical shifts of C-2 and C-3 observed in dienes 100→102 with that reported for monosubstituted olefins.[97]

The ^{1}H-NMR spectrum of 103 was found to be temperature dependent and the chemical shift values for five different temperatures are given table 2.7.

^{1}H-chemical shifts of diene 103

Temp (°K)	CH_3	OAc	NHAc	NH	1-H	2-H	4-H	5-H
229	1.77	1.95	2.10	8.32	5.61	6.53	6.08	6.59
241	1.78	1.95	2.10	8.22	5.62	6.49	6.09	6.59
249	1.78	1.95	2.10	8.00	5.62	6.46	6.10	6.59
273	1.78	1.94	2.09	7.50	5.62	6.43	6.11	6.58
298	1.78	1.96	2.11	v.broad	5.62	6.33	6.13	6.58

Table 2.7: Temperature Dependence of ^{1}H-NMR chemical shifts of diene 103.

The data in table 2.7 indicate that within an experimental error of ±0.01ppm the major variations of chemical shift are those due to 2-H ($\Delta\delta_{229-298}$ = 0.2ppm), 4-H ($\Delta\delta_{229-298}$ = 0.05ppm) along with the N-H ($\Delta\delta_{229-273}$ = 0.82ppm). The plots of change in chemical shift with temperature are given in figure 2.4 for 2-H and 4-H.

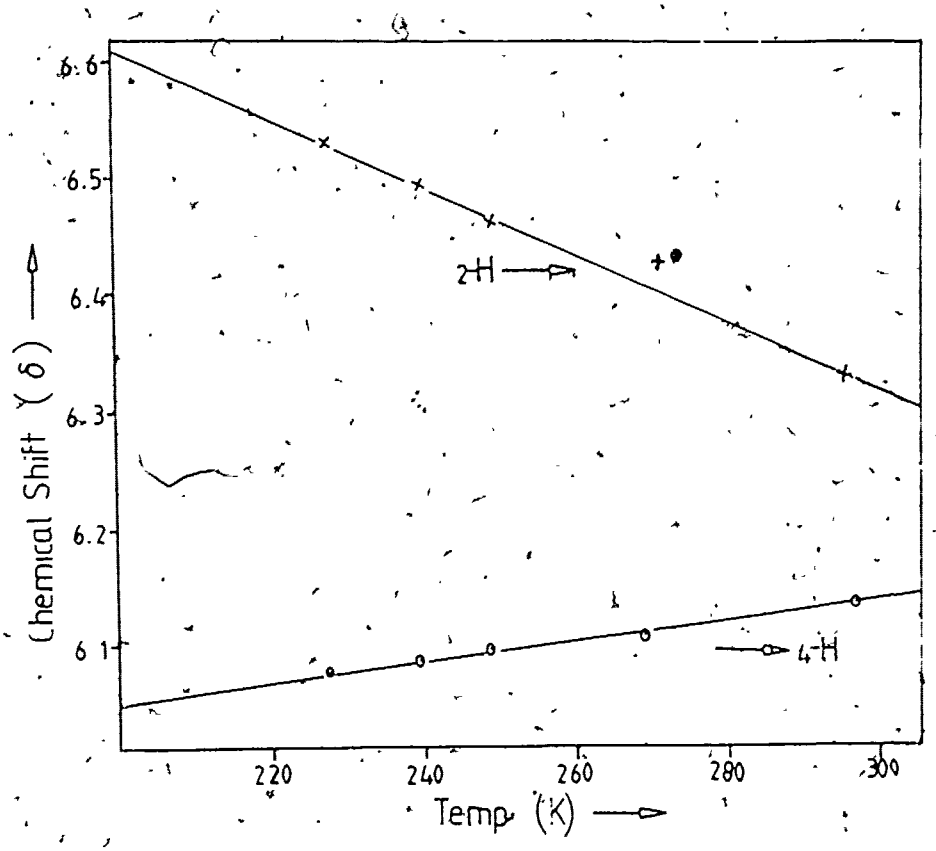
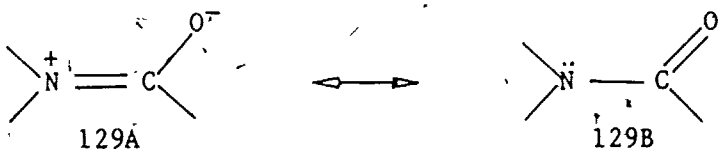


Figure 2.4: Plot of Change in Chemical Shift (2-H and 4-H) with Temperature in Diene 103.

In amides it is known that the C-N bond has partial double bond character, owing to participation of the resonance structures 129 (Scheme 2.10).



129A 129B

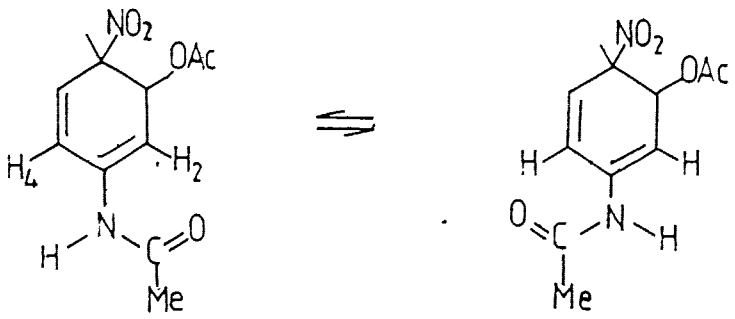
Scheme 2.10

Rotation about the carbonyl nitrogen bond is hindered as a consequence. In monosubstituted amides the rotamers have different energy contents and participate unequally in the thermal equilibrium. It has been established[98] for N-alkyl compounds that the predominant planar rotamer is the one with the alkyl groups (on N and on the C=O group) anti to each other as in 129C (Scheme 2.11).

129C 129D

Scheme 2.11

In the case of diene 103 such a geometry gives rise to two possible limiting structures 103E and 103F (Scheme 2.12), due to rotation about the C_3-N bond.



103E 103F

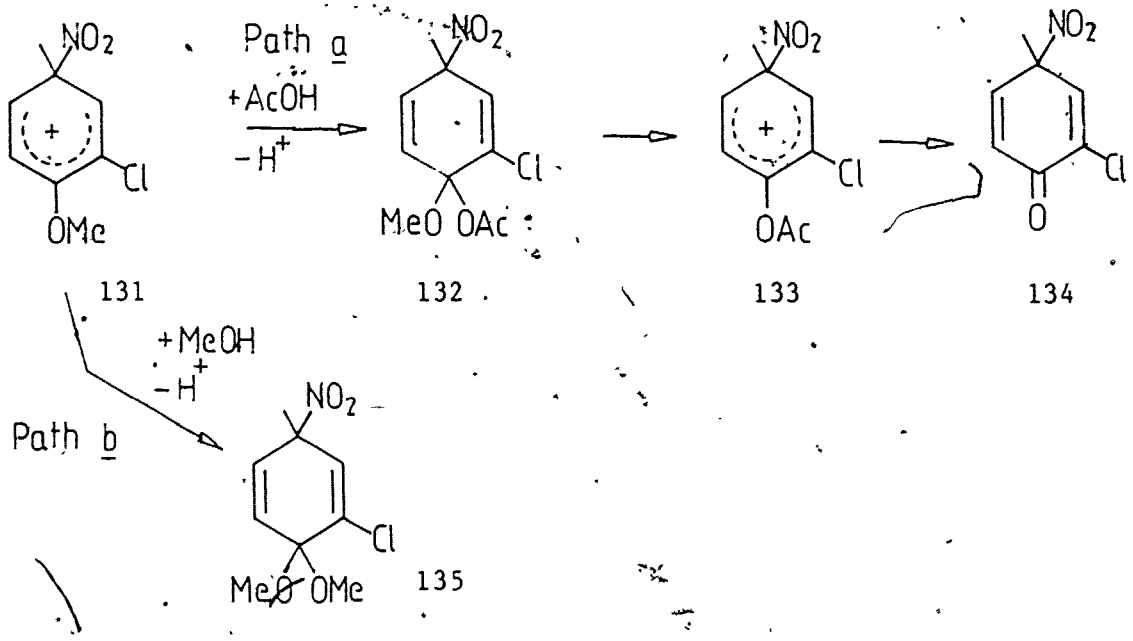
Scheme 2.12

In 103E the 2-H and in 103F the 4-H lie in the deshielding zone of the carbonyl group. The chemical shifts of these protons thus vary with the relative orientation of the carbonyl group, and their values at a particular temperature will be determined by the weighted average of each rotamer population in the equilibrium. From table 2.7 it can be seen that the signal due to 2-H shifts upfield and that due to 4-H downfield with increase in

temperature. This suggests that structure 103F is favored with increase in temperature, and structure 103E is thermodynamically favored over 103F.

2.2.2: Nitration of 4-Methylanisyl Derivatives:

2-Chloro-4-methylanisole (115) was nitrated at -40°C, and the ^{1}H-NMR spectrum of the reaction mixture indicated the presence of 49% (Z)-4-chloro-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (130), 18% 2-chloro-4-methyl-4-nitrocyclohexa-2,5-dienone (134) and 33% 2-chloro-4-methyl-6-nitroanisole (136). The dienone would most likely be formed by addition of acetate (as acetic acid) to the 4-position of W_i^{Me} followed by loss of elements of methyl acetate, as shown in path a of Scheme 2.13:



Scheme 2.13

After low temperature work up, the diene 130 separated out as a solid during evaporation of the solvent. The ^{1}H-NMR spectrum of the remaining mixture indicated the presence of 10.5% starting anisole 115, 56.5% nitroanisole 136, 22.5% 2-chloro-4-methyl-6-nitrophenol 137 and 5.5% 2-chloro-4-methyl-4-nitrocyclohexa-2,5-dienone dimethyl ketal 135. The nitro cresol 137 was apparently formed during work up from decomposition of the dienone. Part of the starting anisole recovered could have been formed from the decomposition of the diene 130. The dimethyl ketal 135 was identified by a comparison (^{1}H-NMR) with the pure sample obtained during reactions of the diene 130. Its formation presumably involved the capture of W_1^{Me} 131 by methanol liberated on the formation of 134, as shown in path b scheme 2.13.

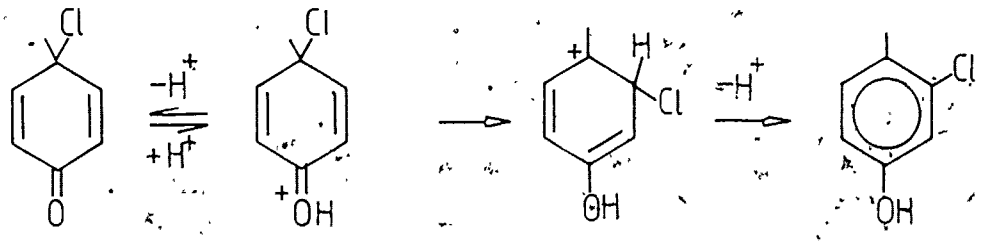
Dienone 134 was identified by comparison with pure

sample prepared by the nitration of 2-chloro-p-cresol 119 at -45°C, with acetyl nitrate. In the reaction mixture 42% dienone 134 and 58% nitrocresol 137 were present. During work up with ammonium hydroxide the nitrocresol 137 was partially extracted into the aqueous layer and the dienone 134 was enriched (88%). The remaining cresol 137 was removed by filtration through basic alumina at -78°C and the pure dienone 134 was obtained by removal of solvent at -50°C. The dienone 134 decomposed to cresol 137 at ambient temperature (half life = 280 sec), in chloroform-d. Similar decomposition occurred at 0°C (half life = 20 min).

Attempts to obtain **ipso** adducts from the nitration of 3-chloro-4-methylanisole 117 failed. Nitration at temperatures ranging from -60°C to -40°C with varying molar proportions of nitric acid and acetic anhydride gave mixtures containing 3-chloro-4-methyl-2-nitro anisole (138), 5-chloro-4-methyl-2-nitroanisole (139) and 3-chloro-4-methyl-4-nitrocyclohexa-2,5-dienone (140). The dienone 140 was prepared by nitrating 3-chloro-p-cresol (120) in chloroform-d at -60°C. The mixture containing 22% dienone 140, 25% 3-chloro-2-nitro-p-cresol (141) and 53% 5-chloro-2-nitro-p-cresol (142) was separated by chromatography on an alumina column at -78°C to yield pure dienone. The nitrocresols 141 and 142 were extracted from alumina and then separated by chromatography on a silica column. No attempts were made to isolate the nitroanisoles 138 and 139 but these were easily idenitifiable in the ^{1}H-NMR spectrum of the reaction mixture. When a solution of dienone 140 in chloroform-d was warmed to 0°C, an equimolar mixture of cresols 141 and 142 was obtained (half life = 10 min).

The 3-chloro-p-cresol (120) was prepared by dienone

phenol rearrangement of 4-chloro-4-methylcyclohexa-2,5-dienone (143) obtained by ipso-chlorination of p-cresol. The mechanism involved in this rearrangement is shown in scheme 2.14.



143 144 145 146

Scheme 2.14 Ref 99

A mixture of 43% 2-bromo-4-methyl-6-nitroanisole (147), 30% (Z)-4-bromo-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate 146 and 27% 2-bromo-4-methyl-4-nitrocyclohexa-2,5-dienone (148) was obtained in the nitration of 2-bromo-4-methylanisole (114) with acetyl nitrate at -40°C. The dienone decomposed during the low temperature work up with ammonium hydroxide and the resultant 2-bromo-6-nitro-p-cresol (149) partially removed during extraction. The ^{1}H-NMR spectrum of the mixture after work up indicated the composition as 47% anisole 147, 38% diene 146 and 16% nitrocresol 149. Pure diene 146 was obtained by crystallization. No attempts were made to obtain pure dienone 148 but it was easily identified by comparison with the chloro analog dienone 140. The nitro-cresol 149 was prepared separately by nitrating 2-bromo-p-cresol 150 and methylated to yield anisole 147. Both 147 and 149 were purified by crystallization and their ^{1}H-NMR spectra were found to be identical to the spectra for each compound in the nitrating reaction mixture.

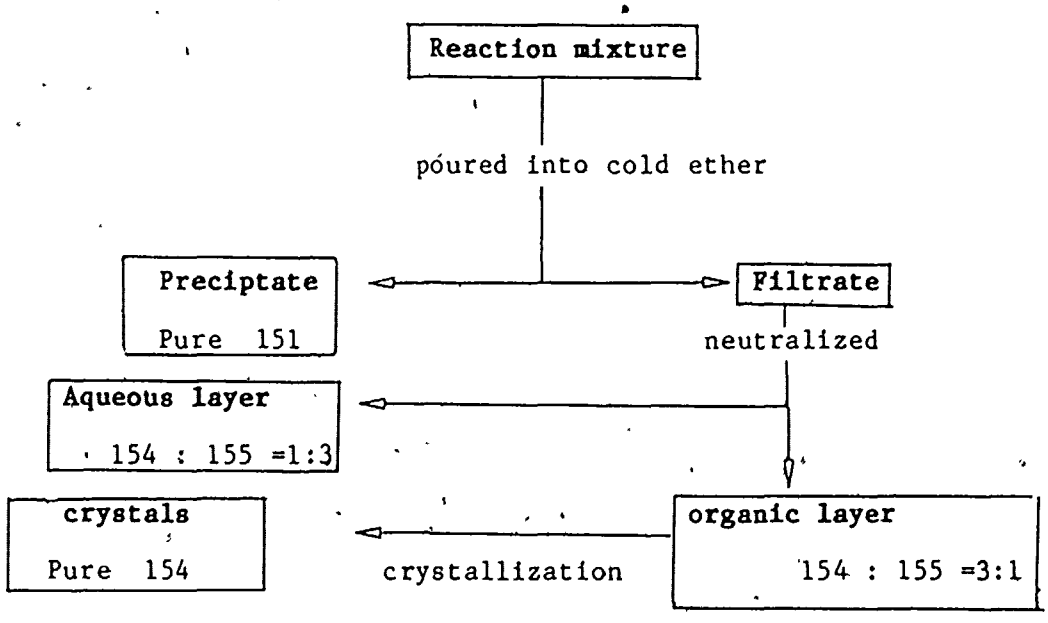
During standardisation of the reaction conditions for the

nitration of 4-methyl-2-nitroanisole (116) it was found that two dienes were formed consistently in substantial yields. In the presence of trifluoroacetic anhydride, minor amounts of two other non-aromatic compounds were detected. The nitration was carried out on larger scale both with and without added trifluoroacetic anhydride. The ^{1}H-NMR spectrum of the reaction mixture containing TFA indicated the presence of 53% (Z)-3-methoxy-6-methyl-2,6-dinitrocyclohexa-2,4-dienyl acetate (151), 5% of its (E)-diastereomer (152), 5% of another non-aromatic compound (153), 25% of (Z)-3-methoxy-6-methyl-4,6-dinitrocyclohexa-2,4-dienyl acetate (154) and 12% 4-methyl-2,6-dinitroanisole (155).

The minor components were isolated when the reaction was done in presence of trifluoroacetic anhydride. These compounds were enriched in the reaction mixture due to the low solubility of diene 151, the major component, and also due to some decomposition of 151 during work up with sodium bicarbonate at 0°C. Careful trituration with ether of the residue obtained after work up gave a mixture of the dienes 151 and 152 as the residue. By fractional crystalization of this residue diene 151 was isolated. From the ether extract diene 151 was separated by crystallization. The components in the mother liquor from recrystallization of 151 were separated by column chromatography. The component 153 was obtained in the 10% ether - 90% petroleum ether fraction. The 30% ether - 70% petroleum ether fraction contained diene 154 along with some 4-methyl-2,6-dinitroanisole (155) from which diene 154 was separated by crystallization. The later fractions contained another compound 156, which was not present in the original mixture. This compound was identified as 4-methyl-2,4-dinitrocyclohexa-2,5-dienone dimethyl

ketal (156) by comparison with an authentic sample whose preparation is described in chapter V.

The major components, dienes 151 and 154 were isolated without difficulty from the mixture obtained from the nitration carried out, in the absence of trifluoroacetic anhydride at 0°C. Compounds 152 and 153 were not found under these conditions. Diene 151 was precipitated by pouring the reaction mixture into cold ether (-78°C). After neutralization of the filtrate with ammonium hydroxide solution the organic layer was enriched with diene (154, 75%) and from which the diene readily crystallized. The aqueous extract was enriched in anisole 155. The solubility difference thus allowed the development of an easy separation method. The schematic representation of the separation procedure is given in scheme 2.15



Scheme 2.15

Addition of 4-methyl-3-nitroanisole (118) to nitrating solutions

invariably produced heterogeneous mixtures. It was difficult to obtain homogeneous ^{1}H-NMR samples even after diluting with aceticanhydride. The major compounds in the reaction mixture were 4-methyl-2,3-dinitroanisole (157) and 4-methyl-2,5-dinitroanisole (158). However, there was a minor amount of a non-aromatic compound 159 present in the reaction mixture. This compound could not be detected after low temperature work up with ammonium hydroxide. When the reaction mixture was filtered at -78°C prior to neutralization it was found that solid material present in the reaction mixture was composed of aromatics 157 and 158. A small amount of compound 159 was present in the filtrate. After low temperature work up only traces of 3,4-dinitro-4-methylcyclohexa -2,5-dienone (160) were detected in the ^{1}H-NMR spectrum. The non-aromatic compound 159 was assigned as (Z)-5,6-dinitro-3-methoxy -6-methylcyclohexa-2,4-dienyl acetate from the ^{1}H-NMR spectrum of the compound in the reaction mixture. Dienone 160 was characterized by comparison of the ^{1}H-NMR spectrum with that reported by Iyer[5] from the nitration of 3-nitro-p-cresol (161).

Diene 130 obtained from the nitration of anisole 115 had characteristic peaks in the IR spectrum due to nitro (1540 cm^{-1}) and acetate (1735 cm^{-1}) groups and had an elemental analysis corresponding to the empirical formula of the adduct. The close similarity between the NMR spectra (both ^{1}H and ^{13}C) of 102 and 130 with the expected differences resulting from the introduction of a 4-chloro-substituent, allowed the assignment of the 4-chloro-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate structure to the new compound. In particular the 71.2 ppm peak in

the ^{13}C spectrum characteristic of the sp^3 ring carbon ($CMeNO_2$) is within 0.5 ppm of the similar peak in 102. The high field vinyl carbon (δ_C 91.1 ppm) has an attached hydrogen and must be adjacent to the methoxyl substituted carbon (δ_C 152.4 ppm). The chlorine substituent must be attached to the carbon at 127.6 ppm, since the carbon shows no strong coupling to hydrogen in the gated spectrum. In the proton spectrum the methine hydrogen is at the consistent position of 5.6 ppm. The vinyl hydrogen adjacent to the methoxy substituent is at high field (5.12 ppm in 130 c.f. 4.97 ppm in 102) and shows the expected 6.5 Hz splitting with the methine proton and the chlorine must be attached to the 4,5-double bond since the 10 Hz splitting present in 102 is absent in 130. The 1.85Hz splitting in the methine proton must reflect a 1,5-coupling and this confirms that chlorine is at the 4-position. Parallel arguments can be made to assign the 4-bromo-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate structure (146) to the diene obtained on nitration of 2-bromo-4-methylanisole (114).

The dienone 134 observed in the reaction mixture of the 2-chloro-4-methylanisole (115) and later on obtained by nitration of the corresponding cresol 137 was characterised on basis of the ^1H-NMR and ^{13}C-NMR spectra. In the ^1H-NMR spectrum there was a single methyl resonance (δ = 2.04 ppm) and three well separated signals in the low field vinylic region. The lowest field signal, (d, δ = 7.34 ppm, J = 2.8 Hz) was assigned to 3-H and the multiplicity could be explained by a four bond coupling with 5-H. The latter proton appeared as a doublet of a doublet (J = 10.1 and 2.8 Hz) and the larger coupling constant was due to coupling with

6-H (δ = 6.52 ppm). The ^{13}C-spectrum indicated the presence of a carbonyl group and agreed with the proposed structure. A similar dienone 148 was observed by ^{1}H-NMR of the reaction mixture obtained in the nitration of 2-bromo-4-methylanisole (114). Its ^{1}H-NMR spectrum also agreed well with the proposed structure.

The dienone 140 detected in the reaction mixture of the 3-chloro-4-methylanisole (117) and later on obtained by the nitration of the corresponding cresol 120 had spectra very similar to dienone 134. In the ^{1}H-NMR spectrum the splitting pattern was almost identical and the changes in the chemical shifts of both ^{1}H and ^{13}C spectra could be easily explained by considering the interchange in the position of chlorine substituent from C-2 in dienone 134 to C-3 in dienone 140.

The molecular formula of the two major dienes 151 and 154 and the minor diene 152 obtained from anisole 116 was found to be $C_{10}H_{12}N_2O_7$, which could be accounted for by the addition of one acetyl nitrate molecule to the starting anisole 116. The IR spectra of these dienes confirmed the presence of acetate and nitro groups. The ^{1}H-NMR and ^{13}C-NMR spectra of diene 154 were very similar to those of dienes 130 and 146 and had an essentially identical splitting pattern. The assigned structure in which the 4-halo substituent is replaced by nitro thus accounts for the structure. The largest difference in the ^{13}C-NMR spectra of 130 and 154 is 18 ppm downfield shift of C-4. This is accounted for by the greater substituent shift effect of the nitro (attached to C-4) than chlorine. In the ^{1}H-NMR spectra the 5-H is 0.6 ppm further downfield in 154 than in 130 and this is explained by the β-substituent effect of the nitro group attached at the other end of

the 4,5-double bond.

The elemental analysis data of diene 151 indicated that it is an isomer of 154 and the general similarity of the ^{13}C-NMR spectra of the two compounds suggests that these are structurally closely related. The most striking difference between the spectra is that the very high field vinyl carbon absorption which appears close to 90 ppm in 102 and its 4-chloro, 4-bromo and 4-nitro derivatives 130, 146, and 154 respectively is absent in 151 for which the highest field sp^2 carbon is at 117 ppm. This suggests that the nitro group in 151 is at C-2 and this is re-affirmed by the ^{1}H-NMR spectra which showed the 10 Hz splitting of adjacent vinyl protons, also present in 102 but not present in the 4 substituted derivatives 130, 146, and 154. This indicates that there are no substituents on C-4 and C-5 in 151 and hence that the location of the nitro group is at C-2. Further confirmation is provided by the downfield shift of the methine proton on the adjacent carbon atom. In the series of compounds in which C-2 is not substituted this proton is consistently close to 5.6 ppm. Thus 151 has the 3-methoxy-6-methyl-2,6-dinitrocyclohexa-2,4-dienyl acetate structure. The ring protons of 151 are readily assigned since the 10 Hz coupling identifies the 4,5-vinylic pair and the 2 Hz splitting present in 1-H is also present in 5-H. In the ^{13}C-NMR spectrum C-1 (δ_C 70.4 ppm), C-3 (δ_C 155.9 ppm) and C-6 (δ_C 88.9 ppm) have the chemical shifts and presence or absence of proton coupling appropriate for their substitution patterns: The C-2 signal (δ_C 123.7 ppm) is readily identified as the remaining substituted vinyl carbon. The signal of the unsubstituted vinyl carbons C-4 (117.2 ppm) and C-5 (138.3 ppm) are assigned on the basis of that the C-5

carbon is downfield (c.f. 100, 101 and 102). Furthermore the nitro group conjugated with the diene system results in an additional downfield shift (10.0 ppm) of C-5.

The third diene 152 had ^{1}H and ^{13}C-NMR spectra which could also be explained on the basis of the 3-methoxy-6-methyl-2,6-dinitrocyclohexa-2,4-dienyl acetate structure. The ^{1}H- and ^{13}C-NMR spectra were closely similar to 151 and it is evident that 151 and 152 are diastereomers. The major isomer 151 (the only isomer obtained in acetic anhydride) is assigned as the (Z)-isomer. The dienes 130, 146 and 154 were also assigned the (Z)-configuration on the basis of the demonstrated cis addition of acetyl nitrate in the nitration of 4-bromotoluene (110). The (E)-diastereomers of dienes 100, 101 and 102 were obtained and characterized during the thermal reactions. The changes in the NMR spectral properties with change in stereochemistry in the series 100, 101, 102, and 151 are consistent for all of these dienes.

From the molecular formula ($C_{12}H_{15}N_3O_{11}$) of the non-aromatic compound 153 obtained from the anisole 116, it is evident that it was formed by the addition of two acetyl nitrate molecules to the substituted anisole. In the IR spectrum there were two strong absorptions (1790 and 1755 cm^{-1}) due to acetate groups. The ^{1}H and ^{13}C-NMR spectra also indicated the presence of the two acetate groups. The peaks at 68.0 and 87.3 ppm have the shifts and proton couplings appropriate to the ring carbons of the CHOAc and $CMeNO_2$ groups respectively and are so assigned. These must be the 1- and 6-carbon atoms (following the enumeration of 102). The single double bond is substituted at one end. It cannot terminate

at C-3 because the carbon has a methoxyl substituent which would send the adjacent unsubstituted vinylic carbon to very high field (90 ppm) whereas the vinylic carbon is at 130 ppm. Thus the double bond must be between C-4 and C-5 and must have the original nitro substituent at C-4, and the second molecule of acetyl nitrate must have been added across the C-2, C-3 positions. The chemical shift of C-2 (87.6 ppm) as well as the directing effect of methoxyl on the addition of nitronium ion indicates that the C-2 substituent is nitro and the second C-3 substituent is acetate. Thus the compound 153 has the structure 3-acetoxy-3-methoxy-6-methyl-2,4,6-trinitrocyclohex-4-enyl acetate. The ^{1}H-NMR is readily assigned as indicated in the figure 2.5 below. The 12.8 Hz coupling identifies the methine protons and that attached to the same carbon as the nitro group is assigned as the highest field signal.

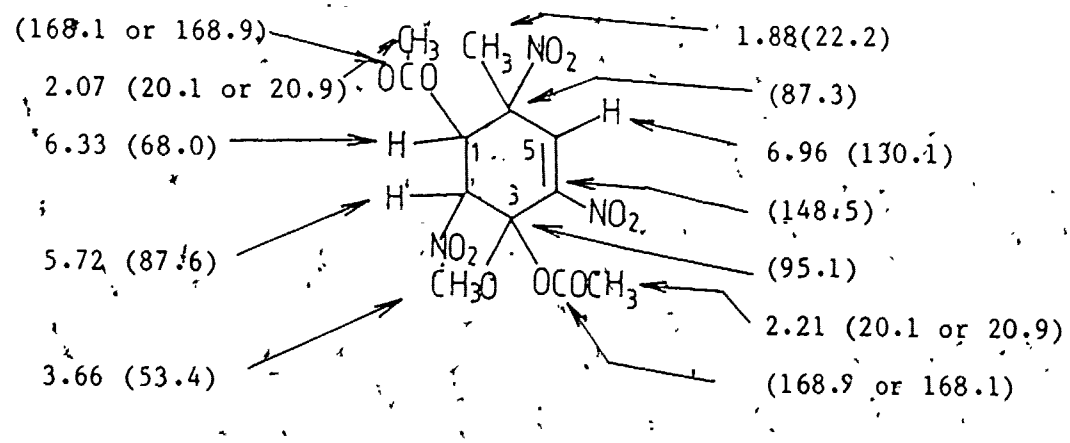
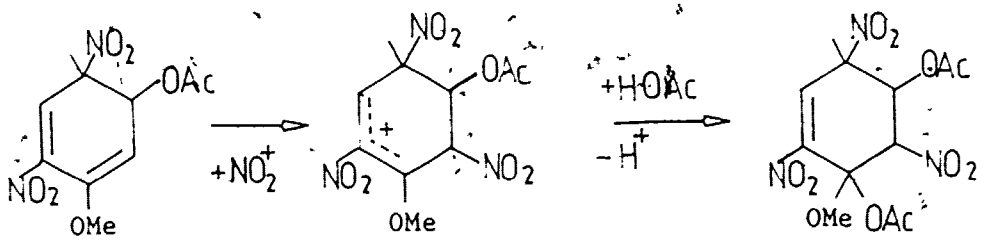


Figure 2.5: ^{1}H-NMR and (^{13}C-NMR) spectral assignment of compound 153

Compound 153 is formed from the second intermediate nitration product 154 by addition of nitronium ion to the 2,3-double bond, strongly activated by the 3-methoxyl group (scheme 2.16). The

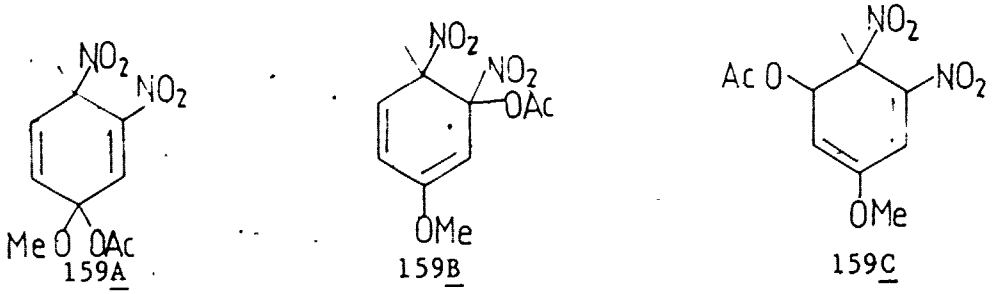
presence of the trifluoroacetic anhydride makes for a more reactive nitrating mixture and increases the likelihood of this reaction.



154 162 153

Scheme 2.16

The diene 159 observed in the nitration of 4-methyl-3-nitroanisole (118) was characterised on the basis of its ^{1}H-NMR spectrum. The cyclohexadienyl cation formed by attack by nitronium ion **ipso** to the methyl group can lead to three possible regioisomeric adducts 159A, 159B, and 159C in scheme 2.17).



159A 159B 159C

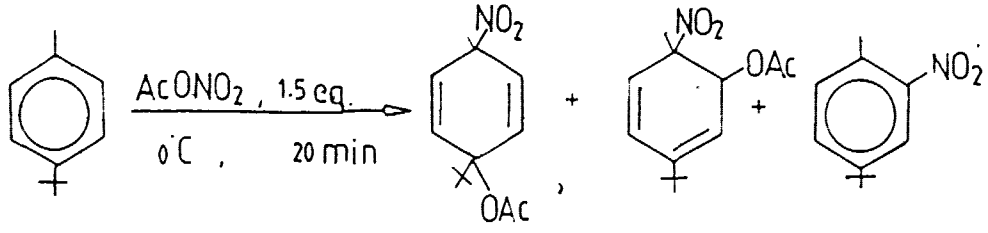
Scheme 2.17

Structures 159A and 159B have adjacent vinylic protons and their ^{1}H-NMR spectrum would exhibit a 10 Hz coupling which is not present in the spectrum of 159. Thus 159 has the structure 159C. The 6.5 Hz coupling between protons at δ 5.32 and 5.58 ppm indicates that these are protons 2 and 1 with the 5.32 ppm assignment being confirmed as 2-H by the 1.5 Hz, 2,4-coupling. The

1-H signal is at the 5.6 ppm position, characteristic of the environmentally identical (to the β-positions) 1-protons in dienes 100, 101, 102, 103, 130, 146, and 154. The 4-H is shifted more downfield, as compared with the 4-H proton of 102, by the vinylic nitro substituent.

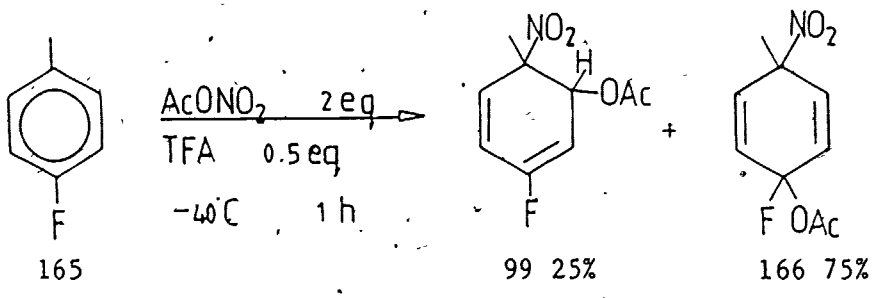
2.2.3 Reactivity of the Aromatics Nitrated:

Nitration of 4-t-butyltoluene (163), 4-fluorotoluene (168) and 4-cyclopropyl-2-nitroanisole (167) are other recent reactions in addition to those described in table 2.1 which led to the formation of 1,2-adducts. These are shown in schemes 2.18, 2.19 and 2.20.



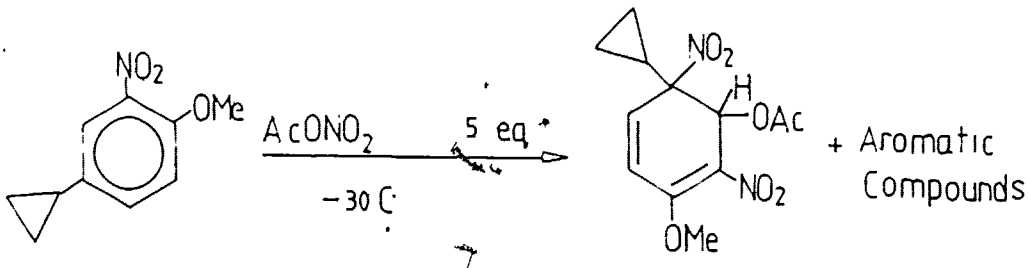
163 — 83 + 104 (59%) — 164 (41%)

Scheme 2.18 Ref 84



165 99 25% 166 75%

Scheme 2.19 Ref 92



167 105 71%

Scheme 2.20 Ref 93

The conditions described for nitration reflect the relative reactivity of the aromatic compounds. A longer reaction time, a higher mole-proportion of nitrating agent, a higher temperature and the presence of trifluoroacetic anhydride are required for deactivated substrates. Based on these features, the substrates belonging to the 4-X-toluene series can be arranged in the order of decreasing reactivity as:

OMe > (tBu, F) > Cl > Br > NHAc.

The lower reactivity of the acetamido compound is unexpected as it is known to be a stronger activating group than alkyl and halogen substituents. The apparent anomaly could however be a consequence of the lower solubility of the substrate in the reaction mixture. Since solid acetanilide was added to the

nitrating agent, the reaction medium was heterogenous at the early stages and the effective concentration of the aromatic in solution was not equal to the amount added.

In the substituted 4-methylanisole series the methoxy group has the strongest activating effect and this should predominate over the effect of the other substituents. However depending on the position of the third substituent the reactivity of the aromatic is affected differently. In 3-chloro-4-methylanisole (117) the directing effect of the chlorine reinforces the effect of the methoxyl group and although it destablizes the Wheland intermediates from attack of nitronium ion at C2, C4 and C6, the destabilization is less than that caused by meta-chlorine. In contrast, the positions C4 and C6, in 2-chloro-4-methylanisole (115), activated by methoxyl group are meta to the chlorine atom and the activation of the methoxyl is offset to a greater extent by the deactivation by the chlorine. This necessitates higher temperatures and longer reaction time in the case of anisole 115 than in the case of 117. In 4-methyl--3-nitroanisole (118), the nitro group destabilizes the transition state leading to the Wheland intermediate formed by attack at positions ortho and para to the methoxyl group (also ortho or para to the nitro group). These positions are however meta to the nitro group in 4-methyl-2-nitroansole (116) and while their reactivities are reduced they are reduced less than in the case of the ortho or para nitro group. The nitration of compound 118 thus required two mole proportions of trifluoroacetic anhydride, whereas 116 could be nitrated in the absence of trifluoroacetic anhydride. The role of trifluoroacetic anhydride in enhancing the reactivity of the nitrating agent can be explained by the following equilibria:

$$Ac_2O + HNO_3 \rightleftharpoons AcO.NO_2 + AcOH$$

$$AcONO_2 + H^+ \rightleftharpoons AcONO_2.H^+ \rightleftharpoons AcOH + NO_2^+$$

$$AcOH + (CF_3CO)_2O \rightleftharpoons CF_3COOAc + CF_3CO_2H$$

Scheme 2.21

The acetic acid is replaced by the considerably stronger acid and weaker nucleophile, trifluoroacetic acid. If the active electrophile is nitronium ion formed at its equilibrium concentration then the recombination of the nitronium ion with trifluoroacetic acid is less favoured and the effective concentration of nitronium ion is increased by the addition of trifluoroacetic anhydride. If protonated acetyl nitrate is the effective electrophile or if the nitronium ion is formed within the encounter pair of protonated acetyl nitrate and substrate then the increased acidity of trifluoroacetic acid will increase the concentration of protonated acetyl nitrate. Either effect would cause an increase in the reaction rate.

2.2.4 Positional Selectivity (Proportion of Ipso adducts)

The amount of each positional isomer obtained in electrophilic aromatic substitution depends among other factors on the reactivity of each position on the ring. The concept of partial rate factors has been developed to compare the reactivity of each position in an aromatic substrate[62]. The partial rate factor for a given group and a given reaction can be defined as the rate of substitution at a single position in the substituted benzene

relative to that at a single position in benzene. Very few partial rate factors are known for **ipso** attack. They have however been estimated for nitration of toluene in acetic anhydride[63] and the relative partial rate factors have been given in the introduction. Partial rate factors for the nitration of the halobenzenes, anisole and acetanilide are given in table 2.8. Values for i_f are not known but are probably of similar order to m_f and are thus close to zero.

Ph-X	o_f	m_f	p_f	Ref
F	0.04	0	0.77	100
Cl	0.029	0.0009	0.137	101
Br	0.033	0.0011	0.112	101
OMe	35.5	-	29	102
NHAc	36.0	-	28	103

Table 2.8: Partial rate factors of monosubstituted benzene derivatives PhX.

Attempts have been made to predict product distributions for nitration of substituted benzenes by using the principle of additivity.[2] This principle assumes that two or more substituents on a ring would each modify the reactivity of a particular position of a benzene ring by the same amount as in the corresponding monosubstituted compound, resulting in an additive influence. In such a case the calculated partial rate factor for a particular position would therefore be given by the product of the appropriate partial rate factors for the corresponding positions in the monosubstituted compounds. This principle does not allow for any

interaction between the substituents and ignores steric effects. For the 4-X-toluenes the amount of **ipso**-products observed and those predicted by the principle of additivity are given in table 2.9.

X	Calculated	Observed
F	95.5%	100%
Cl	72%	70%
Br	78%	64%
OMe	28%	30%
NHAc	30%	35%

Table 2.9: Percentage Ipso Product from Nitration of 4MePhX

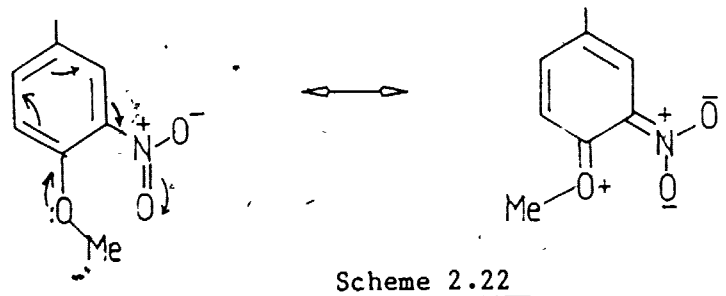
From table 2.9 it can be seen that there is surprisingly good agreement in the prediction of the extent of **ipso** attack in these compounds. These values are significantly larger than those observed by Schofield and his coworkers[104] in the nitration reactions carried out with mixed acid, and, as pointed out by him, this could be due to incomplete capture of the W_i^{Me} by water in presence of sulphuric acid. This would lead to aromatization after rearrangement to isomeric cations.

In the 2-X-4-methylanisoles 114, 115 and 116 the effect of X on position C-4 and C-6 should be equal since both these are meta to it. Thus the product distribution (1/2 o:i) obtained in 4-methylanisole (112) should be carried over to 115, 114 and 116 and the ratio of **ipso** methyl adduct to the 6-nitro product should

be (30:35=) 1:1.16. The values obtained are 2:1 for X=Cl, 1.3:1 for X=Br and 7.3:1 for $X=NO_2$ and indicate that more **ipso** methyl attack occurs than is predicted. These values (X=Cl) are in close agreement with those observed by Schofield and his coworkers in the nitration with sulfuric acid[106]. This could be due to the following reasons:

a) The presence of the group X adjacent to methoxyl group on C-1 results in a strong buttressing effect at ring site C-6. In the series NO_2, Cl and Br the mutual electronic repulsions with the methoxy lone pair would be a maximum for NO_2 and a minimum for Br which would lead to minimum attack at C-6 for the former, as observed.

b) There is a specific mutual interaction between the nitro and methoxy group as shown in scheme 2.22



Scheme 2.22

This would lead to breakdown of the additive influence of substituents in controlling the product ratio.

c) Also related to the question of the extent of **ipso** attack observed is the effectiveness of the acetate ion as a trapping agent for the **ipso** cation and the possibility of reversal of the **ipso** adducts to the W_i^{Me} in the nitration reaction mixture. The W_i^{Me} could then collapse to aromatic compounds via the encounter pair or via nitro shifts. Other reactions could also occur prior to isolation or measurement of the **ipso** product(s).

The last factor suggests that the amount of **ipso** adducts detected could be less than the amount of W_i^{Me} actually formed. Since more rather than less **ipso** attack is observed than is predicted, the effects mentioned in a) and b) seem to be the dominant factors leading to lower reactivity at C-6.

In the nitration of 3-chloro-4-methylanisole (117) no cyclohexadienyl acetate was obtained. Instead the W_i^{Me} formed the dienone 140. Nucleophilic attack by acetate anion at either C-3 or C-5 to give the cyclohexadienyl acetate would lead to steric crowding on vicinal carbons, hence is disfavoured in contrast to

attack at C-1 which leads to the dienone 140. In the dienone the chlorine atom is not planar with either of the substituents on C-4 (i.e. Me or NO_2), The Cl activates the para position (C-6 in the anisole 117) more than the ortho positions (C-4 and C-2), thus the predicted ratio of nitro products (C-6:C-4:C-2 = 5.5:1:1.1) parallels the observed ratio (C-6:C-4:C-2 = 2.2:1:1.1).

In case of 4-methyl-3-nitroanisole (118) there was some nucleophilic trapping of W_1^{ie}, possibly due to the greater reactivity of the cation. The positive charge in the W_1^{Me} is in part delocalized on to C-3 which bears the nitro group making the cation less stable and more reactive than the cation from 4-methylanisole (112). The resulting diene was unstable, as would be expected from the steric crowding around the sp^3 atoms and decomposed during work up. From the ^{1}H-NMR spectrum of the reaction mixture the extent of **ipso** attack was less than 10% of the total nitration reaction. After work up equimolar proportions of both aromatic compounds 157 and 158 were obtained. In the nitration of nitrobenzene a high ortho-para ratio (~3:1) is obtained. Thus a greater proportion of attack at C-2 (in anisole 118) than C-6 is expected. However the 2,3-dinitro compound 157 is also expected to suffer considerable steric strain. These two effects act in opposite directions. The net result is that a greater proportion of 2-nitro compound is obtained from nitroanisole 118 than from chloroanisole 117.

2.2.5 Regioselectivity in nucleophilic trapping

In the W_1^{Me} intermediates, delocalization of the positive

charge on the ring carbons (ortho and para with respect to the methyl group) allows it to behave as a polydentate electrophile towards the acetate anion. In the 4-X-toluene series, attack at C-2 and C-6 leads to the same conjugated 1,3-diene, whereas attack at C-4 would yield a 1,4 diene. The latter diene bearing an oxygen substituent and a leaving group on the same carbon is expected to be unstable and to decompose to the dienone. Such a process has been used to explain the formation of 2-nitro-p-cresol (168) during the nitration of 4-bromotoluene (110) and 4-methoxytoluene (112) by Wright and his coworkers[105].

It is conceivable that one (1,3 or 1,4) diene is the product of thermodynamic control whereas the other is the product of kinetic control. Table 2.10 shows that the ratio of 1,3- and 1,4-dienes obtained at -40°C from toluene and 4-X-toluenes:

There appears to be some discrepancy in the experimental results reported by Wright et al.[105] The ^{1}H-NMR spectrum of 4-methyl-4-nitrocyclohexa-2,5-dienone (56) as reported by them differs markedly from that given in the literature[69]. When the reactions were repeated by later workers[92] using Wright's conditions, no dienone was observed in the ^{1}H-NMR spectrum of the reaction mixture. Pure samples of the dienone 56 have been characterized unambiguously by various workers and its formation at higher temperatures from 4-methylanisole (112) is now well established.

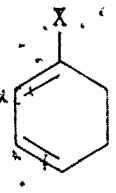
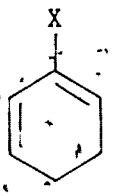
X =	H[a]	Me[b]	NHAc	OMe	F[c]	Cl	Br
1,3/1,4	0/1	0/1	1/0	1/0	1/3	1/0	1/0

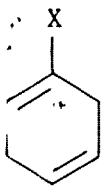
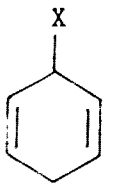
a: Ref 79; b: Ref 82; c: Ref 92

Table 2.10: Ratio of 1,3 and 1,4-dienes obtained in the nitration of toluene and 4-X-toluenes

In the formation of 1,4-dienes from the W_i^{Me} there is a smaller change in bond orders (1 1/3) than in the formation of 1,3-dienes (2). On the basis of principle of least motion[107,65] the former process has been argued to be the faster. These arguments however fail to explain the preferred formation of the conjugated dienes in the cases studied in this thesis.

Conjugated cyclohexa-1,3-diene is more stable than the isomeric non-conjugated 1,4-diene. Ab initio molecular orbital calculations show that the difference between the two is only 1.4 kJ/mol[108]. For substituted cyclohexadienes the difference in energy varies with the nature and position of the substituent as shown in table 2.11.

X	169A	169B	169C	169D	169E
F	0	6.1	31.2	5.1	37.8
OH	0	8.6	36.5	7.5	41.1
H	0	0	0	1.4	1.4
NO_2	0	4.5	3.2	3.4	6.2
CN	0	3.5	31.0	4.1	33.4
CH_3	0	2.4	16.6	3.4	18.0

Table 2.11 Relative Energies (kJ/mole) for Lowest Energy Conformations of Substituted 1,3 and 1,4-Cyclohexadienes.

The two possible isomers from nucleophilic trapping by acetate anion of W_1^{Me} are 169B and 169E. The energy difference between these is small when X=NO_2 or H, but is large for other substituents. The observed trend seems to indicate that isomer 169B, the conjugated diene, should be favoured under thermodynamic conditions. The presence of other functional groups on the ring will alter the energy difference and the conclusions should be considered with caution. However in the cases which have been examined (X=F, OH, OMe (=OH?), H, CH_3) only in that of X=OMe is formation of the conjugated diene favoured over formation of the nonconjugated 1,4-diene. This suggests that the addition of acetyl

nitrate is subject to kinetic rather than thermodynamic control and there is experimental evidence to this effect. The nitration of 4-ethyltoluene yields a pair of diastereomeric adducts (Z)-81 and (E)-81. It has been shown that a single diastereomer equilibrates to its epimer on prolonged exposure (18h) to acetic anhydride at ambient temperature but remains unchanged when stirred in the nitrating mixtures under conditions at which nitration was carried out[109]. Nitration of 2-methylphenoxy-isobutyric acid (170) gave a pair of diastereomeric dienes (Z)-66 and (E)-66 in the ratio 5.5:1. When diene (Z)-66 was reacted with 10% trifluoroacetic acid in chloroform, an equilibrium mixture containing (Z)-66 and (E)-66 in 1:4 ratio was recovered[76]. Both these experiments suggest under the nitration reaction conditions equilibration of diastereomers is negligible.

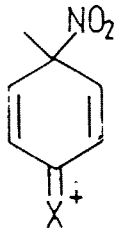
It should be noted here that the dienone formation step is irreversible and will change the conjugated to unconjugated diene ratio by selectively removing the unconjugated diene from the system. Consequently it would be erroneous to measure that ratio in the presence of any dienone. Neither should its formation be taken as an indication of greater thermodynamic stability of 1,4-dienes.

In accordance with the Hard-Soft Acid Base principle[110] the acetate anion (a relatively hard nucleophile) will attack the position of highest electron deficiency in the cyclohexadienyl cation. The substrates studied bear substituents which donate electrons via orbital overlap and withdraw electrons via the inductive effect. These two effects will contribute in opposite directions towards the product distribution.

In the series N, O and F and Br, Cl, and F, the most electronegative element is F. Consequently there is greater

positive charge at C-4 in the cyclohexadienyl cation (with respect to 4-X-toluene) when X=F and an increase in reactivity of C-4 is expected. This explains the fact that the 1,4-diene is formed in 4-fluorotoluene.

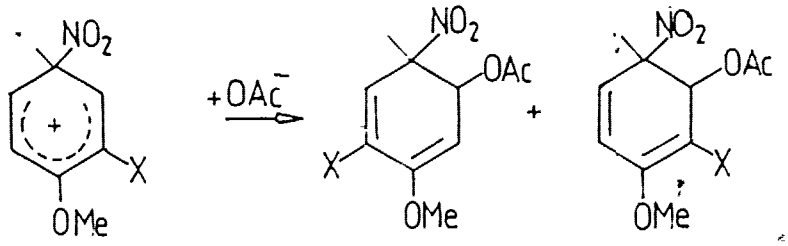
As to why no 1,4-diene is formed at all for other substituents it could be argued that in the quinonoid form 170 (figure 2.6), the largest orbital coefficients are on the terminal carbon, i.e. C-2. This would make the reaction at C-2 a more favoured process over reaction at C-4.



170

Figure 2.6: Quinonoid Form of Ipso Wheland Intermediate.

Two possible regioisomers exist for the 1,3-dienes obtained from 2-X-4-methylanisoles 114, 115, and 116 as shown in scheme 2.23.

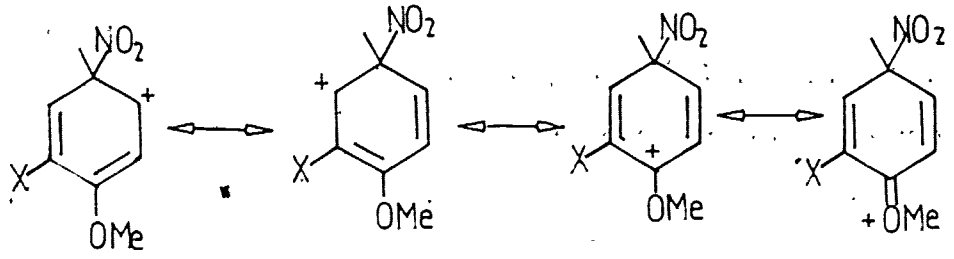


171 171A 171B

Scheme 2.23

The regioisomer 171B is sterically crowded but is still the major product when X=NO_2. Generally the major resonance contributor to

W_i^{Me} (171) is the quinonoid form 172D[111] shown in scheme 2.24.



172A 172B 172C 172D

Scheme 2.24

The reactivity of the two double bonds in such a structure is different. In the presence of π-acceptors such as the nitro group the C-3 will be electron deficient and will be susceptible to nucleophilic attack at a faster rate than C-5. This agrees with the lowering of the energy of the lowest unoccupied molecular orbital of olefins brought about by π-acceptors ($Z=NO_2$). (Fig 2.7). In contrast, for an olefin containing a π-donor the LUMO of this double bond has a higher energy and is less reactive than the unsubstituted double bond. Consequently no isomer (171B) is obtained.

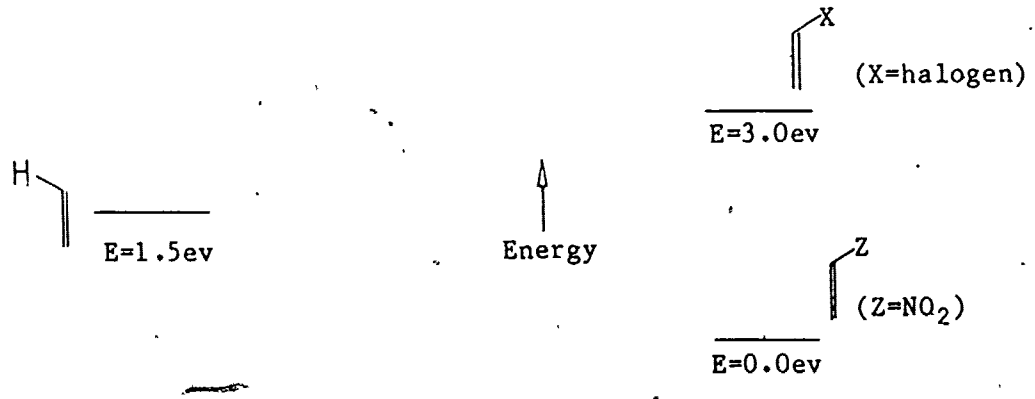


Figure 2.7: Energies of LUMO of substituted olefins. Ref 112.

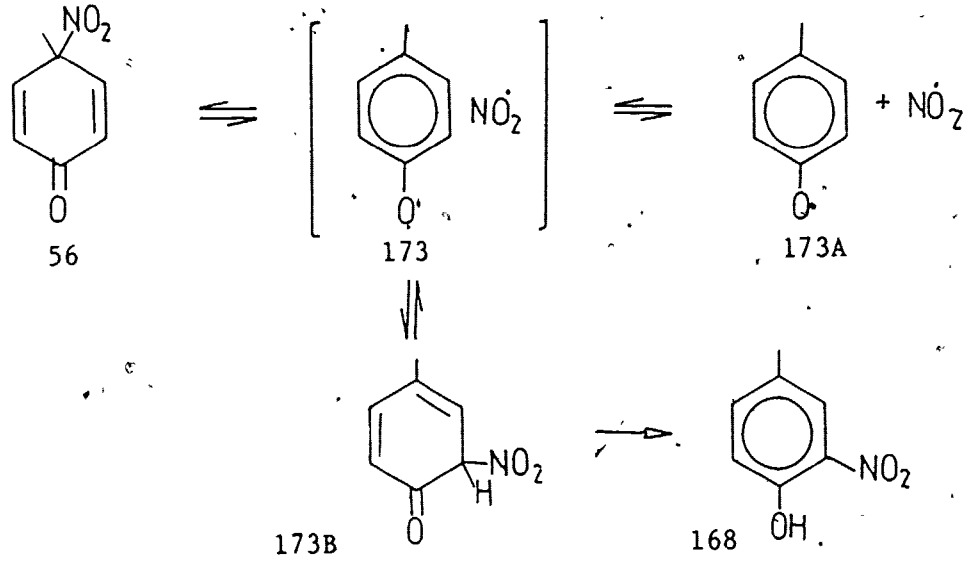
CHAPTER III: THERMAL REACTIONS OF IPSO ADDUCTS.

3.1 Introduction:

The isolation of non aromatic compounds from nitration reactions can be traced back to the last century. Auwers reported the isolation of 2,4-dinitro-3,4,6-trimethylcyclohexa-2,5-dienone (64) in 1896[73]. Nitro-dienones are major examples of such compounds but the systematic search and synthesis of **ipso**-nitro derivatives is relatively recent. The major reason that made it difficult for the early workers to isolate **ipso** adducts is their thermal instability. Even now **ipso** adducts are at times detected in reaction mixtures but elude isolation. Several interesting modes of reactivity have emerged during the study of the thermal reactions of **ipso**-nitro compounds. The major outcome of thermolysis is aromatization but depending on the substrate, solvent and other conditions different mechanisms may be involved. In some instances intermediate dienes have been isolated.

The cyclohexa-2,5-dienones obtained by **ipso**-nitration of suitably substituted anisoles, phenols or phenyl acetates can undergo a 1,3-nitro shift by a radical dissociation and recombination process. This is important in neutral or weakly acidic solvents such as hexane and acetic acid. Crossover studies using labelled dienones[113] have shown that in hexane about one third of the reaction occurs within the solvent cage and the remainder occurs between reactants which have diffused from the solvent cage. The extent of the cage reaction increases with an increase in solvent viscosity without affecting the reaction rate. Added radical scavengers also do not alter the reaction rate but do

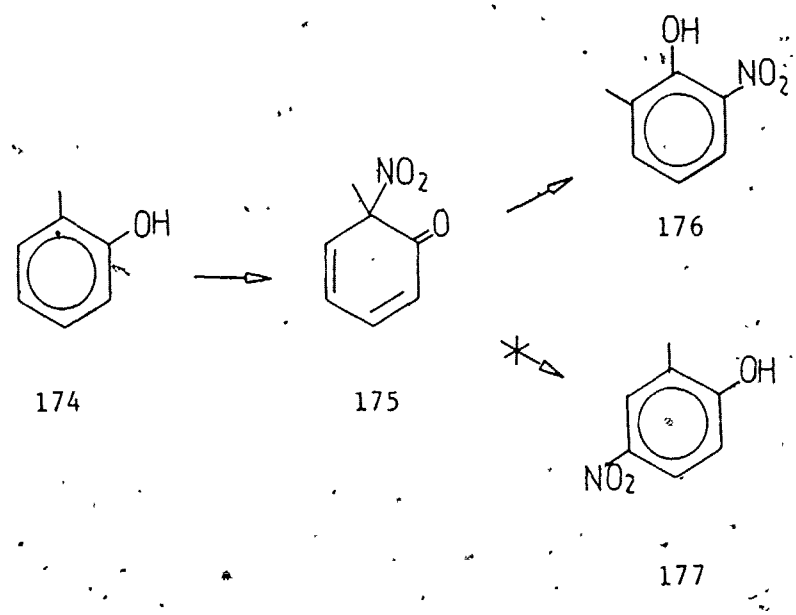
reduce the yield of nitrophenol products 168 and increase that of the alkyl phenol products. A radical dissociation-recombination mechanism as shown in scheme 3.1 with a rate determining dissociation step can account for all of these observations.



Scheme 3.1

However it is not possible to distinguish a radical dissociation recombination reaction occuring within a solvent cage from a true intramolecular 1,3-nitro shift.

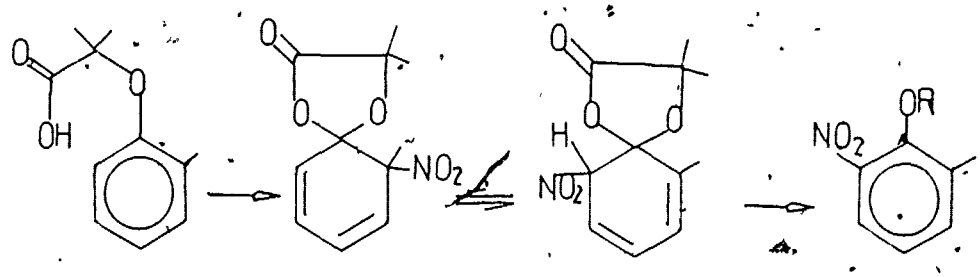
The radical mechanism invoked for the 1,3-nitro shift fails to explain the high regioselectivity of the nitro shifts observed in some instances. The intermediate 6-methyl-6--nitrocyclohexa-2,4-dienone (175) obtained by the **ipso** nitration of o-cresol (174) decomposes selectively to 6-nitro-o-cresol (176)[114]. A radical process in this case would be expected to lead to the formation of some 4-nitro-o-cresol (177) (Scheme 3.2).



174 175 176 177

Scheme 3.2

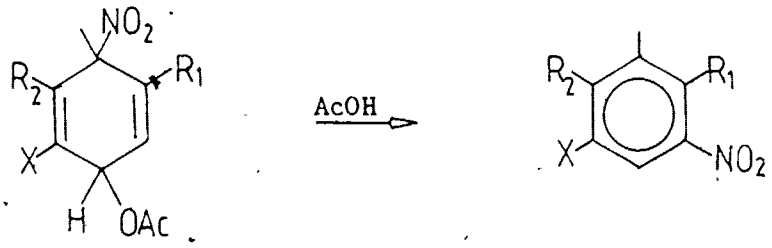
A concerted regiospecific 1,5-sigmatropic shift of nitro group has been recognized recently[115]. The spirodienone 66 which is a protected analog of dienone 175 was prepared by Bapat[76] by nitrating 2-methylphenoxyisobutyric acid (178). The dienone 66 underwent a 1,5-sigmatropic shift of the nitro group to yield an unstable diene 179, which aromatized under weakly basic conditions to yield the 6-nitro compound 180. The overall route to compound 180 can then be represented as in scheme 3.3



178 66 179 180

Scheme 3.3

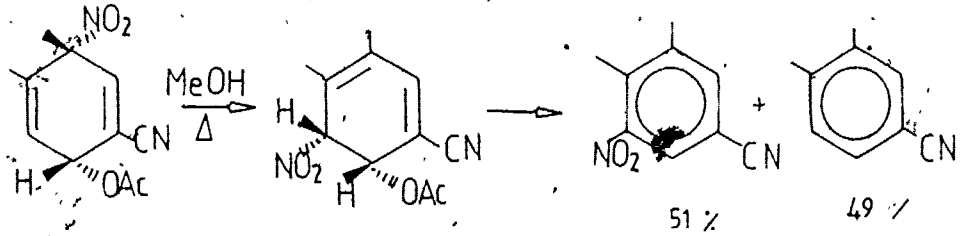
Other dienes have also been found to exhibit a regioselective mode of aromatization. The dienes 88, 89 and 93 exhibited a 1,3-nitro shift during aromatization in weakly acidic or neutral media (scheme 3.4).



	R_1	R_2	X	Ref
89	Me	H	CN	116
88	H	Me	CN	117
93	Me	H	NO_2	115

Scheme 3.4

In one instance this regioselective 1,3-nitro shift was shown to be a sigmatropic process[76]. The diene 89 from 3,4-dimethylbenzonitrile (185) isomerized to diene 184 prior to aromatization as depicted in scheme 3.5.



Z 89 184 181 185

Scheme 3.5 Ref 76

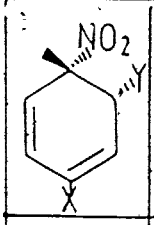
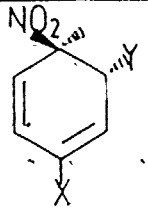
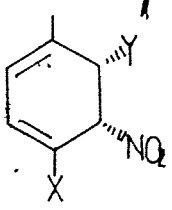
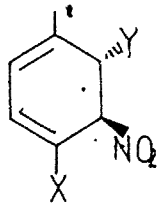
Much of the aforementioned work on sigmatropic shifts in nitrodienes was carried out in conjunction with the related work described in this dissertation. In the present chapter the results of the thermal reactions of **ipso**-nitrocyclohexadienyl derivatives are described.

3.2 Results and Discussion

3.2.1: Formation and Characterization of Isomerized Dienes.

A summarized description of the reactions leading to the mixture from which the dienes were isolated and characterized is given in table 3.1 and the ^{1}H-NMR and ^{13}C-NMR spectral data of these dienes are given in tables 3.2 and 3.3 respectively.

Table 3.1 Summary of large scale thermal isomerizations

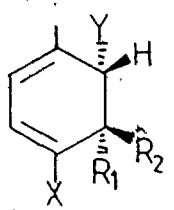
	Solvent Temp Time.				Other Products
X=Cl	C_6H_6	189	187	188	186
Y=OAc	76°C	(5%)	(35%)	(35%)	(11%)
100	2h				
X=Br	C_6H_6	192	190	191	193
Y=OAc	74°C	(4%)	(35%)	(35%)	(trace)
101	1h				
X=OMe	C_6H_6	196	194	195	197
Y=OAc	78°C	(5%)	(21.5%)	(21.5%)	(15%)
102	4h				
X=NHAc	$CDCl_3$	-	198	-	125 (22%)
Y=OAc	35°C	-	(23%)	-	113 (11%)
103	30min				
X=Cl	$CDCl_3$	-	-	208	111 &
Y=Cl	75°C	-	-	(52%)	209 (39%)
201	2h				
X=Cl	$CDCl_3$	-	-	210	-
Y=OMe	50°C	-	-	(61%)	
202	4h				
X=Cl	$CDCl_3$	-	212	-	214
Y=OH	amb	-	(45 %)		(trace)
204	21h				
X=Br	$CDCl_3$	-	-	206	110 & 207
Y=Cl	75°C	-	-	(50%)	(50%)
200	2h				
X=Br	$CDCl_3$	-	-	211	-
Y=OMe	amb	-	-	(44%)	
203	18h				
X=Br	$CDCl_3$	-	214	-	215
Y=OH	amb	-	(53.5%)		(trace)
205	18h				

[2] The reaction was carried out in the presence of 0.33 mol proportion of cresol 215.

#	Chemical Shifts (ppm)							Coupling Constants (Hz)					
	CH_3	Y	X	1-H	3-H	4-H	6-H	1,6	1,3	1,Me	3,4	3,Me	4,6
Z-187	1.84	2.19	-	5.91	5.85	6.46	5.26	8.74	2.46	1.50	6.22	1.86	-
E-188	1.85	2.15	-	5.96	5.94	6.44	5.15	3.31	-	-	6.43	1.45	-
Z-190	1.82	2.17	-	5.91	5.79	6.69	5.35	8.70	2.65	1.00	6.25	1.63	-
E-191	1.83	2.15	-	5.93	5.86	6.66	5.24	3.47	-	-	6.32	1.04	-
Z-194	1.78	2.17	3.64	5.83	5.87	5.36	5.14	8.50	?	?	6.80	1.70	-
E-195	1.79	2.12	3.67	5.94	5.89	5.29	5.09	4.32	-	-	6.57	1.05	-
Z-198	1.86	2.09	2.12	5.91	6.13	6.49	5.51	2.05	-	-	6.73	1.57	1.04
E-208	1.95	-	-	4.96	5.91	6.40	5.14	1.84	-	-	6.30	1.47	-
E-211	1.90	3.43	-	4.23	5.87	6.48	5.19	2.50	-	-	6.00	1.75	-
Z-212	1.87	2.80	-	4.84	5.61	6.31	4.95	7.40	2.50	1.30	6.20	1.64	-
E-206	1.96	-	-	4.96	5.88	6.81	5.28	1.79	-	-	6.38	1.20	-
E-210	1.90	3.48	-	4.16	5.75	6.58	5.24	2.40	-	-	6.20	1.50	-
Z-214	1.91	3.00	-	4.90	5.68	6.60	5.10	7.40	2.58	1.50	6.10	1.50	-

Table 3.2: ^{1}H-NMR data for 1-Y-5-X-2-methyl-6-nitrocyclohexa-2,4-dienes.

Table 3.3: ^{13}C-NMR data for 1-Y-5-X-2-methyl-6-nitrocyclohexa-2,4-dienes.



						Chemical Shifts (ppm)									
X	Y	R_1	R_2	St	#	CH_3	X	Y	C1	C2	C3	C4	C5	C6	C=O
Cl	OAc	NO_2	H	Z	187	17.8	-	20.5	71.0	134.8	119.0	129.9	122.1	86.5	169.8
Cl	OAc	H	NO_2	E	188	19.9	-	20.7	70.7	134.9	122.8	127.9	120.7	88.8	169.8
Br	OAc	NO_2	H	Z	190	18.0	-	20.5	70.9	135.1	119.5	134.1	109.5	87.5	169.8
Br	OAc	H	NO_2	E	191	19.9	-	20.7	70.8	132.5	122.4	132.2	109.1	90.1	169.8
OMe	OAc	NO_2	H	Z	194	16.4	54.6	20.6	70.2	125.6	117.8	99.1	148.3	83.4	169.1
OMe	OAc	H	NO_2	E	195	19.3	55.7	20.5	72.0	124.8	122.1	97.9	147.9	87.1	169.9
Cl	Cl	H	NO_2	E	208	19.9	-	-	56.3	133.9	121.5	128.4	120.8	89.1	-
Br	Cl	H	NO_2	E	206	20.1	-	-	56.7	127.3	122.2	132.7	109.1	91.1	-
Br	OMe	H	NO_2	E	210	19.2	-	55.7	79.9	137.7	131.9	120.3	112.6	89.8	-

On heating a solution of diene 100 in benzene at 76°C for 2h a mixture of three new dienes (75%), 5-chloro-o-cresyl acetate (186) (11 %), and unreacted diene 100 (14 %) was formed. Pure samples of (Z)-5-chloro-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate (187) and its E-diastereomer 188 were obtained by fractional crystallization of the mixture from ether-pentane solution at -20°C. After removal of the major portion of these dienes, the third diene 189 was enriched to ~10% of the remaining mixture. During recrystallization some 4-chloro-3-nitrotoluene (122) was formed. The dienes 187 and 188 were extremely labile in the presence of nucleophiles and they eliminated acetic acid to yield 122. In order to reduce the number of components in the mixture (from six to four) prior to column chromatography the remaining amounts of dienes 187 and 188 were converted to 122 by treatment with ammonium hydroxide. The mixture thus contained 30% diene 100, 27% cresyl acetate 186, 35% toluene 122 and 8% diene 189. Chromatographic separation of this mixture on a silica gel column at -40°C gave diene 189, enriched to 95% in the 10% ether-petroleum ether fractions. This diene could not be crystallized and it readily isomerized to diene 188, thus it was characterized in solution as (E)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate.

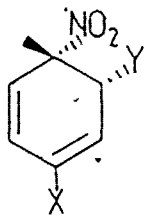
When a solution of diene 101 in benzene was heated at 74°C, for 1h a mixture of three new isomeric dienes (190-192, 74%) unreacted diene 101, (26%) and traces of 5-bromo-o-cresyl acetate (193) and 4-bromo-3-nitrotoluene (124) were obtained. The compounds (Z)-5-bromo-2-methyl-6-nitro-cyclohexa-2,4-dienyl acetate (190), and its E-diastereomer (191) were isolated as crystalline solids and the minor compound (E)-3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl

acetate (192) was obtained as an oil (95%) using the same procedure as described beforehand for the chloro analog 189.

After 4h at 78°C a solution of diene 102 yielded a mixture containing 48% of the three isomerized dienes 194-196, 15% 5-methoxy-o-cresyl acetate (197) and 37% of unreacted diene 102. Attempts to separate the mixture by fractional crystallization failed and only a single crop of crystals of the starting diene 102 was obtained. The remaining mixture was separated by chromatography on a silica column at -40°C. None of the dienes 194-196 could be crystallized from the enriched solutions and they were characterized in the mixtures as (Z)-5-methoxy-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate (194), its (E)-diastereomer 195 and (E)-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (196). The acetate 197 was obtained pure from an early column fraction.

On heating a solution of diene 103 (from the nitration of 4-methylacetanilide (113)) in chloroform-d at 35°C for 30 min a mixture containing 11% of 113, 22% of 4-methyl-2-nitroacetanilide (125), 23% of (Z)-5-acetamido-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate (198) and 44% unreacted diene 103 was obtained. When the temperature of the reaction was raised to 60°C the aromatization reaction became faster, and the ^{1}H-NMR spectrum of the reaction mixture indicated the composition as 52% of 113, 35% of 125 and 12% 2,6-dinitro-4-methylacetanilide (199).

Apart from the dienes obtained from direct nitration reactions, several other (Z)-3-X-6-methyl-6-nitrocyclohexa-2,4-dienyl derivatives were prepared from the chloro and bromo-dienes 100 and 101 during the study of acid catalyzed and nucleophilic reactions. These dienes also underwent isomerization



X	Y	
Br	Cl	200
Cl	Cl	201
Cl	OMe	202
Br	OMe	203
Cl	OH	204
Br	OH	205

Scheme 3.6

reactions similar to that described above. The structures of these dienes are given in scheme 3.6.

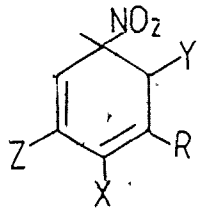
Heating a solution of diene (200) in benzene-d_6 for 2h at 75°C gave a mixture containg 50% (E)-5-bromo-2-methyl-6-nitrocyclohexa-2,4-dienyl chloride (206) and 50% of a mixture of 4-bromotoluene (110) and 4-bromo-2-chlorotoluene (207). Apart from these compounds there were some other non-aromatic compounds present in minor quantities (~5%). Attempts to crystallize out diene 206 failed and filtration of the reaction mixture through silica gel at -40°C led to decomposition of a major portion of this diene. Similarly diene 201 gave (E)-5-chloro-2-methyl-6-nitrocyclohexa-2,4-dienyl chloride (208, 52%) together with 2,4-dichlorotoluene (209), 4-chlorotoluene (111) and unreacted diene 201 (9%).

When diene 202 was heated in chloroform-d (E)-5-chloro-2-methyl-6-nitrocyclohexa-2,4-dienyl methyl ether (210) was obtained in a mixture with aromatic compounds and small amounts of unidentified dienes. Similarly diene 203 gave (E)-5-bromo-2-methyl-6-nitrocyclohexa-2,4-dienyl methyl ether (211). Attempts to purify dienes 208, 210, and 211 were unsuccessful.

The compound 204 after 21h at ambient temperature gave a mixture of (Z)-5-chloro-2-methyl-6-nitrocyclohexa-2,4-dienol (212, 45%), unreacted dienol 204 (55%) and traces of 5-chloro-o-cresol (213). The bromo analog 205 after 19h at ambient temperature gave (Z)-5-bromo-2-methyl-6-nitrocyclohexa-2,4-dienol 214 (53.5%) and unreacted dienol 205 (46.5%) together with the original 5-bromo-o-cresol (215). It should be noted here that trace amounts of other dienes were formed in the isomerization of dienes 200-203, but were absent in the reactions of dienes 204 and 205.

3.2.2 Structure and Stereochemistry of 3-X-6-methyl-6-nitrocyclohexa-2,4-dienes

The ^{1}H-NMR and ^{13}C-NMR spectra of dienes 189, 192 and 196 resembled closely those of the starting dienes 100, 101 and 102 respectively. In the ^{1}H-NMR spectra the two vinylic protons had a large coupling constant (J_{45} = 10Hz) and the methyl group appeared as a singlet. In the ^{13}C-NMR spectra the chemical shift of the two sp^3 ring carbons and their splitting pattern in the gated spectra indicated the presence of $CMeNO_2$ (δ_C = 87ppm, singlet) and CHOAc (δ_C = 70ppm, doublet). The dienes were thus assigned as epimers of the starting dienes. Since the crystal structure of diene 101 confirmed that it had the (Z) configuration, the diene 192 was assigned the (E) configuration. The differences in the NMR spectral properties of these two epimers are also present between the epimers of the other dienes and these differences are highlighted in table 3.4.



#	Z	X	Y	R	stereo chem	^{1}H Chemical shifts and coupling constants						δ_C
						Y $OCOCH_3$	1-H	2-H	5-H	1,5	J_{12}	CH_3
100	H	Cl	OAc	H	Z	1.99	5.53	6.12	6.55	1.65	6.13	23.2
189	H	Cl	OAc	H	E	2.08	6.26	5.92	6.07	0.00	3.99	20.7
101	H	Br	OAc	H	Z	1.98	5.48	6.37	6.45	1.76	6.15	23.1
192	H	Br	OAc	H	E	2.13	6.23	5.94	6.23	0.00	3.00	18.2
102	H	OMe	OAc	H	Z	1.95	5.62	4.97	6.56	1.52	6.57	22.6
196	H	OMe	OAc	H	E	2.15	5.17	4.79	6.12	0.00	5.61	20.2
104	H	tBu	OAc	H	Z	1.95	5.53	5.74	6.38	1.2	5.60	24.0
104	H	tBu	OAc	H	E	2.10	6.37	5.48	5.94	0.00	2.90	18.0
151	H	OMe	OAc	NO_2	Z	1.97	6.57	–	7.09	2.06	–	22.8
152	H	OMe	OAc	NO_2	E	2.10	7.04	–	6.36	1.60	–	21.8
103	H	NHAc	OAc	NO_2	Z	1.95	5.62	6.49	6.59	1.53	6.59	23.3
154	NO_2	OMe	OAc	H	Z	1.99	5.64	5.27	6.99	2.02	7.29	22.5
201	H	Cl	Cl	H	Z	–	4.96	6.13	6.64	1.70	6.70	23.3
200	H	Br	Cl	H	Z	–	4.89	6.36	6.54	1.72	6.47	24.2
202	H	Cl	OMe	H	Z	–	4.07	6.16	6.48	1.55	5.67	23.2
203	H	Br	OMe	H	Z	–	3.96	6.38	6.36	1.70	5.15	22.3
204	H	Cl	OH	H	Z	–	4.45	6.07	6.35	0.00	6.00	22.1
205	H	Br	OH	H	Z	–	4.37	6.30	6.25	0.00	5.43	22.1

Table 3.4 Selective NMR data illustrating differences between E and Z diastereomers of 3-X-6-methyl-6-nitrocyclohexa-2,4-dienyl derivatives

The two possible conformers of each diastereomer are shown in fig. 3.1.

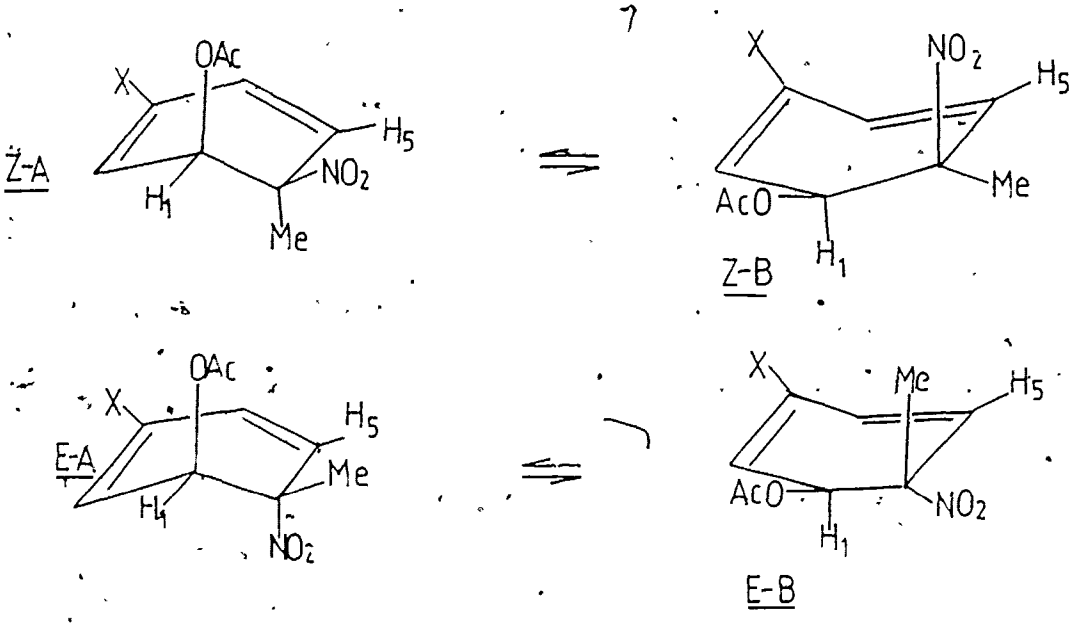
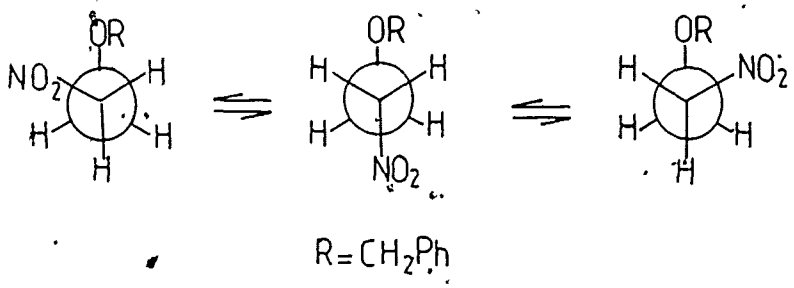


Figure 3.1: Conformers of each Diastereomer of 3-X-6-methyl-6-nitrocyclohexa-2,4-dienes

In the (Z)-diastereomers the conformer Z-A has fewer gauche interactions than Z-B and is therefore favoured. 1,3-Diaxial interactions are less important in cyclohexadienes as there are no axial protons.

In the (E)-diastereomer the conformer E-A has fewer gauche interactions than conformer E-B. However there are two offsetting factors which would of themselves favour conformer B. These are i) the preference of nitro and acetoxy groups to be gauche as in E-B (nitro and acetoxy are gauche in both Z-conformers). The preference of both nitro and alkoxy group to remain gauche have been observed in the conformational analysis of 1-benzyloxy-2-nitroethane (216) where the synclinal conformers (216-A and C, scheme 3.7) are predominant [118].



R=CH_2Ph

216A 216B 216C

Scheme 3.7

ii) Possible repulsion between the axial nitro group (in E-A) and the diene π-cloud (This factor would make Z-A preferred over Z-B).

Consequently; whereas Z-A is expected to be the dominant Z-conformer, E-B is expected to have a significant contribution to the population of (E)-conformers.

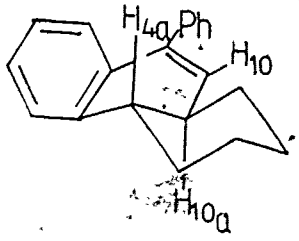
The (4-H and 5-H) and (1-H and 2-H) ring protons were assigned on the basis of long range couplings. In the (E)-epimers only one of the protons (1H or 2H) was coupled (J≈1.5Hz) with either 4-H or 5-H. This could be a 1,5 or 2,4 coupling. The angular orientation between 2-H and 4-H protons is the same in the two conformers of the two epimers and the consistent long range coupling is more likely between 2-H and 4-H protons and not between 1-H and 5-H protons. In Z-A the dihedral angle between the 5-H proton and the nitro group ($H-C_5-C_6-NO_2$) is close to zero whereas this angle is close to 90° in E-A; thus the 5-H proton is deshielded in the Z-A and shows an upfield shift in the E-A/E-B mixture relative to its position in Z-A.

In the (E)-diastereomers the 1-H is cis to the nitro group and in the (Z)-diastereomers these are trans. Therefore the 1-H lies closer to the deshielding zone of the nitro group in the

(E)-diastereomer. This effect is accentuated by flattening of the ring, thus 1-H is shifted downfield in the (E)-diastereomer relative to its position in Z-A.

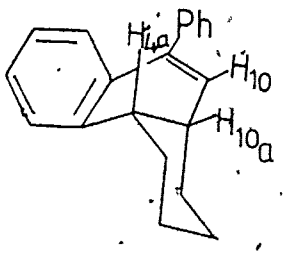
The coupling between 1-H and 5-H present only in the Z diastereomer, is due to a 4 bond through space coupling which is possible if these two protons are coplanar. In Z-A the 1-H proton is equatorial and lies near the plane of the C_1-C_6-C_5 framework whereas in E-B the 1-H is axial and is orthogonal to this plane. Thus $J_{1,5}$ coupling constant should be lower in the E-A/E-B mixture. No coupling is observed. However in diene 152 the presence of the nitro group on C-2 destabilizes the equatorial orientation of the acetate group, and the increased population of conformer E-A with equatorial 1-H is reflected in the $J_{1,5}$ (=1.6Hz) which larger than that observed for other (E)-diastereomers.

Katritzky and his coworkers[119] have shown that in the cis- and trans-9-phenyl-1,2,3,4,4a,10a-hexahydrophenanthrene (217C) and (217T) respectively (figure 3.2), the coupling constant between the ethylenic 10-H and vicinal axial 10a-H is 2.0Hz in the trans isomer. The corresponding $J_{10,10a}$ value for the pseudoequatorial proton in conformer C is 7.0Hz.



$J_{10,10a}$=2Hz

217T



$J_{10,10a}$=7Hz

217C

Figure 3.2: Cis & Trans-9-phenyl-1,2,3,4a,10a-hexahydrophenanthrene

The 1-H is axial in the conformer E-B (Figure 3.1). Consequently the vicinal coupling ($J_{1,2}$) in the cyclohexadienes is expected to be less in the (E)-diastereomers than in the (Z)-diastereomers, as observed.

In the (E)-diastereomers the methyl group (on C-6) is gauche to the acetate group in both conformers E-A and E-B, whereas in the (Z)-diastereomers these are anti to each other in the preferred conformer. The well known γ-gauche effect[120] predicts that the chemical shift of a carbon atom is shifted upfield when it is gauche to a hetero atom, as observed in the present case for the (E)-diastereomers.

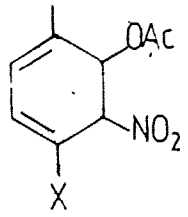
Based on the above observations it is possible to assign the diastereomers 100, 102 and 151 as the (Z)-diastereomers and the epimers 189, 196 and 152 as (E)-diastereomers. The values for the t-butyl derivatives 104Z and 104E have also been included in table 3.4 to extend the analogy. No epimer of diene 103 was obtained during the course of the thermal reactions but the ^{1}H-NMR spectrum of 103 agreed well with that of the other dienes obtained in the nitration reaction. Since all of these major dienes are formed by

cis addition of acetyl nitrate, diene 103 was also assigned to be the (Z)-diastereomer, the product of cis addition. The dienes 200-205, were also each obtained as single diastereomers following subsequent reactions of dienes 100 and 101 and their NMR characteristics as shown in table 3.4 also indicate that these are (Z)-diastereomers.

3.2.3 Structure and Stereochemistry of 5-X-2-methyl-6--nitrocyclohexa-2,4-dienes:

The elemental analysis of each of the pure dienes 187, 188, 190 and 191 gave an empirical formula identical to that of the respective starting diene. In the IR spectra of these dienes characteristic peaks due to nitro (1550 cm^{-1}) and acetoxy (1750 cm^{-1}) groups were present. The UV spectra ($\lambda_{max.}$ = 280nm, ε 200 $m^2 mol^{-1}$) indicated the presence of a conjugated diene chromophore. The ^{13}C spectra of all these dienes had peaks due to two sp^3 methine carbons (δ ~87 and 70ppm). Of the three conjugated diene structures possible from 4-X-toluenes, shown in chapter II (scheme 2.9), only the structure 126 (1,3-diene) can accomodate two sp^3 methine carbons. The high field methine carbon has chemical shifts (δ_C =70ppm) identical to C-1 of dienes obtained by nitration and the chemical shift of the other sp^3 methine carbon (δ_C=87ppm) is similar to that of C-6 of the same compound. These carbons have attached acetate and nitro substituents respectively in dienes 100 and 101. Thus the methine carbons of 187, 188, 190 and 191 must have an acetate group (δ_C~70ppm) attached to one and the nitro group attached to the other (δ_C=87ppm). It follows that the nitro group must have migrated from

a tertiary to a secondary carbon in the transformation of 100 to 187 and 188 and of 101 to 190 and 191 and that these dienes have the structure 5-X-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate (A) (Fig 3.3).



A

Figure 3.3: Structure of 5-X-2-methyl-6-nitrocyclohexa-2,4-dien-yl acetate.

The allylic coupling exhibited by the methyl group in the ^{1}H-NMR spectra and the upfield shift noted in the ^{13}C-NMR spectra (δ_C< 20ppm) confirms that the methyl group is attached to a double bond. The absence of a 1OHz vinylic coupling confirms the absence of adjacent vinylic protons. In the ^{13}C-NMR spectra, the position of one of the substituted sp^2-ring carbons varied on changing the substituent X (Cl, Br, OMe, NHCOMe) in a manner similar to the

change in chemical shifts in the dienes 100 to 103, as would be expected for the X-substituted carbon of A.

In the ^{1}H-NMR spectra of all of these dienes the ring protons appeared as four sets of multiplets. The two methine protons (1-H and 6-H) could be assigned on the basis of single frequency decoupling experiments in the ^{13}C-NMR spectra. On irradiation of the signal at ~5.2ppm of dienes 187, 188, 190 and 191 the C-6 signal in the off resonance decoupled ^{13}C spectra (~87ppm, $HC-NO_2$) appeared as a singlet whereas the multiplicity of the other carbons remained unchanged. Thus the doublet at ~5.2ppm in the ^{1}H-NMR spectrum was assigned to 6-H. The 1-H was identified as the proton coupled to 6-H ($J_{1,6}$ was ~4Hz in one diastereomer and ~8Hz in the other). The chemical shift of 6-H is more sensitive to the change in substituent X than 1-H and this confirms the assignment which puts 6-H on the carbon attached to X. The acetyl methyl group resonated as a sharp singlet whereas the methyl group on the ring (C-2) was split by a single proton in the (E)-diastereomers 188 and 191 and by two chemically non-equivalent protons in the (Z)-diastereomers 187 and 190.

In the (E)-diastereomers 188 and 191 the proton, allylic to methyl (3-H), could be easily distinguished from its splitting pattern (dq). It collapsed to a doublet (J=6.4Hz) on irradiating the methyl signal. On irradiation of the 3-H signal, the doublet due to the methyl protons and the low field doublet (J=6.4Hz) in the vinyl region collapsed to a singlet. The latter doublet could thus be assigned to 4-H.

In the ^{1}H-NMR spectrum of the methoxy dienes 194 and 195 the position of 4-H (and of C-4 in the ^{13}C-NMR spectrum) was shifted upfield due to the effect of the vinylic methoxy group,

apart from which all other chemical shifts were similar to those for the corresponding bromo and chloro-dienes. The coupling pattern was also very similar except that in the (Z)-diastereomer 194 the chemical shifts of 1-H and 2-H were very close and it was not possible to determine $J_{1,3}$ and J_{1,CH_3}. The methyl signal appeared as a broad doublet (J=1.70Hz) from which it is possible to determine the allylic coupling between CH_3 and 3-H.

The ^{13}C-NMR spectra of these dienes were easily interpreted on the basis of the structures assigned and the C-3 and C-4 peaks were assigned from single frequency decoupling experiments. Irradiation of 4-H gave a singlet for C-4 following which C-3 was assigned to the only other proton-bearing sp^2 carbon. In elucidating the structure of dienes 198, 208, 206, 210, 211, 212 and 214, the information from the ^{1}H-NMR and ^{13}C-NMR spectra of the dienes 188, 189, 190, 191, 194 and 195 was used. The allylic methyl splitting was present and the 10Hz coupling due to vicinal coupling ($J_{4,5}$ in the starting dienes) was absent in all the isomerized dienes. The ^{13}C-NMR spectra of the dienes 206 and 208 also agreed with the 5-X-2-methyl-6-nitrocyclohexa-2,4-diene framework in that the peaks due to the two sp^3 methine carbons and two sp^2 methine and two substituted sp^2 carbons were present.

An important feature in the spectra of these compounds is the subtle yet consistent differences introduced with change in stereochemistry. In the presence of radical traps the dienes 187 and 190 were formed stereospecifically from the dienes 100 and 101, assigned the (Z)-configuration and obtained by nitration of the respective toluenes.

In a series of substituted dihydronaphthalenes (Figure 3.2) studied by Katritzky and his coworkers[119] the cis isomers were found to have a larger coupling constant ($J_{a,e}$=6.5 Hz) between the two vicinal secondary protons compared to the coupling of the diequatorial protons in the trans isomer ($J_{e,e}$≅2Hz). Later on these values were used by Bartoli and his coworkers[121] to assign stereochemistry of similar compounds. Based on this analogy it is possible to assign the stereochemistry of the dienes 187, 190, and 194 as Z, since these dienes have a larger ($J_{1,6}$) coupling constant than the other diastereomer. This assignment agrees with a mechanism involving a concerted nitro shift, since the starting diene in this case (101) has a (Z) configuration as shown by its X-ray crystal structure.

In an attempt to confirm the assignment of the stereochemistry, shift reagent studies with $Eu(fod)_3$ were carried out on dienes 187 and 188. Complexation of the shift reagent with the acetate group was expected to induce a greater shift of the 6-H when this is cis to the acetate (i.e. in the E isomer). Similar methods have been successful in assigning stereochemistry of 1,4-dienes. However this method failed to produce any conclusive results. The maximum shift induced by addition of one mole proportion of shift reagent was only ~0.35ppm in either diastereomer. Steric crowding on vicinal carbons probably prevented significant complexation of the metal to the acetate group. Thus attention was directed to crystal structure determination by X-ray diffraction studies. Crystals of diene 190 were found to survive for an extended period at ambient temperature and proved to be suitable for X-ray diffraction studies. The diagram of the

structure so determined is given in figure 3.4 and the relevant bond lengths and angles are given in tables 3.5 and 3.6. The structure indicates clearly that the compound (190) is the Z-diastereomer.

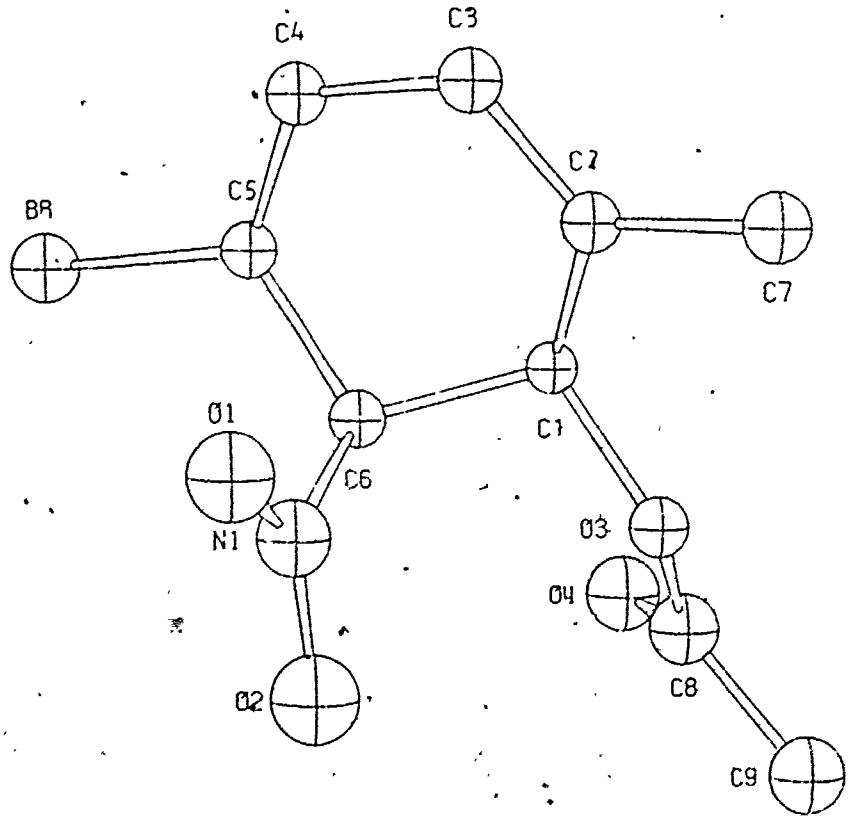


Figure 3.4: Molecular Structure of (Z)-5-bromo-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate (190).

Table 3.5

Interatomic Distances (Å) for 190

Atoms	Distance	Atoms	Distance
C(5) - Br	1.86 (2)	C(6) - C(5)	1.51 (3)
N(1) - O(1)	1.17 (2)	C(3) - C(4)	1.51 (3)
N(1) - O(2)	1.22 (3)	C(2) - C(3)	1.33 (3)
C(1) - O(3)	1.46 (2)	C(1) - C(2)	1.53 (3)
C(8) - O(3)	1.36 (3)	C(7) - C(2)	1.53 (3)
C(8) - O(4)	1.18 (3)	C(6) - C(1)	1.55 (3)
C(6) - N(1)	1.53 (3)	C(9) - C(8)	1.52 (3)
C(4) - C(5)	1.33 (3)		

Estimated standard deviations are given in brackets.

Table 3.6

Bond Angles (degrees) for 190

Atoms	Angle	Atoms	Angle
C(8) - O(3) - C(1)	116(2)	C(7) - C(2) - C(1)	118(2)
O(2) - N(1) - O(1)	125(3)	C(2) - C(1) - O(3)	108(2)
C(6) - N(1) - O(1)	123(2)	C(6) - C(1) - O(3)	110(2)
C(6) - N(1) - O(2)	113(2)	C(6) - C(1) - C(2)	115(2)
C(4) - C(5) - Br	122(2)	C(5) - C(6) - N(1)	108(2)
C(6) - C(5) - Br	116(2)	C(1) - C(6) - N(1)	110(2)
C(6) - C(5) - C(4)	122(2)	C(1) - C(6) - C(5)	108(2)
C(3) - C(4) - C(5)	121(2)	O(4) - C(8) - O(3)	121(2)
C(2) - C(3) - C(4)	120(2)	C(9) - C(8) - O(3)	111(2)
C(1) - C(2) - C(3)	117(2)	C(9) - C(8) - O(4)	128(3)
C(7) - C(2) - C(3)	124(2)		

Estimated standard deviations are given in brackets

It is now possible to explain the spectral differences in the diastereomers from the defined structure. The axial orientation of the nitro group on C-6 is preferred, as this minimizes any repulsive interaction with the adjacent bromine atom which is coplanar with C-5 and C-4. This orientation of the nitro group should remain unchanged in the other diastereomer, and the angular relationship between the allylic protons 4-H and 6-H should thus remain the same. From figure 3.4, these two protons appear almost coplanar, i.e. they are at 0° to each other. The magnitude of allylic coupling reaches a minimum when the two protons are either at 0° or 180° with each other. As table 3.2 shows there is no coupling between these protons in either diastereomer. The acetate group is in a pseudo-equatorial position in the (Z)-diastereomer and the proton 1-H **ipso** to it is almost perpendicular to the allylic counterpart 3-H. In this orientation the $J_{1,3}$ coupling constant approaches the theoretical maximum (3Hz). In the (E)-diastereomer the acetate group and the proton 1-H would interchange positions, which would bring the allylic protons (1-H, 3-H) almost coplanar to each other and reduce the coupling constant. In fact no coupling is observed. The closeness of the methyl group on C-1 to the acetate group on C-1 causes an uptield shift of the methyl resonance in the ^{13}C spectra of the (Z)-diastereomers due to steric crowding.

The isomerization of dienes 103 and 200 - 205 contrasts with that of the dienes 100 - 102 with respect to the observed stereoselectivity. The dienols 204 and 205 and diene 103 isomerized almost stereospecifically and the ^{1}H-NMR spectra of the reaction mixtures had no unexplained peaks. The dienes 200 - 203 isomerized stereoselectively.

The diene 103 obtained as the exclusive nonaromatic product in the nitration of acetanilide 113 was assigned the (Z)-configuration. The major distinguishing feature in the ^{1}H-NMR spectrum of the isomerized diene 198 was the presence of a $J_{4,6}$-coupling, which is absent in any other diene. This allylic coupling is possible if the 6-H proton is not on the same plane as the 4-H along the C5-C4 double bond, which suggests the nitro group is pseudo-equatorial and the 6-H pseudo-axial. In other isomerized dienes the nitro group was shown to prefer the pseudo-axial orientation with an X-substituent on C-5. It is likely that hydrogen bonding involving the amido proton and the nitro group leading to a stable six membered ring as shown in figure 3.5 forces the molecule to adopt the configuration with an equatorial nitro group. The 6-H proton is then pseudo axial and is thus split by the allylic proton 4-H.

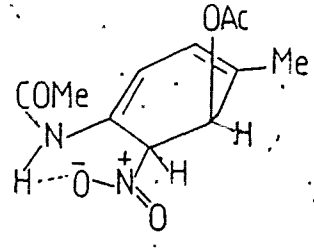


Figure 3.5: Structure of Diene 198.

In the hexahydrophenanthrenes 217T and 217C, mentioned before, the J_{aa} coupling between the two sp^3 protons (10a and 4a) is ~9.5Hz in the trans isomer 217T, whereas in the cis isomer the J_{ae} coupling is 6.5Hz. The $J_{1,6}$-coupling constant in diene 198 is

2.1Hz. This value is closer to J_{ae} than to J_{aa} (Figure 3.2) and suggests that if the 6-H is pseudo-axial the 1-H is pseudo equatorial. Consequently the acetate group in 198 has to be pseudo-axial and therefore cis to the nitro group. In this orientation the OAc-Me gauche interaction is removed but the OAc-NO_2 gauche relationship is preserved. Thus diene 198 has the (Z)-configuration and it is formed by a stereospecific concerted nitro shift with retention of configuration.

The dienols 204 and 205 are prepared by transesterification of dienes 100 and 101 (chapter V) involving an $A_{Ac}2$ mechanism wherein the (Z)-configuration is retained. The ^{1}H-NMR spectrum of the isomerized dienes resembled that of the (Z)-diastereomers 187 and 190 in that there is no $J_{4,6}$ allylic coupling (therefore the H-6 is pseudo-equatorial and NO_2 is pseudo-axial) and the $J_{1,6}$ splitting (7Hz) corresponds to a J_{ae} value and to the splitting observed in the (Z)-diastereomers (therefore OH is pseudo-equatorial). Consequently these isomerized dienes were also formed by the stereospecific concerted process. This can be anticipated as the cresols 213 and 215 formed simultaneously in the isomerization reaction would suppress the stereorandom process. p-Chlorophenol or p-cresol when present in catalytic amounts have been shown to suppress the stereorandom process in dienes 100 and 101. Either 4-methylacetanilide (113) or its nitro derivative 125 could potentially act as a similar inhibitor of the stereorandom process and explain the stereospecific isomerization of diene 103. When a solution of diene 100 in chloroform-d, containing 0.25 mol proportion of 4-methylacetanilide (113) was heated at 60°C for 2h, only diene 187 was formed. Similar reaction in the presence of 125 or in the absence of any additive

yielded a mixture of (187) and (188), thus demonstrating that compound 113 but not 125 is an effective inhibitor of the stereorandom process.

The major dienes 206, 208, 210 and 211 from 200, 201, 202 and 203 respectively were assigned the (E)-configuration on the basis of the ^{1}H-NMR spectra which resembled those of the (E)-diasterebmers of the other dienes. The small $J_{1,6}$-coupling (2Hz) and the absence of any allylic $J_{4,6}$- and $J_{1,3}$-coupling suggest that both nitro and the hetero substituent are pseudo-axial and antiperiplanar to each other. In the isomerized reaction mixtures there was formation of more than one diene but the (E)-diastereomer is predominant (~90% of nonaromatic products). As a consequence, the (Z)-diastereomer and the epimer of the starting diene, if formed, remain uncharacterized. Such a high stereoselectivity is difficult to explain, especially since the process occurs via an inversion of stereochemistry and must proceed via a radical process. In fact when a solution of diene 200 was heated at 60°C in chloroform-d containing 0.3 mol proportion of p-cresol for 2h, no isomerization occurred. Some aromatization to halotoluenes 110 and 207 along with formation of 2-nitro-p-cresol from p-cresol was evident from the ^{1}H-NMR spectrum. Reaction under identical conditions (60°C, 2h) in the absence of p-cresol led to the formation of diene 206, (45%). These observations show that the [1,5] sigmatropic process in diene 200, if it occurs at all, is very slow. The radical process predominates and favours the formation of the (E)-diastereomer 200. Dienes 201, 202 and 203 appear to exhibit similar behaviour. A previous report[115] showing that these dienes undergo a [1,5] sigmatropic shift is in error. The stereoelectronic

interactions in the (Z)-diastereomer of the isomerized dienes could possibly explain its absence in the product mixture.

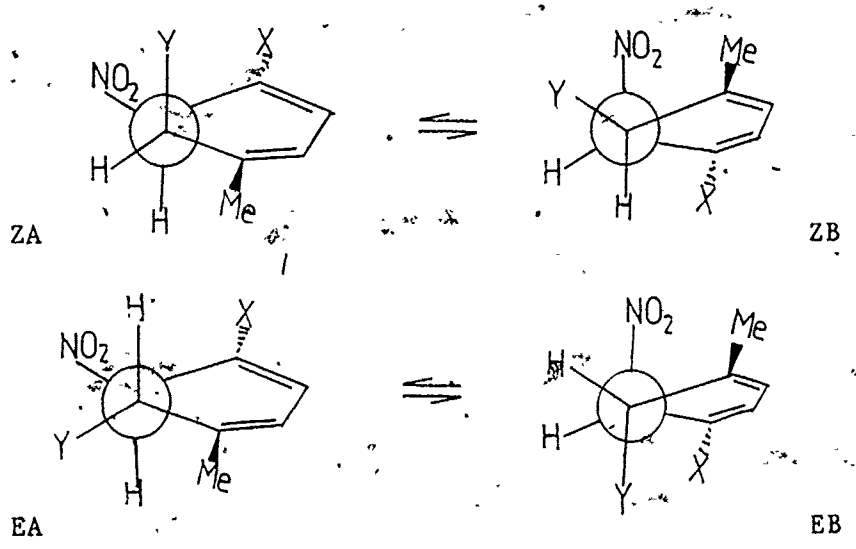


Figure 3.6: Conformers of each Diastereomer of 1-Y-5-X-2-methyl-6-nitrocyclohexa-2,4-dienes.

The pseudo-axial orientation of the nitro group in diene 190 was attributed to strong repulsive interactions between the nitro group and the vicinal hetero atom (X) on C-5. In dienes 206, 208, 210 and 214 the second heteroatom (Cl and OMe in figure 3.6) occupies a pseudo-equatorial position in conformation Z-B leading to similar strong repulsions as the nitro and Y groups are gauche to each other. In the other conformation ZA the situation is compounded as the nitro group approaches coplanarity with X and still remains gauche to Y. In the (E)-diastereomer, conformer EB has the nitro group antiperiplanar to Y but remains perpendicular to X. The axial orientation of the Y group also releases steric strain between the methyl group on C-2. These arguments would lead to the conclusion that the (E)-diastereomer of the rearranged diene should be the favoured product. This is what was observed when Y=Cl or OMe but is not the case when Y=OH or OAc. Hydrogen bonding between the hydroxyl and nitro groups which would stabilize the (Z)-diastereomer

could explain the result for Y=OH, but the Y=OAc case remains an anomaly.

3.3: Mechanism of the Thermal Isomerization.

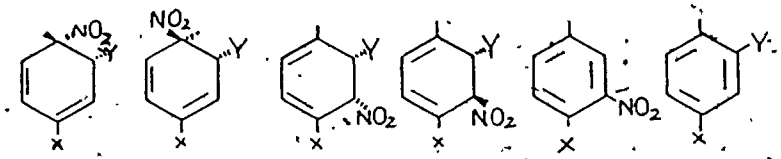
The general features of the mechanism involved in the isomerization process emerged from small scale (0.1 mmol) reactions carried out in the presence and absence of radical traps and an initiator. Representative data from these reactions are summarized in tables 3.7 and 3.6.

The amount of aromatic products, particularly 4-X-3-nitrotoluenes 122 and 124, increases with increase in the nucleophilicity of the solvent. This is expected, since the secondary hydrogen 6-H, α to the nitro group, is acidic and is readily abstracted by such weakly basic solvents. Thus the overall elimination of acetic acid becomes faster. When the isomerized dienes 187 and 188 in pyridine-d_5 were warmed to ambient temperature instantaneous aromatization was observed.

The rate of disappearance of starting diene increases with temperature but remains unaffected with change in solvent polarity. The fact that the isomerization reaction occurs in non-polar solvents such as carbon tetrachloride, chloroform-d and benzene suggests that a non-ionic pathway is involved in the isomerization process. Added p-cresol, p-chlorophenol, thiophenol, and 4-methylacetanilide suppress the process leading to epimeric products, but do not stop the isomerization process. Thus there appears to be two distinct pathways by which the isomerization can take place viz:

a) A stereospecific path via a concerted [1,5]-sigmatropic shift of the nitro group;

Table 3.6 Examples from the Isomerization of Dienes.



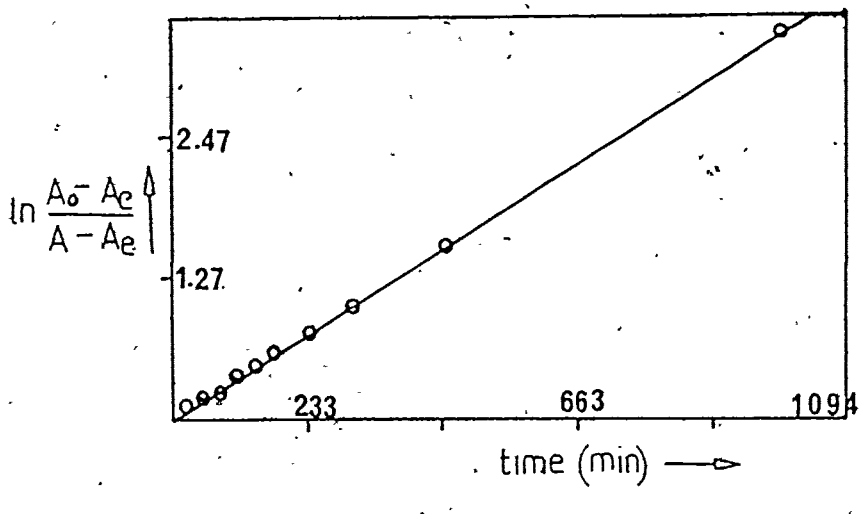
Number	X	Y	Solvent	Temp °C	Time h	Additive mol prp						
101	Br	OAc	$CDCl_3$	60	2	p-cresol 0.25	73	–	27	–	–	–
190	Br	OAc	$CDCl_3$	60	2	p-cresol 0.25	10	–	90	–	–	–
191	Br	OAc	$CDCl_3$	60	2	p-cresol 0.25	–	11	–	82	–	7
200	Br	Cl	$CDCl_3$	60	2	p-cresol 0.25	>95	–	a	–	–	
100	Cl	OAc	Ac_2O-d_6	60	11	–	7	a	33	32	27	–
100	Cl	OAc	CH_3NO_2	60	18	–	6	a	29	29	21	15
100	Cl	OAc	CD_3CN	60	2	–	65	a	12	12	11	–
100	Cl	OAc	CD_3CN	60	18	–	–	–	–	–	100	–
100	Cl	OAc	$CDCl_3$-Ac_2O(9:1)									
				60	9	–	25	a	30	30	–	
100	Cl	OAc	CCl_4	72	3	–	27	a	31	31	–	
100	Cl	OAc	C_6D_6	60	4	–	28	a	31	31	a	a
100	Cl	OAc	C_6D_6	75	1.5	–	25	a	33	33	9	–

Table 3.7 Examples from the Isomerization of Dienes in $CDCl_3$ in the Presence of Additives.

#	Temp °C	Time	Additive mol prop	Percentage Products 100	189	187	188	186
100	50	4h	b 0.25	55	-	45	-	-
100	50	9h	c 0.25	53	-	47	-	-
100	70	3.5h	d 0.25	23.5	a	28	28	20
100	60	1.5h	e 0.25	56	a	26	17	-
100	60	7h	f 0.25	55	-	45	-	-
100	60	2h	g 0.25	45	a	30	25	-
100	70	10h	h 1.00	28	-	46	-	26
100	70	5.5h	h 0.50	31	-	62	-	7
100	70	7h	h 0.25	25	-	55	-	10i
100	60	2h	h 0.25	75	-	25	-	-
187	60	2h	h 0.25	9	-	91	-	-
188	60	2h	h 0.25	-	12	-	76	13

a = traces of this compound were detected but integration was not possible; b = thiophenol; c = p-chlorophenol; d = mesitylene; e = benzoyl peroxide; f = 4-methylacetanilide; g = 4-methyl-2-nitroacetanilide; h = p-cresol; i = 10% of 122 was also formed.

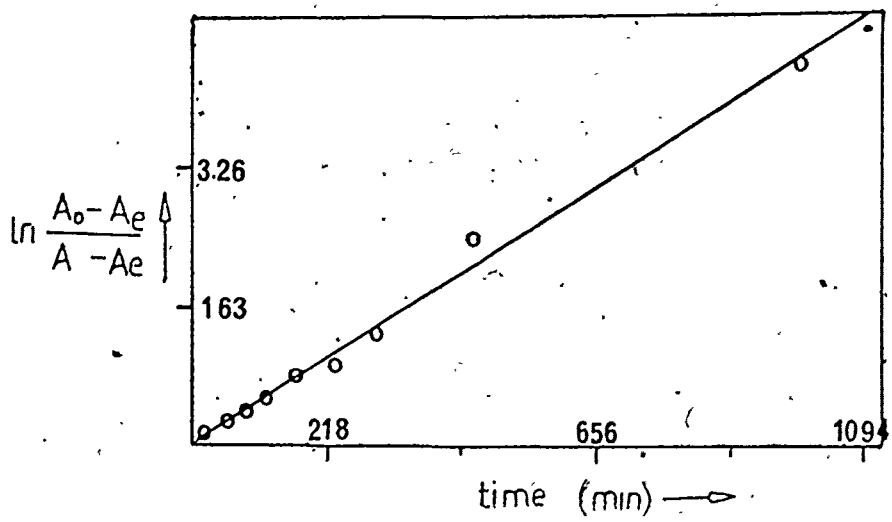
b) A radical path leading to both epimerization and isomerization. The 1,5-sigmatropic rearrangement of the nitro group in a suprafacial manner is a thermally allowed process in accordance with symmetry rules. The rate constants of the sigmatropic reactions were evaluated using data from the reactions followed on the Fourier Transform - 250 MHz NMR instrument. The plots of log $(A_0-A_e)/(A-A_e)$ (where A_0 = initial concentration of starting diene, A_e = equilibrium concentration of starting diene, A = concentration of starting diene at time t mins) against time, t minutes, gave good correlation coefficients (0.98±0.01) and are shown in figures 3.7 to 3.10.



Slope = 3.4×10^{-3} min^{-1}; Correl. Coeff. = 0.99;

K_{eq} = 2.5; $k_1 = 2.45\times10^{-3}$ min^{-1}; $k_{-1} = 0.95\times10^{-3}$ min^{-1}.

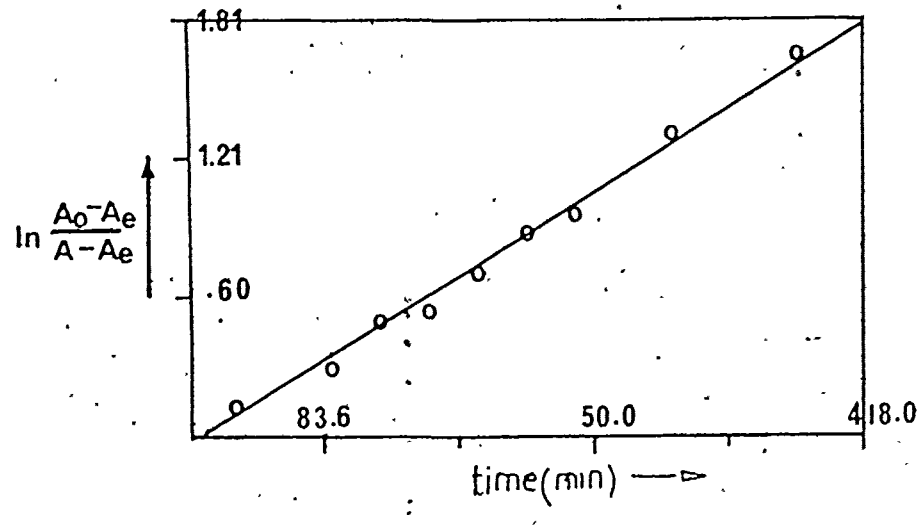
Fig 3.7: Plot of $\ln(A_0 - A_e)/(A - A_e)$ vs. time (min) for the Isomerization of Diene 100 in the presence of p-cresol at 58.5°C.



Slope = 4.59×10^{-3}; Correl. Coeff. = 0.99; $K_{eq} = 2.9$;

$k_1 = 3.4 \times 10^{-3}$ min^{-1}; $k_{-1} = 1.2 \times 10^{-3}$ min^{-1}.

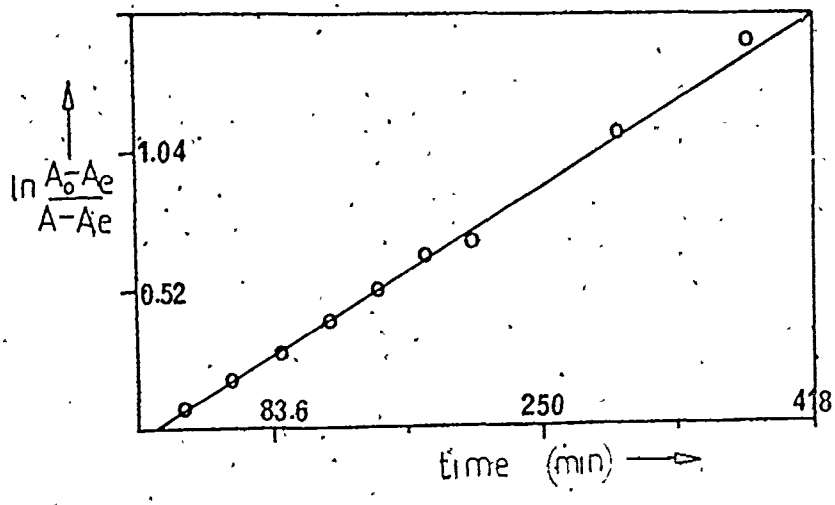
Figure 3.8 Plot of $\ln (A_0 - A_e)/(A - A_e)$ vs. time (min) for the isomerization of diene 101 in presence of p-cresol at 58.5°C



Slope = 4.38×10^{-3}; Correl. Coeff. = 0.99; $K_{eq} = 0.34$;

$k_1 = 3.26 \times 10^{-3}$ min^{-1}; $k_{-1} = 1.12 \times 10^{-3}$ min^{-1}.

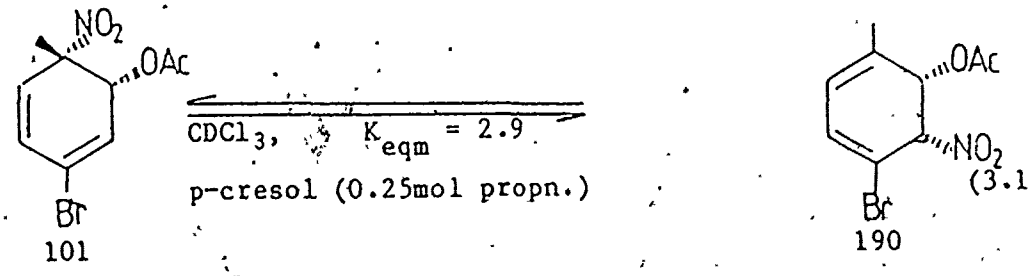
Figure 3.9 Plot of $\ln (A_0 - A_e)/(A - A_e)$ vs. time (min) for the isomerization of diene 190 in presence of p-cresol at 58.5°C

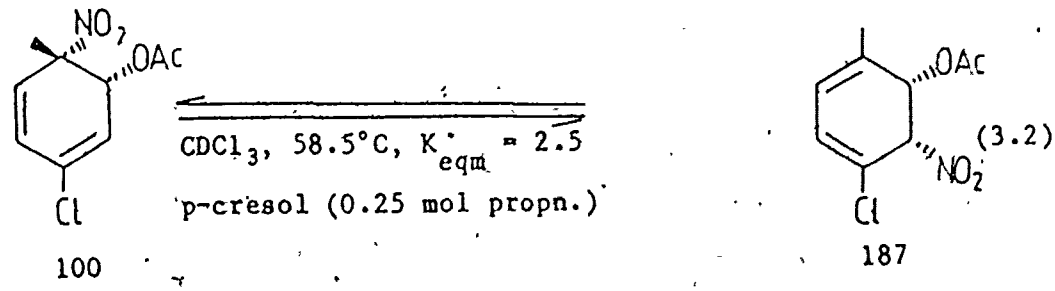


Slope 3.71×10^{-3} min^{-1}; Correl. Coeff. = 0.99; K_{eq} = 0.4;
$k_1 = 1.06\times10^{-3}$ min^{-1}; $k_{-1} = 2.65\times10^{-3}$ min^{-1}.

Figure 3.10: Plot of ln $(A_0 - A_e)/(A-A_e)$ vs. time (min) for the isomerization of diene 187 in the presence of p-cresol at 58.5°C.

Identical equilibrium concentrations were obtained for the isomerization reactions of dienes 100 and 187 and of dienes 101 and 190, carried out in the presence of p-cresol at 58.5°C in chloroform-d, as shown in equations 3.1 and 3.2 respectively.





The plots of percent product against time for dienes 100 and 188 in the absence of any trapping agent are given in figures 3.11 and 3.14. From these plots it can be seen that after a period of time the concentrations of dienes reach a plateau following which there is a gradual decrease, accompanied by an increase in the concentration of aromatic acetate.

However, if we ignore the aromatization reaction and express the concentration of each diene as a fraction of the total concentration of dienes, the plots 3.15 to 3.18 do not show the decrease from the plateau but the levelling off in the concentration still remains.

Symbol	Compound
o	100
▲	186
×	187
•	188
¦	189

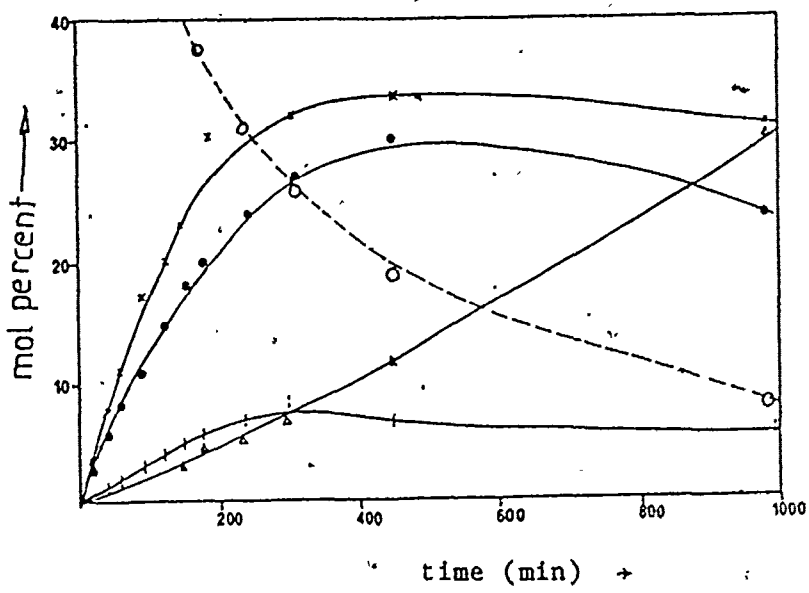


Figure 3.11: Plot of product composition vs. time (min) for the isomerization of diene 100 in $CDCl_3$ at 58.5°C.

Symbol	Compound
o	100
▲	186
×	187
•	188
¦	189

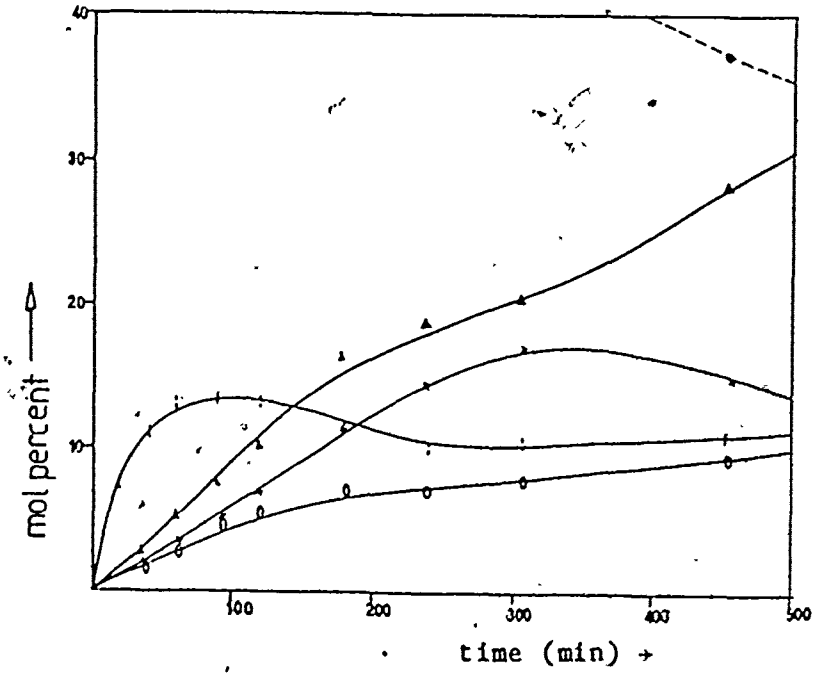


Figure 3.12: Plot of product composition vs. time (min) for the isomerization of diene 188 in $CDCl_3$ at 58.5°C.

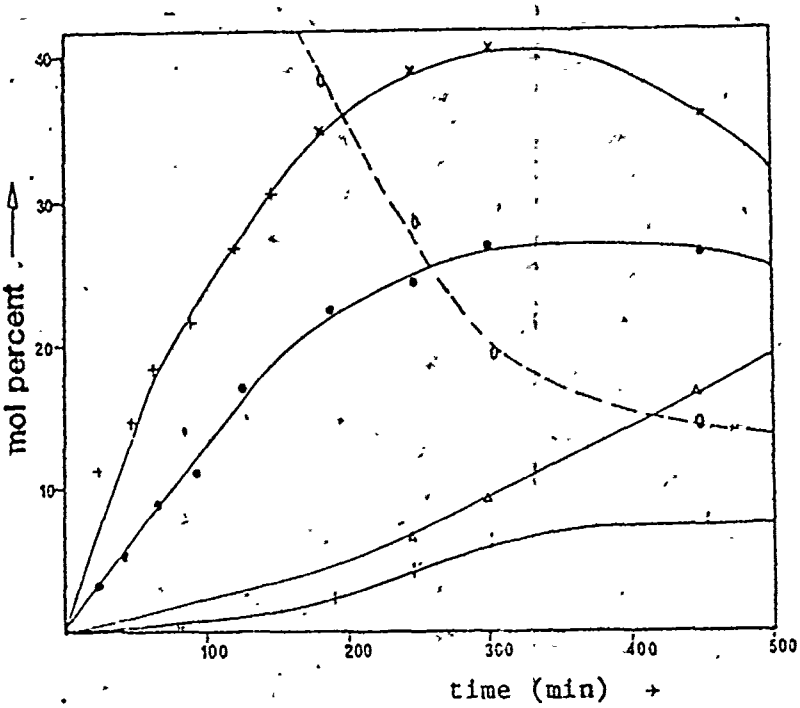


Figure 3.13: Plot of product composition vs. time (minutes) for the isomerization of diene 101 in $CDCl_3$ at 58.5°C.

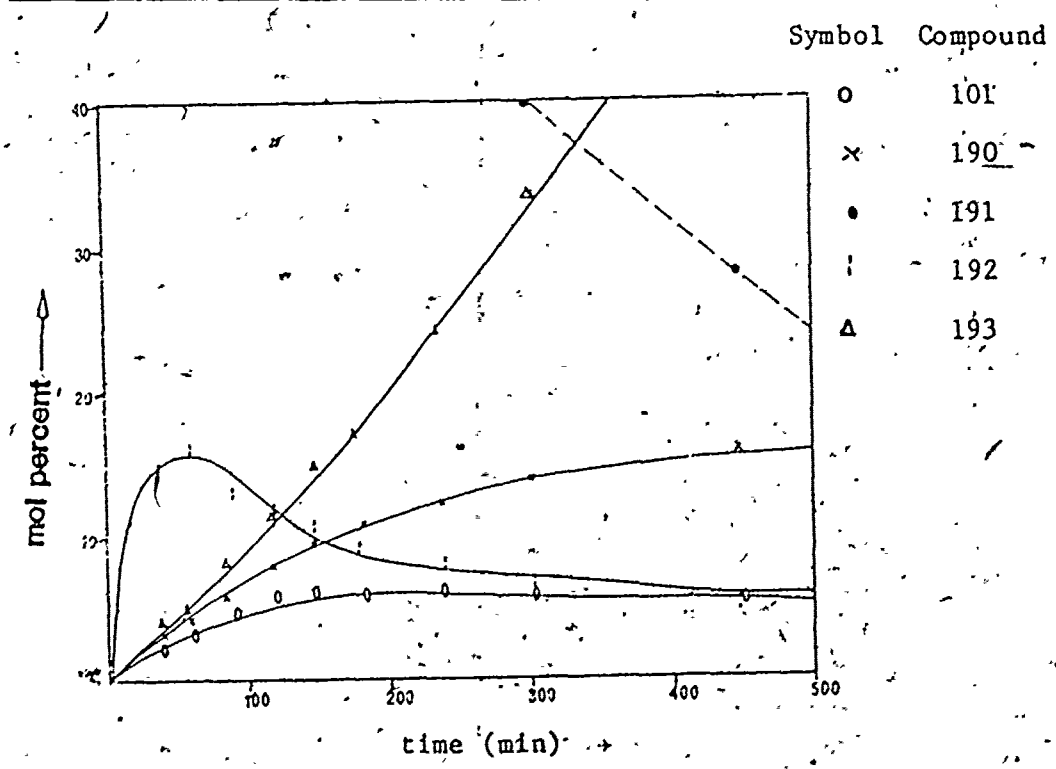


Figure 3.14: Plot of product composition vs. time (minutes) for the isomerization of diene 191 in $CDCl_3$ at 58.5°C

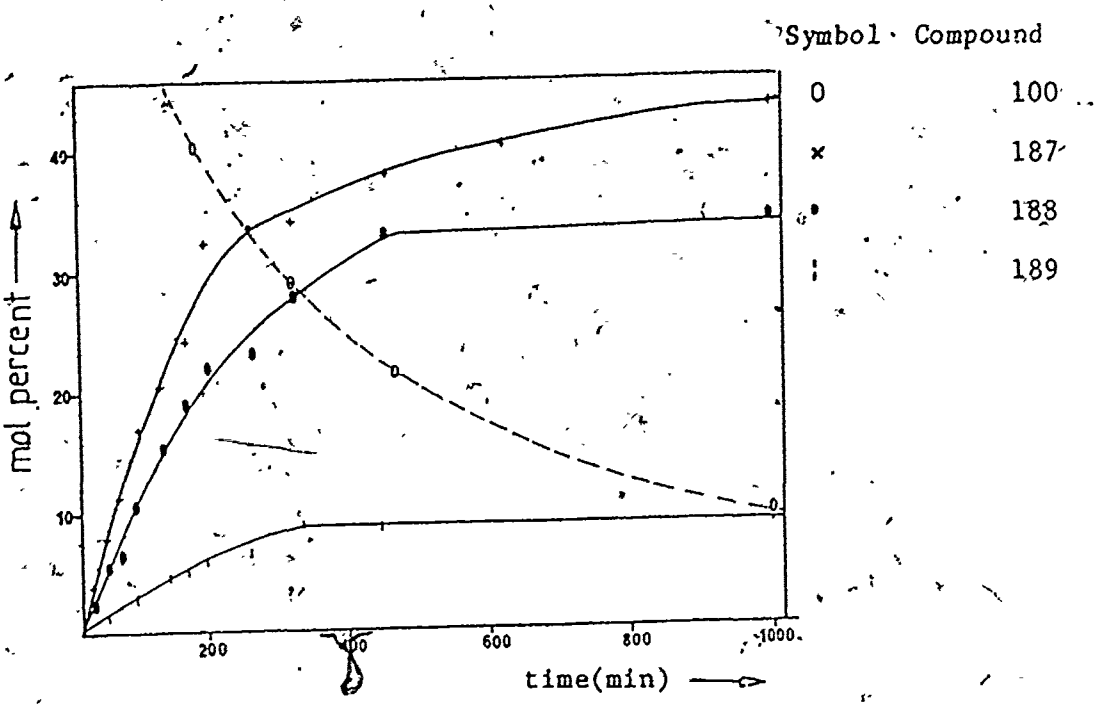


Figure 3.15: Plot of percent of dienes as a fraction of total diene conc. in the isomerization of diene 100 in $CDCl_3$ at 58.5°C.

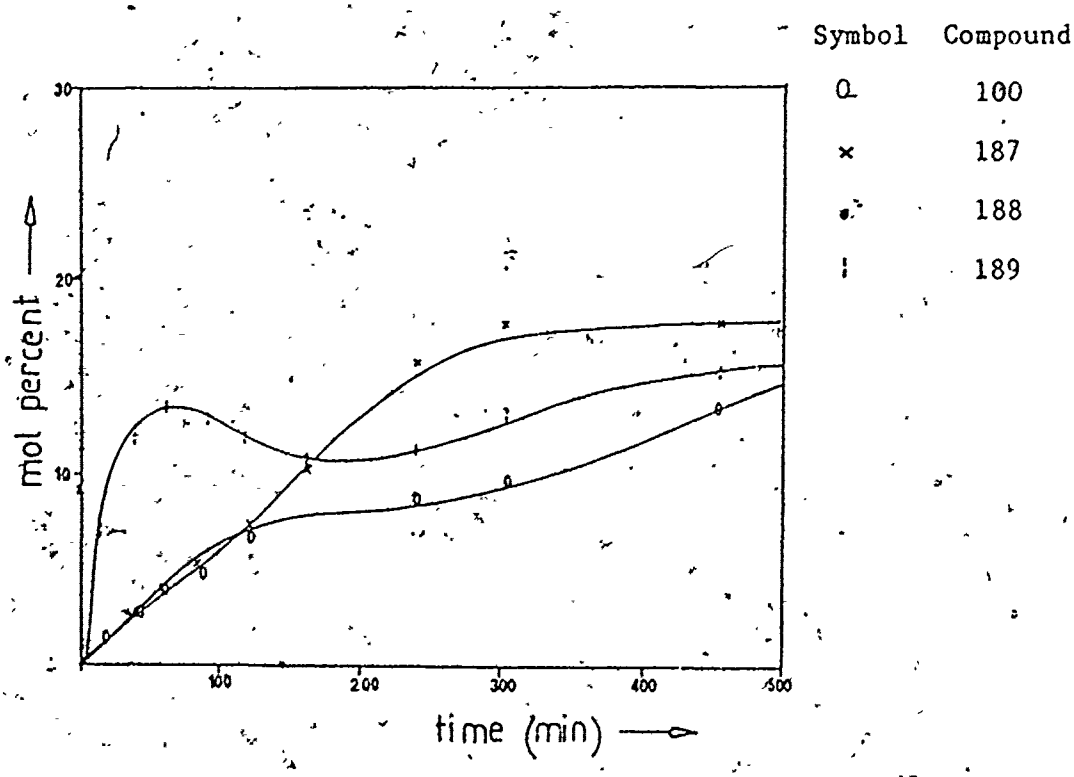
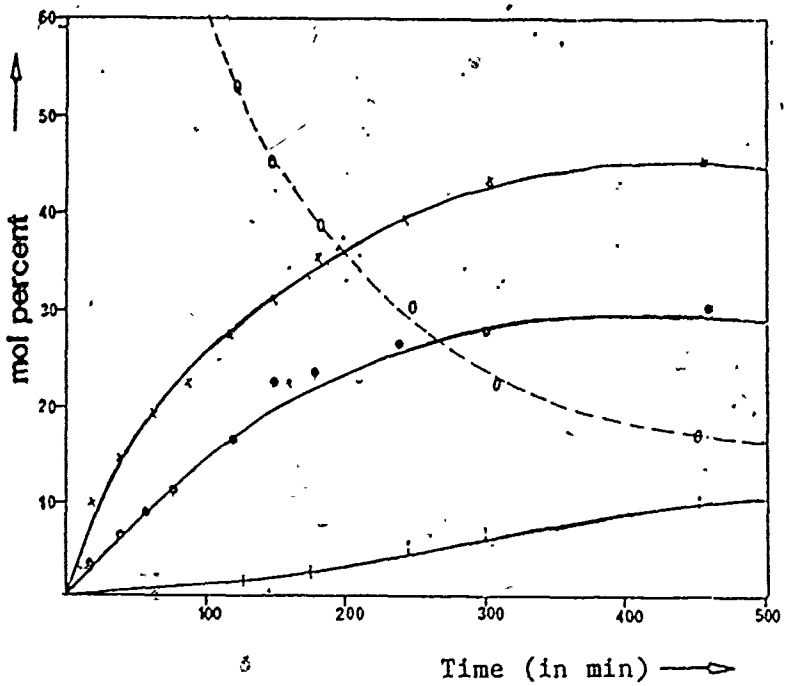
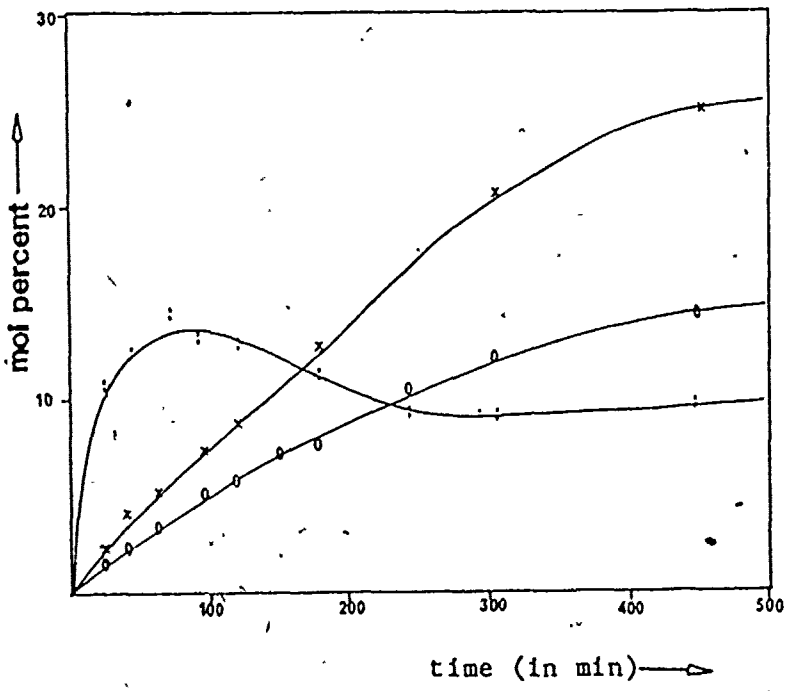


Figure 3.16: Plot of mol percent of dienes as a fraction of total diene conc. in the isomerization of diene 188 in $CDCl_3$ at 58.5°C.



Symbol	Compound
0	101
×	190
•	191
¦	192

Figure 3.17: Plot of mol percent of dienes as a fraction of total diene conc. in the isomerization of diene 101 in $CDCl_3$ at 58.5°C.



Symbol	Compound
0	101
×	190
•	191
¦	192

Figure 3.18: Plot of mol percent of dienes as a fraction of total diene conc. in the isomerization of diene 191 in $CDCl_3$ at 58.5°C.

It is evident from fig 3.15-3.18 that equilibrium between the four dienes has not been achieved even after 500 min reaction time. Because of the irreversible aromatization process (to the aryl acetate) equilibrium may never be achieved. However it is possible to draw some conclusions regarding the relative reactivities and stabilities of the dienes from fig 3.15 to 3.18 viz:

i) The conversion of a diene into its 1,5-rearrangement product of the same stereochemistry is faster than any other process and this holds true even in the situation in which that product is apparently the least stable of the four dienes.

ii) The 5-X-2-methyl-6-nitrocyclohexa-2,4-dienes appear to be thermodynamically more stable than the 3-X-6-methyl-6-nitrocyclohexa-2,4-dienes (the reactions carried out in the presence of radical traps show that this is certainly true for the (Z)-isomers).

The effect of p-cresol and other agents which inhibit the radical reaction is catalytic. In the absence of any added catalyst, inhibition of the rate of reaction by small proportions of additives is diagnostic of a chain reaction[122].

It is possible that dissolved oxygen present in the reaction mixture could act an an initiator and the radical traps merely behave as antioxidants. Phenols and amines are known to function as antioxidants and inhibitors in chain processes. If such a process was occurring then added peroxides would increase the rate of isomerization, but when a solution of diene 100 and benzoyl peroxide (0.25 mol proportions) in chloroform-d was heated there was no noticeable change in the rate of disappearance of diene 100. The

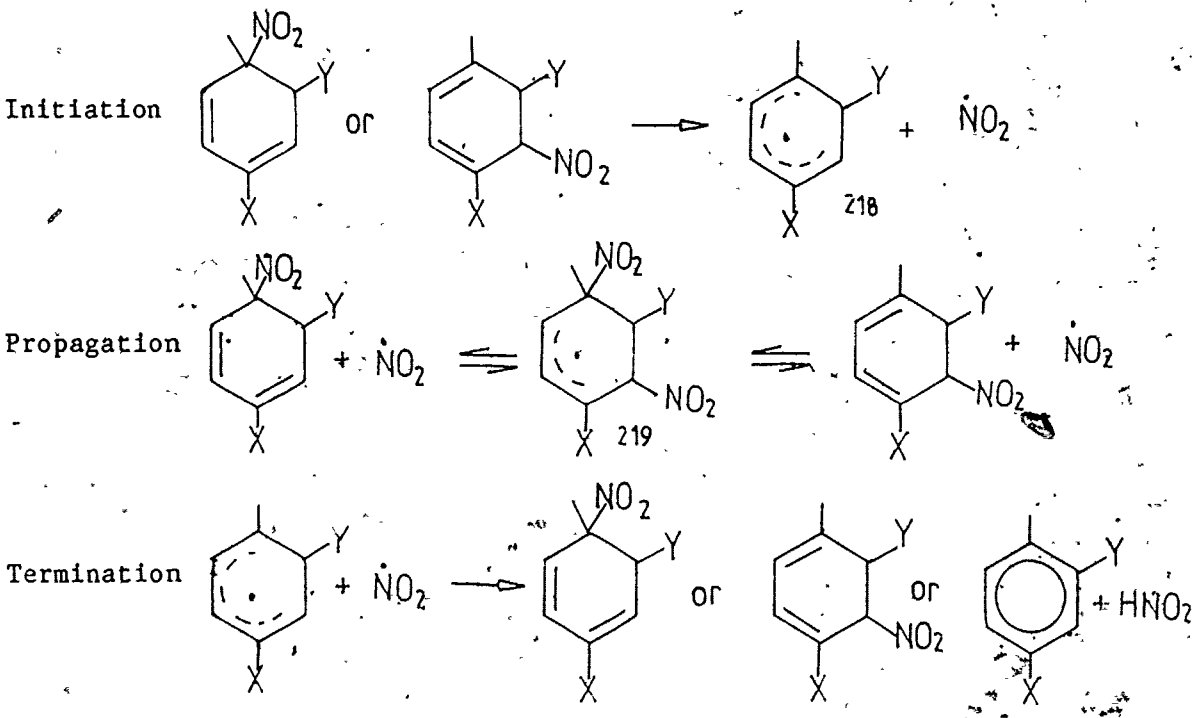
product composition was also identical to that observed in the case of reactions without any additive. This implies that oxygen does not act as an initiator in this mechanism. Cresols, added to inhibit the radical process, are slowly converted to nitrocresols over a period of time and when no cresol remains the reaction becomes stereorandom. Thus when a solution of the (E)-diene 191 was heated in the presence of p-cresol, the reaction remained stereospecific for the duration of 4h, during which period the p-cresol became completely conver ted to 2-nitro-p-cresol. After this time the reaction became stereorandom and the dienes 190 and 101 belonging to the (Z) series were formed.

The $C-NO_2$ bond in nitromethane is weaker than the C-X bond in other methyl compounds as shown in table 3.9.

Table 3.9: Bond Strengths (D) of Methyl Derivatives in kJ/mol.

Bond	D	Ref
CH_3-H	435.1	123a
CH_3-OH	380.7	123a
CH_3-OAc	376.6	123a
CH_3-Cl	351.5	123a
CH_3-OCH_3	338.9	123a
CH_3-Br	292.9	123a
CH_3-NO_2	239.7	123b

A likely radical chain process for epimerization and isomerization of the dienes would involve fission of the $C-NO_2$ bond in the initiation step and the overall mechanism can be represented as in scheme 3.8.

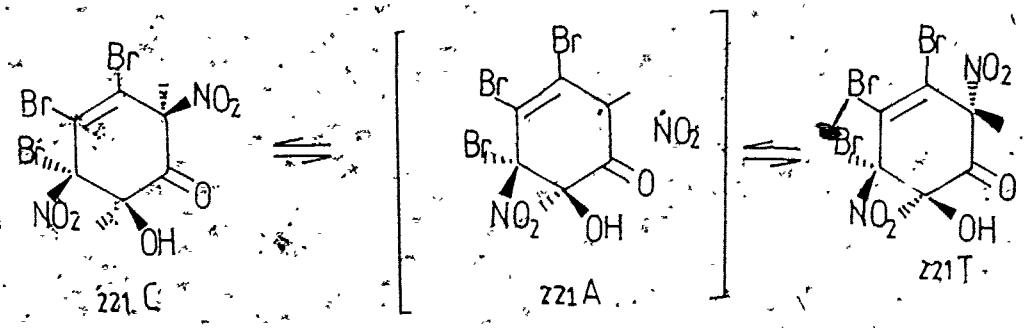


218

Scheme 3.8

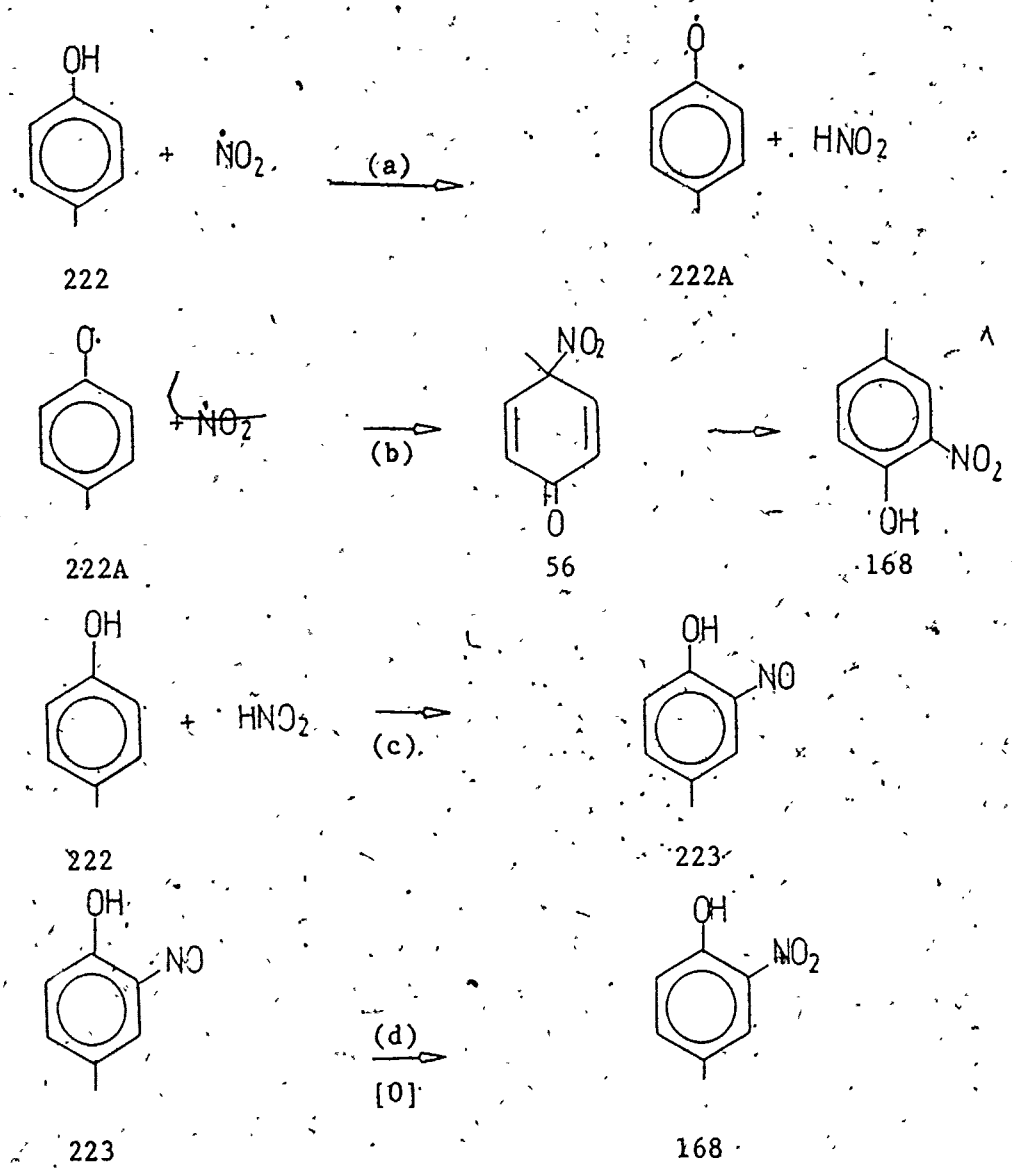
The attack of $NO_2^{\bullet}$ on the diene during propagation should take place at the site of highest electron density viz. the carbon (C-2) vinylic to the electron donating heteroatom X, in the case of 3-X-6-methyl-6-nitrocyclohexa-2,4-dienes. When the attack takes place on 5-X-2-methyl-6-nitrocyclohexa-2,4-dienes, it should be at C-2 which, being the terminal carbon of the conjugated diene system and farthest from the heteroatom, should have the largest coefficient in the HOMO. This explains the regioselectivity observed in the radical process. Since the addition of $NO_2^{\bullet}$ to the diene leads to the regeneration of $NO_2^{\bullet}$ in this step, these steps constitute a chain process.

The contribution towards the radical process may not be equal from all sets of regioisomers, that is to say epimerization would occur predominantly from either 3-X-6-methyl-6-nitrocyclohexa-2,4-dienes, or from 5-X-2-methyl-6-nitrocyclohexa-2,4-dienes since these are interconvertible via the sigmatropic step reaction. Epimerization of tertiary nitro compounds via the nitrogen dioxide radical is known but the similar process at a secondary carbon is not known. Hartshorn and coworkers[124] reported the epimerization of the cis-dinitrocompound 221C obtained from the nitration of 3,4,5-tribromo-2,6-dimethylphenol (220) to 221T under thermal conditions and proposed a mechanism involving a dissociation-recombination of nitrogen dioxide within a solvent cage (221A) as shown in scheme 3.9.



Scheme 3.9

The formation of nitrocresol 168 from p-cresol (222) and its role as an inhibitor can be explained by the stepwise mechanism shown in scheme 3.10.



Scheme 3.10

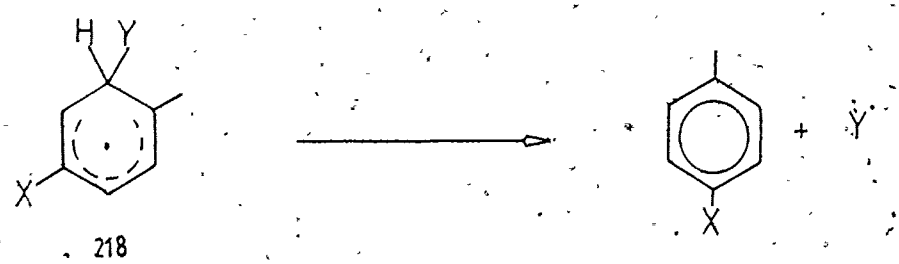
Added mesitylene or cresyl acetates (186, 193, 197) formed as products do not inhibit the epimerization process. Even if these

are sufficiently reactive to trap $NO_2^{\bullet}$, they must be less reactive than the diene, whereas the phenol is more reactive than the diene.

The nitrocresol 168 obtained in the inhibited isomerization can be formed by direct combination of the cresoxy radical 222A and the $NO_2^{\bullet}$ as in step (b) or via nitrosation by nitrous acid followed by oxidation as in steps (c) and (d). The overall stoichiometry however demands that, irrespective of the mode of nitration, the amount of nitrocresol 168 should be equal to the amount of 4-X-2-Y-toluene formed, provided that toluene is the only product of those radicals which are not captured by $NO_2^{\bullet}$. If there is some escape of $NO_2^{\bullet}$ from the system the amount of toluene could exceed the nitrocresol but could not be less. This agrees with observation. When a solution of diene 100 in chloroform-d was heated in presence of p-cresol (0.2 mol proportion), for 16h, 28% of it underwent nitration and the ratio of nitrocresol 168 and cresyl acetate 186 was 1:1.75. Similar results were obtained from other dienes.

The formation of 4-X-toluene accompanies the isomerization reactions in certain cases and as shall be seen later its formation becomes more important at elevated temperatures. There are two possible pathways leading to formation of 4-X-toluene viz:

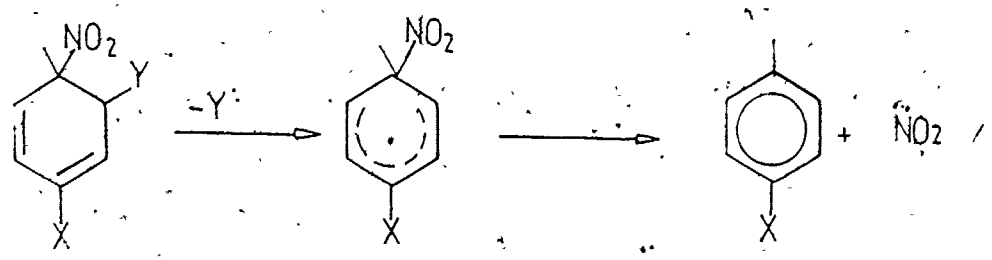
1) ejection of $Y^{\bullet}$ from the intermediate radical 218 as in scheme 3.11.



218

Scheme 3.11

ii) preferential homolysis of the C-Y bond prior to cleavage of nitro group followed by ejection of $NO_2^{\cdot}$ as in scheme 3.12



224

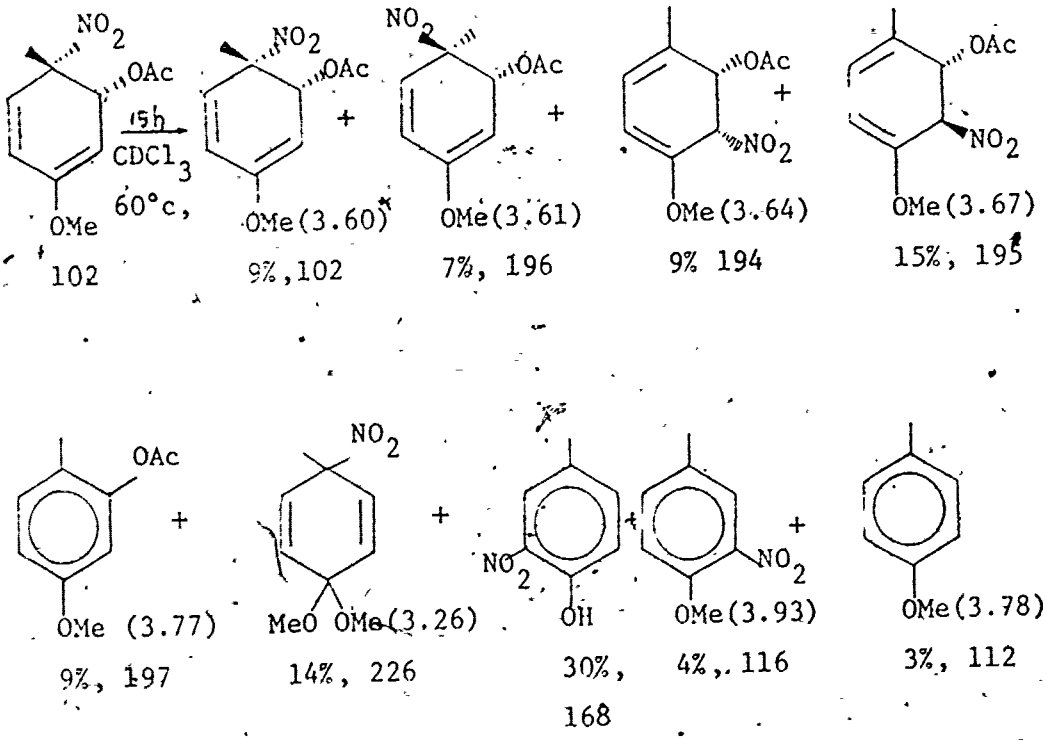
Scheme 3.12

Either of these two processes is important when the C-Y bond is of comparable energy to the C-NO_2 as is the case when Y=Br. Thus when a solution of (Z)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl bromide (225) in benzene-d_6 was heated to 80°C, 4-chlorotoluene (111) was formed within 30 minutes and no isomerized diene was detected.

When X is a strong electron donating group it can stabilize the radical 224 and facilitate the homolysis of C-Y bond (scheme 3.12). The radical 218 formed by cleavage of the NO_2 group

has no resonance contribution from the X group. When X=NHCOMe this appears to be an important pathway as diene 103 yields 58% 4-methylacetanilide (113) after 30min at 60°C, however at 0°C to -20°C the amount of 113 is close to zero.

The reactions of diene 102 from 4-methylanisole (112) lead to a complex mixture of products as shown in scheme 3.12 and 3.13.

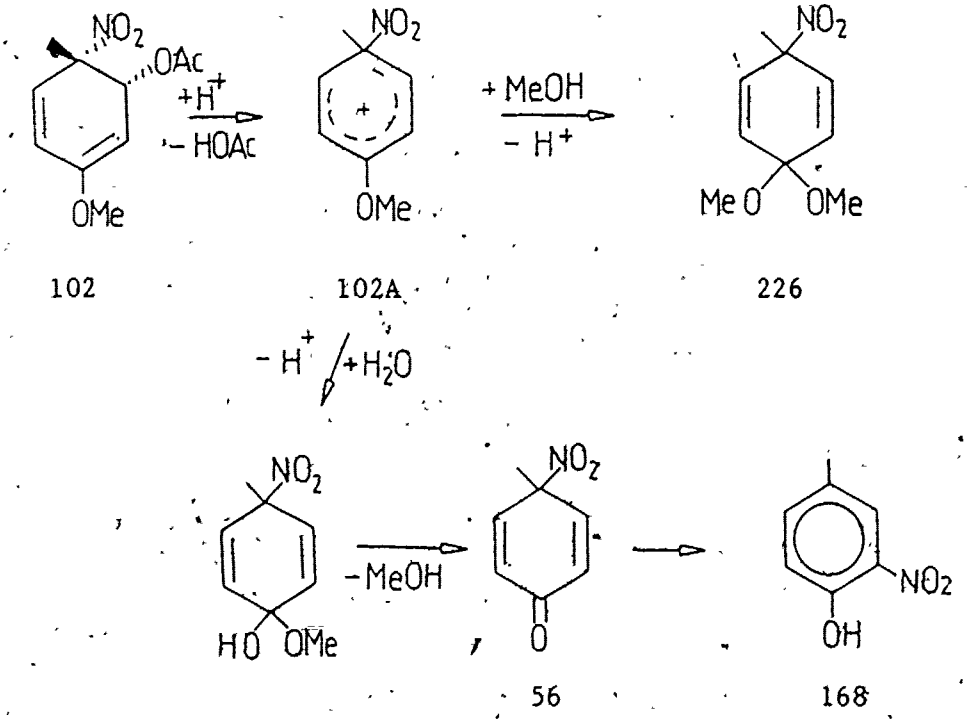


102 $\xrightarrow[\text{p-cresol, (0.25 mol propn.)}]{CDCl_3,\ 60°C,\ 15\ h}$ (102 +194 + 195 + 196) 18% + (226) 28% + (168) 33% + (197 + 112 + 116) 21%

Scheme 3.13

* The figures in the brackets are the chemical shifts of OMe which was used to determine product ratio.

The formation of dienes 194-196, acetate 197 and anisoles 112 and 116 can be explained from the isomerization reactions and related aromatizations discussed in the preceding sections, but the products 226 and 168 cannot be accounted for by similar processes. The presence of p-cresol does not suppress the epimerization process; instead in its presence the amount of products 226 and 168 increases. Acid catalysed reactions on diene 102, discussed in the next chapter, have shown that the nitrocyclohexdienyl cation 102A is formed readily under mildly acidic conditions and can be trapped by various nucleophiles leading to 1,4-dienes of the type 226. This reaction is autocatalytic since acetic acid and nitrous acid, formed in this reaction, aid the dissociation of the diene. In the present case a similar mechanism, shown in scheme 3.14, can explain the products 226 and 168.

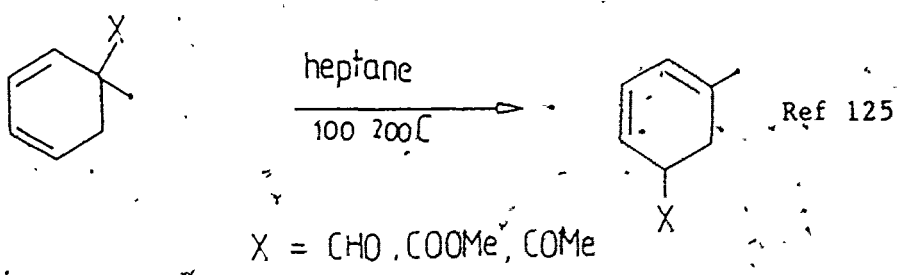


Scheme 3.14

In scheme 3.14 the proton source could be traces of water present

in the system, which would also account for the nucleophilic attack in the second stage. The methanol formed in the final step competes as a nucleophile in the subsequent stages and leads to ketalization. The p-cresol, when present in the system, acts as a proton source and thus aids the protonation and loss of HOAc leading to ion 102A and, in turn, 168 and 226. A possible explanation for the failure of p-cresol to inhibit the reaction is that the methoxy-substituted system is more reactive towards NO_2^+ than is p-cresol.

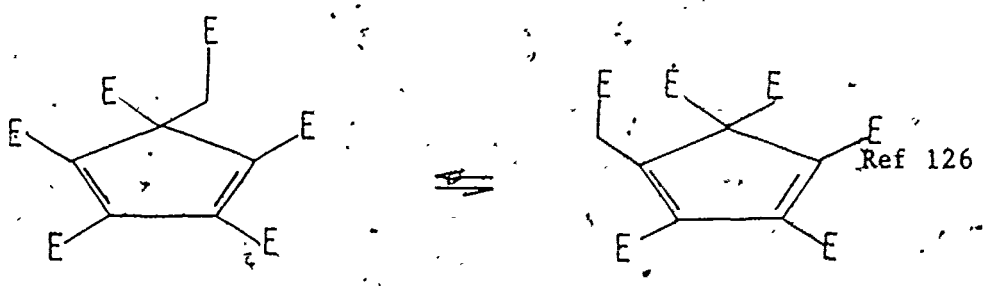
Cyclohexadienes and cyclopentadienes are known to rearrange via a [1,5]-sigmatropic shift of substituent as shown in scheme 3.15 and scheme 3.16.



X = CHO, COOMe, COMe

227A 227B

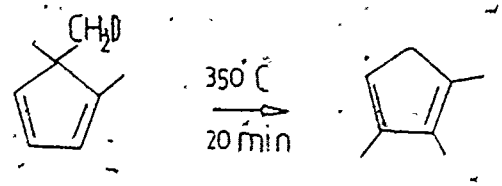
Scheme 3.15



228A E = COOMe 228B

Scheme 3.16

Complications arising from competetive radical chain processes have also been recognized in some cases. Thermolysis of deuterium substituted 1,5,5-trimethylcyclopentadiene (229) for long periods of time led to deuterium scrambling as shown in scheme 3.17, which was explained by a radical chain process[127].



229A

d_0	5.4%
d_1	90.5%
d_2	3.7%
d_3	0.4%

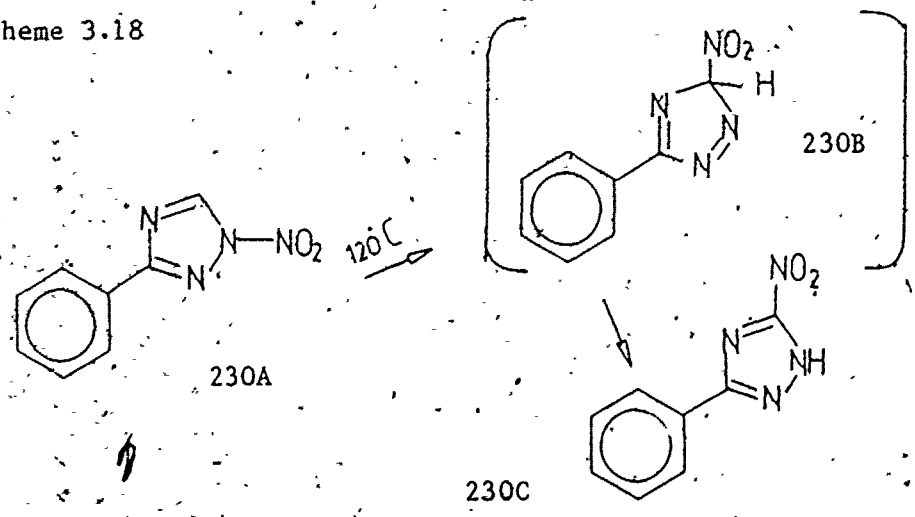
229B

d_0	23.0%
d_1	60.0%
d_2	15.0%
d_3	2.0%

Ref 127

Scheme 3.17

There is a relative paucity of clear-cut examples of heteroatom sigmatropic migration. The known examples of a nitro group involved in [1,5]-shift are those in the di- and triazole systems as shown in scheme 3.18



Scheme 3.18 Ref 128

The intermediate secondary nitro compounds readily undergo a [1,5]-hydrogen shift. The behaviour of ipso-nitrocyclohexadienes described here and by Bapat[76] is unique in that these are the only known examples of [1,5]-sigmatropic nitro shift along a carbon skeleton. The competing radical process leading to epimerization also has remarkable regioselectivity and is at times the more favourable process. The only example where no radical process accompanies the sigmatropic shift is that reported by Bapat for the spiro dienes from acid 178. The only observable isomerization is a stereospecific shift of the nitro group. However the possibility that trace phenols formed as products from accompanying aromatization could act as radical traps has not been considered.

The substituents X and Y have been shown to have considerable effects on the nature of the process operating which can be classified as:

a) A stereorandom process in the absence of a radical trap leading to the epimeric pairs of both regioisomers (X=Cl, Br, OMe; Y=OAc)

b) A stereoselective radical process in the absence of radical trap leading to inversion of configuration (X=Cl, Br; Y=Cl, OMe)

c) A stereospecific (sigmatropic) process in the presence of a radical trap (X=Cl, Br; Y=OAc, OH, NHAc).

The substituent X is removed from the migrating nitro group and it can affect the rate of the sigmatropic shift by altering the electron density of the migrating termini. The rate constants of isomerization of dienes 102 and 103 were not obtained but on a qualitative basis the process is facile for these dienes relative to dienes 100 and 101 as would be expected since the group X in 102 and 103 should increase the coefficients of C-2 more than in dienes 100 and 101.

From table 2.9 in chapter II it can be seen that terminally substituted cyclohexa-1,3-dienes are more stable than the other regioisomers. The difference in energy between these regioisomers is, however, small (1.4kJ mol^{-1}). The free energy differences, calculated from equilibrium constants for some of the dienes studied here, are shown in table 3.10. These values are also small and account for the reversible process.

System		K_{eq}	Temp °C	$\Delta G°$ kJ/mol
100	187	2.5	58.5	-2.51
101	190	2.9	58.5	-2.90
189	188	5.0	58.5	-4.47
205	214	1.1	25.0	-0.32
204	212	0.9	25.0	+0.29

Table 3.10: Equilibrium Constants and Free Energy Differences of Various Dienes.

When X=Cl or Br, there is no major difference in the rates or equilibria of the reactions for different Y groups. The effect of the methoxyl group in making the secondary reactions more important was discussed before.

The effects of the (X=) acetamido group in the overall process are unique and these can be summarized as:

i) the acetanilide 113 product acts as an inhibitor and makes the reaction stereoselective

ii) hydrogen bonding in the final isomerized diene stablizes the diene 198 and speeds up the reaction (33% isomerized diene after 30 min at 35°C)

iii) the strong electron-donating power of the acetamido group facilitates the cleavage of the acetoxy group. It is possible that this stabilization is great enough to make acetoxy group cleavage competetive with that of the nitro group. This would increase the amount of acetanilide 113 formed.

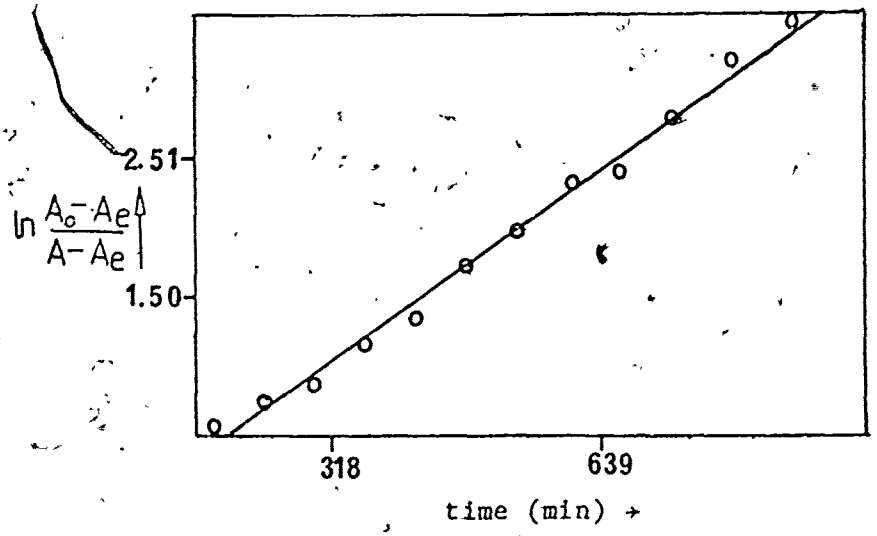
iv) the nitroacetanilide 125 presumably arises from base catalyzed elimination of acetic acid. Such elimination occurs for all 5-X-2-methyl-6-nitrocyclohexa-2,4-dienes in nucleophilic solvents. In the case of diene 103 because 103 itself contains a basic centre (-NHAc) which can catalyze the elimination.

Factors (ii)-(iv) all contribute towards the ready disappearance of the diene 103 and can explain its inherently labile nature and the difficulties experienced in attempts to isolate the diene from the nitration of p-methylacetanilide (113).

The transition state of a [1,5]-sigmatropic shift involves a planar arrangement of the five carbon atoms in the conjugated framework with the sixth sp^3 carbon (bearing Y) out of the plane. Since the starting dienes have the (Z)-configuration the substituent Y lies on the same side of the plane as the nitro group and does not influence the nature of the process. When Y=OAc, the isomerization process involves both sigmatropic and radical process, but when Y=OH the latter process is less important as the resultant cresol acts as an inhibitor.

The rate of sigmatropic shift for the diene 204 was determined at ambient temperature and the plot for the first order reversible rate equation is shown in fig 3.19. The rate constant for the forward reaction (2.1×10^{-3} min^{-1}) is comparable to that of diene 100 at 58.5°C, which suggests that when Y=OH the sigmatropic shift is more facile than when Y=OAc, as would be expected due to

smaller bulk of OH and possible attractive interaction with the nitro group via hydrogen bonding.



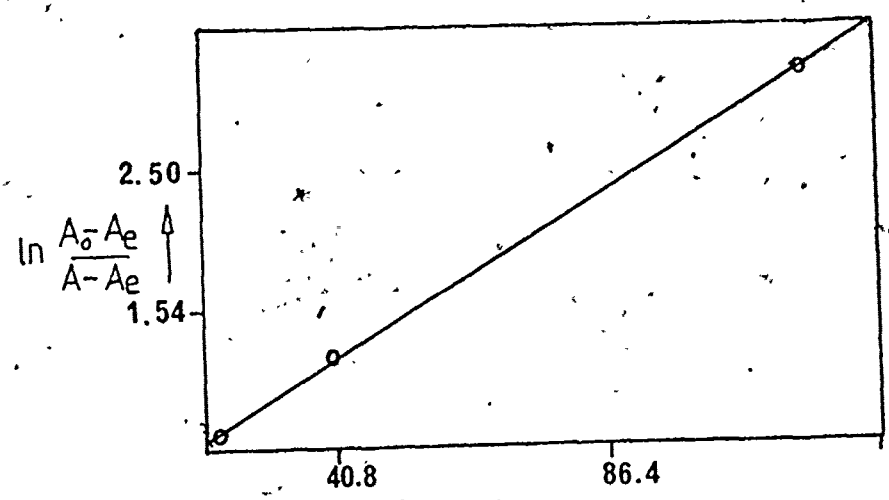
Slope = 4.5×10^{-3}; Correlation coefficient = 0.99;

$K_{eq} = k_1/k_{-1} = 0.9$; $k_{-1} = 2.4 \times 10^{-3}$ min^{-1}; $k_1 = 2.1 \times 10^{-3}$ min^{-1}.

Figure 3.19: Plot of $\ln(A_0-A_e)/(A-A_e)$ vs. time (min) for the isomerization of diene 204 at ambient temperature.

When Y=OMe or Cl the former process (sigmatropic shift) is less important, possibly due to retarding stereoelectronic interactions in the transition state as mentioned before. It is difficult to explain why such retarding effects are important when Y=OMe but not when Y=OAc.

In the E-diastereomers the substituent Y lies on the opposite side of the migrating nitro group. Thus Y has no retarding effect of the sigmatropic shift and the rate is faster than the (Z)-diastereomers. The rate constant for the sigmatropic shift of diene 189 to 188 in the presence of p-cresol at 58.5°C is greater than that of the (Z)-diastereomer by a factor of 8. The relevant plot is shown in figure 3.20.



Slope = 2.46×10^{-3} min^{-1}; Correl. coeff. = 0.99;

K_{eq}^{-1} =5.05; $k_1 = 4.06 \times 10^{-3}$ min^{-1}; $k_{-1} = 20.5 \times 10^{-3}$ min^{-1}.

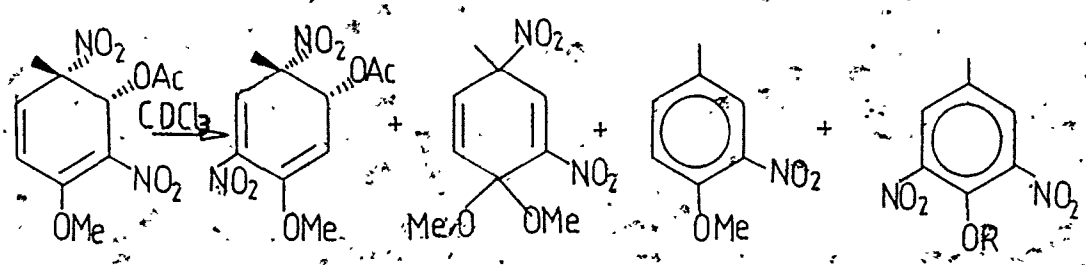
Figure 3.20: Plot of ln $(A_\infty - A_e)/(A - A_e)$ vs. time (min) for the isomerization of diene 188 to 189 in the presence of p-cresol at 58.5°C.

3.4 Thermal reactions of dienes from 2-X-4-methylanisoles

The diene 130 from the chloroanisole 115 aromatized over a period of 70 days in chloroform-d to the nitrocresol 137 at ambient temperature. The ^{1}H-NMR spectra of the reaction mixture at intermediate stages indicated the formation of the dimethyl ketal 135. The rate of decomposition of the diene increased on increasing the temperature to 60°C and after 12h a mixture of cresol 137 (80%) and anisole 136 (20%) was obtained.

At ambient temperature the diene 151 in chloroform-d after 32 days gave a mixture of diene 154 (18.5%), dimethyl ketal 156 (5.5%), together with aromatic compounds 116, 155 and 231 (35%).(scheme 3.19). After 80 days the ^{1}H-NMR spectrum of the mixture indicated that aromatics were the major proportion of the product but dienes 151 (4.5%), 154 (5.5%) and 156 (9%) were still present. When the reaction was repeated at 60°C a mixture

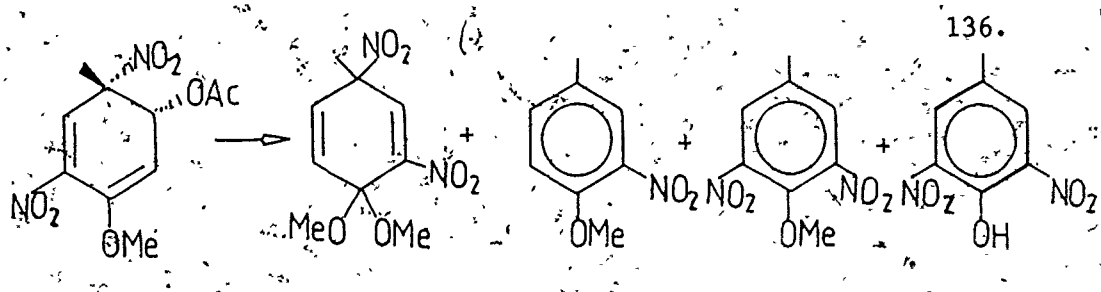
containing diene 154 (26%), anisoles 116 (18%) and 155 (8%) together with unchanged diene 151 (48%) was obtained after 24h. On further heating the extent of aromatization increased but the ratio of dienes 151 and 154 remained unchanged.



	151	154	156	116	R=Me,155	R=H,231
ambient temp						
32 days	18.5%	5.5%		5%	12%	18%
80 days	5.5%	9%		12%	29%	39%
60°C, 24h	26%			18%	8%	

Scheme 3.19

The diene 154 in chloroform-d at ambient temperature yielded a mixture of cresol 231 (22%), anisoles 155 (35%) and 119 (28%), dimethyl ketal 156 (1.%) along with unchanged diene 154 (14%) after 80 days. At 60°C after 17h a similar mixture of products was obtained, as shown in scheme 3.20.



	151	156	119	155	231
22 C	14%	80 days 1 %	28%	35%	22%
60 C	50%	17 h 14%	0	15%	22%

Scheme 3.20

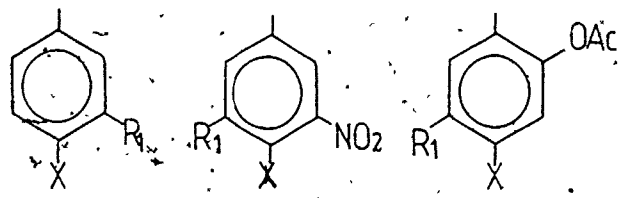
Dienes from a [1,5]-nitro shift are not observed in the products of the reactions of these compounds, but the 6-nitroanisole derivatives obtained are likely to have been formed via aromatization of such undetected intermediate dienes. The additional heteroatom substituent will make the proton α to the nitro group more acidic and thus facilitate the elimination of acetic acid from the proposed 5-methoxy-4-X-2-methyl-6--nitrocyclohexa-2,4-dienyl acetate intermediate.

In diene 151 the stereoelectronic repulsion introduced by placing the nitro group of C-2 (between acetate and methoxy) is relieved by isomerization to the other regioisomer, diene 154. The [1,5] shift of the acetate group can proceed via a direct [3,5]-sigmatropic shift or by dissociation and recombination of acetate (probably acid catalyzed by traces of acetic acid also liberated). The cyclohexadienyl cation, from the loss of acetate group, can be trapped by nucleophiles (such as trace water) which would account for the nitro cresols (formed via a dienone intermediate). This behaviour resembles that of diene 102 from

4-methylanisole (112). More information regarding the behaviour of these cations was obtained during reactions carried out in presence of acids and is discussed in chapter IV.

3.5 Aromatization of Dienes at Pyrolytic Conditions (150°C).

Under pyrolytic conditions (150°C) all dienes obtained from nitration decomposed instantaneously with the evolution of brown fumes to yield the parent toluene derivatives by elimination of acetyl nitrate as well as the 3-nitrotoluenes and cresyl acetates. The products obtained are shown in table 3.11.



Compound	R_1	X			
100	H	Cl	111 (31%)	122 (3%)	186 (66%)
101	H	Br	110 (20%)	124 (tr)	193 (80%)
102	H	OMe	112 (80%)	116 (5%)	197 (15%)
130	Cl	OMe	115 (20%)	136 (67%)	232 (16%)
154	NO_2	OMe	116 (27%)	155 (73%)	
151	NO_2	OMe	116 (34%)	155 (66%)	

Table 3.11: Products (percentages) obtained from the pyrolysis of dienes.

The formation of nitrotoluenes was regiospecific in all of these dienes. Renitration of the starting 4-chloro or 4-bromotoluene should yield some 4-X-2-nitrotoluene, but this is not formed. Isomerization to the 6-nitro diene followed by loss of

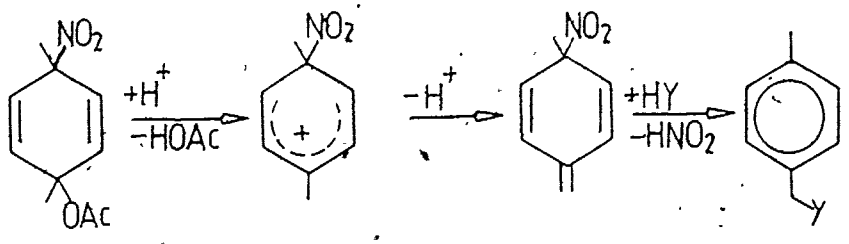
acetic acid could account for such regioselectivity. In order to test this hypothesis the isomerized dienes 187 and 188 were heated to 180°C but the cresyl acetate 186 was the major product in both cases. A radical dissociation-recombination mechanism as shown in scheme 3.1 could account for the regiospecificity.

CHAPTER IV: ACID CATALYZED REACTIONS OF IPSO ADDUCTS.

4.1 Introduction:

Ipso-Wheland intermediates (nitrocyclohexdienyl cations) can be regenerated from cyclohexadienyl acetates by protonation of the acetate group followed by loss of acetic acid. The fate of this cation depends primarily on its structure and on the reaction conditions.

Substrates bearing alkyl groups located para to the ipso position can form alkenyl cyclohexadiene intermediates by loss of proton. These intermediates on solvolysis of the nitro group give rise to a benzylic cation which can be trapped to yield benzylic compounds[82] as shown in scheme 4.1.



80 80a 80b 232

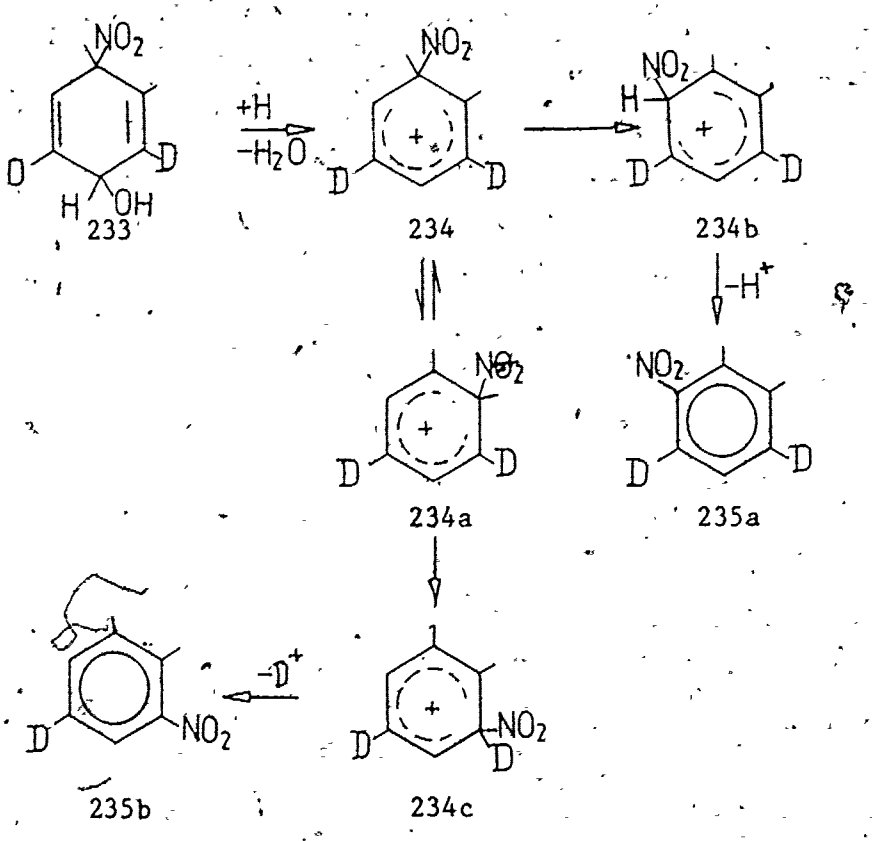
Y = OMe^-, OAc^-, ONO_2^-, NO_2^-, etc

Scheme 4.1

These reactions explain the apparent anomalous nitrations in which side chain substitution occurs as was shown in scheme 1.20. Formation of the ipso cation from the nitrocyclohexdienyl acetate can be used to investigate the reactions of such species.

Under non-nucleophilic conditions migration of the nitro group by a concerted 1,2-shift followed by deprotonation to yield

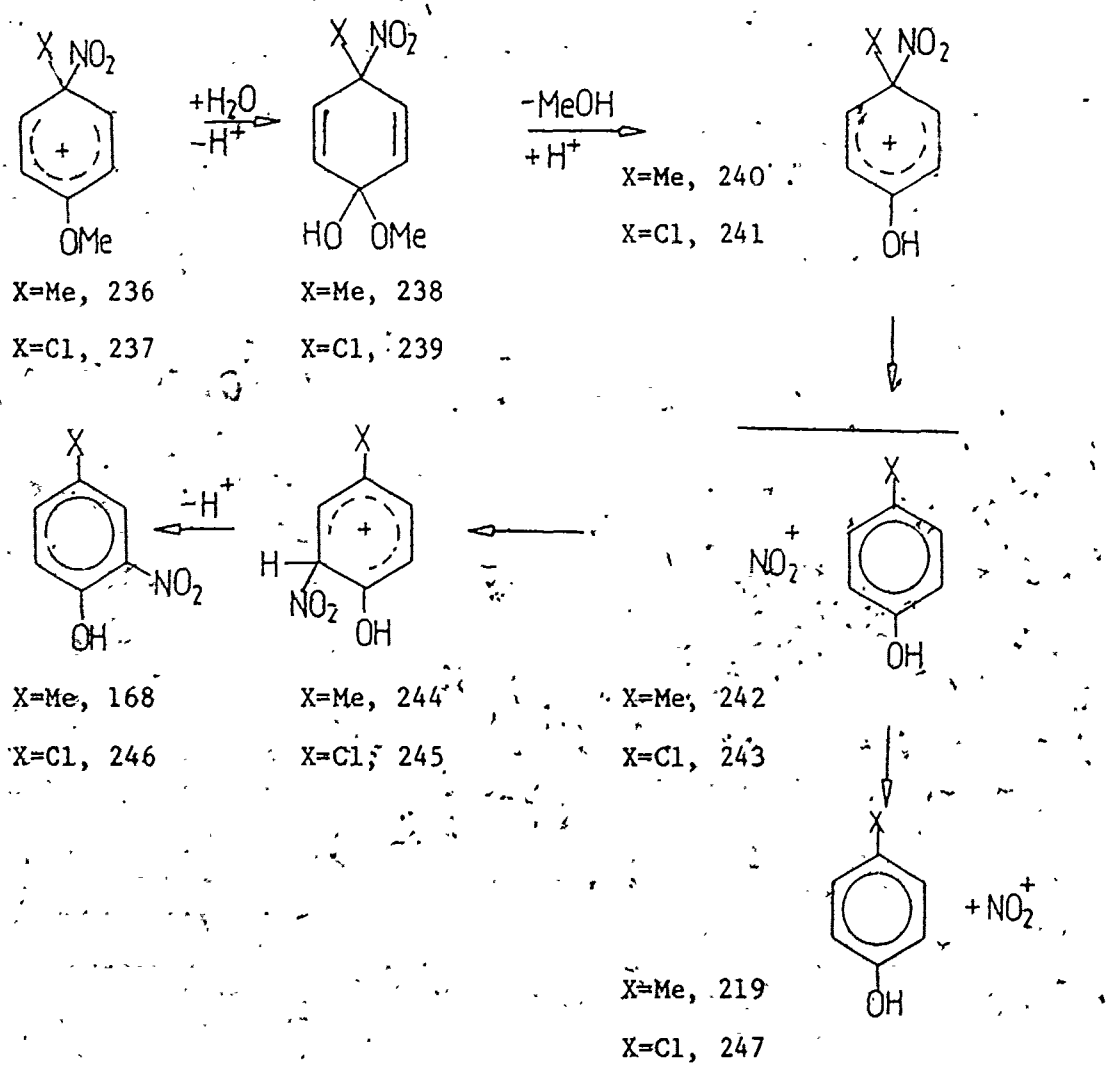
nitroarenes has been identified as the predominant mode of reaction (scheme 4.2). When the ortho position is substituted a second nitro shift follows. The rate of migration to a methyl substituted position has been shown by Myhre[129] to be fifty times faster than to an unsubstituted position. Consequently such cations are well equilibrated prior to proton loss. These two sequential 1,2-shifts (scheme 4.2) of the nitro group thus represent an overall 1,3-nitro shift.



Scheme 4.2

It is necessary to distinguish the 1,2-shift process from extramolecular migration[130] which occurs via the encounter pair, as shown in scheme 4.3. In substrates where the ipso-position is activated by strong electron donating groups such as OH and OCH_3, the

nitrocyclohexadienyl cation can lose nitronium ion to form an encounter pair. The fate of the encounter pair is determined by the reactivity of the substrate. For reactive substrates which react at the encounter rate the encounter pair collapses to an isomeric Wheland intermediate via attack by the nitronium ion at a second activated position (ortho or para to OH) and which is deprotonated to a nitro arene. When the substrates are less reactive the nitro group can diffuse out of the solvent cage resulting in denitration (scheme 4.3).

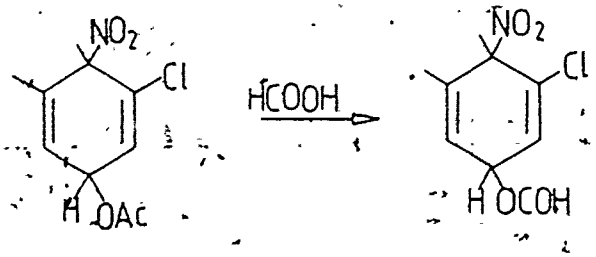


Scheme 4.3

Coombes and his coworkers[114] have shown that in the nitration

of p-cresol (219), 40% of the product 2-nitro-p-cresol (168) is formed via extramolecular migration of the nitro group in the intermediate dienone. In the case of the nitration of 4-chloroanisole (237) the intermediate dienone gives 4-chlorophenol (247) by leakage of the nitro group from the encounter pair. The presence of chlorine deactivates the substrate and it does not react at the encounter rate, thus the leakage is pronounced and detectable. The dienone intermediate is formed as a result of the presence of water in the reaction mixture but its formation is not a necessary criterion for extramolecular migration. In the absence of water it can be expected that the Wheland intermediate 240/241 can directly collapse to the encounter pair 242/243 and the nitronium ion can then either renitrate 219/247 or escape to the bulk solvent.

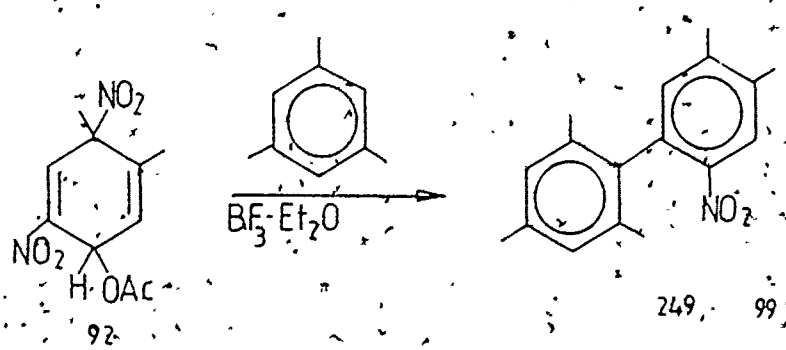
Reaction with ^{18}O-enriched water has shown that dienone formation involves attack of the nucleophile on the ring rather than S_N2 displacement of the methyl group[74]. In principle this resembles the 1,4-addition of nitronium acetate in the nucleophilic trapping of the ipso-Wheland intermediate. Using this sequence (regeneration of the ipso cation followed by nucloephilic trapping) it is possible to synthesize nitrocyclohexadienyl derivatives by exchanging the acetate for other groups, as shown in scheme 4.4.



94 248

Scheme 4.4 Ref 87b

In order to exploit this route to other cyclohexadienes it is necessary to determine the conditions under which complications due to competing reactions are at a minimum. Weak nucleophiles can be trapped by generating very reactive cations. The ipso-adducts 92 and 93 from nitroxylenes[65] were shown to be effective in alkylating mesitylene to yield biphenyl derivatives (e.g. 249 from 92, scheme 4.5) after aromatization of the intermediate adducts via the loss of nitrous acid:

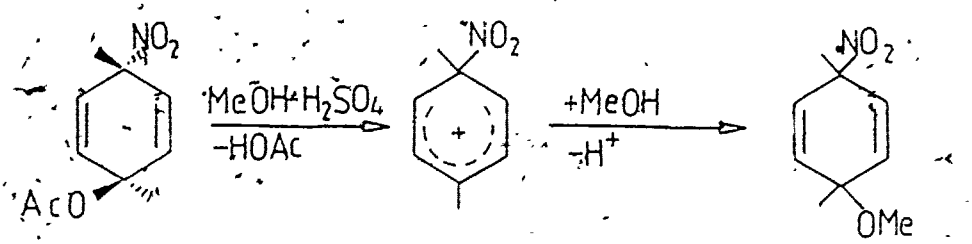


92 249, 99%

Scheme 4.5 Ref 65

The presence of the nitro group is responsible for such reactivity. In some cases the presence of strongly deactivating substituents can lead to modifications in the reactivity of the acetate

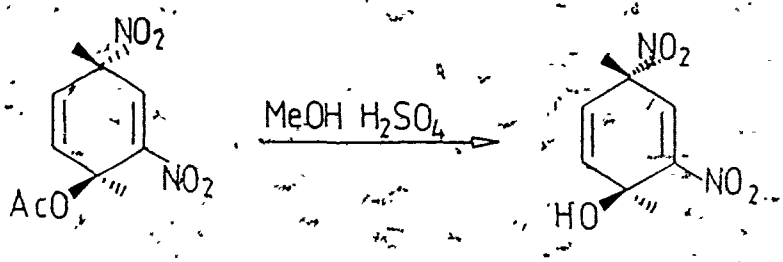
group. Acid catalyzed ester hydrolysis usually take place via $A_{AL}1$ or $A_{AC}2$ mechanisms. With decreasing acidity and increasing nucleophilicity of the solvent the $A_{AC}2$ mechanism becomes important. The generation of the nitrocyclohexadienyl cation from the acetate is, on the other hand, an example of the $A_{AL}1$ process. Under identical conditions (acidity and solvent nucleophilicity) the $A_{AL}1$ mechanism favours alkyl groups which form stable cations. Thus, for **ipso**-adducts with deactivating substituents the $A_{AC}2$ mechanism should become more important in nucleophilic solvents and at lower acidities. For example the **ipso**-adduct E-76 from p-xylene reacts in methanolic sulphuric acid to yield a diastereomeric pair of methyl ethers (E)- and (Z)-250, by an $A_{AL}1$ mechanism (Scheme 4.6).



E-76 76a E- and Z-250

Scheme 4.6 Ref 82

Under similar conditions the **ipso** adduct 251 from 2-nitro-p-xylene (253) gave a single diastereomer of the dienol 252 via an $A_{Ac}2$ mechanism (scheme 4.7). The presence of the nitro group on the ring destablizes the transition state leading to the cyclohexadienyl cation and favours the $A_{Ac}2$ mechanism.



E-251 E-252

Scheme 4.7 Ref 65

The importance of reactions proceeding via the cyclohexadienyl cation formed by loss of nitrite anion also increases with increasing solvent nucleophilicity and reduced acidity. These reactions are discussed in the following chapter (V).

The cyclohexa-2,4-dienyl acetates formed in the ipso-nitration of toluene derivatives 100-116 are expected to show a wide range of reactivity due to the different substituents present. A study of reactions at different acidities and in different solvents will reveal the pertinent role of substituents in controlling the reactivity of secondary cyclohexadienyl acetates.

The factors governing the unique regioselectivity and stereoselectivity observed in the formation of adducts can be exploited to synthesize other cyclohexadienyl derivatives with similar selectivities.

The isomerized dienes obtained from thermal reactions are amongst the few known cyclohexadienes bearing secondary nitro and acetoxy groups and reactions on these adducts will reveal their possible role in the overall nitration reaction.

4.2 Results and Discussion:

The results of the acid catalyzed reactions of the ipso adducts are discussed below, following which a general mechanistic

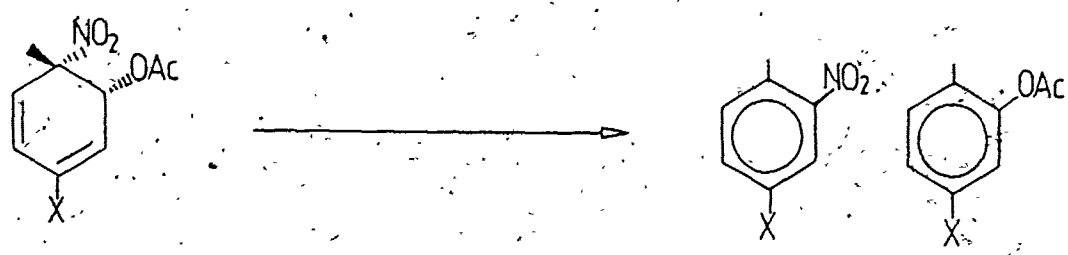
scheme is presented which provides an interpretation of the various factors governing the reactivity of these compounds.

4.2.1 Reactions of 3-X-6-methyl-6-nitrocyclohexa-2,4-dienyl acetates

Dienes 100 and 101 aromatized instantaneously to the corresponding 4-X-2-nitrotoluenes 121 and 123 in the presence of strong protic and Lewis acids. In the presence of weaker acids (CF_3CO_2H), in non-nucleophilic solvents ($CDCl_3$, CD_2Cl_2), mixtures containing 121/123 and the 5-X-o-cresyl acetates 186/193 were obtained. The amount of the acetate increased and a longer reaction time was needed on decreasing the acid concentration. With increase in reaction time some 5-Br-4-nitro-o-cresyl acetate 254 was obtained from the nitration of the cresyl acetate 193.

Reactions of dienes 100 and 101 with trifluoroacetic acid in methanol-d_4 (a nucleophilic solvent) required longer time periods than reactions carried out in non-nucleophilic solvents. The amount of 4-X-2-nitrotoluenes decreased and that of 4-X-3-nitrotoluenes increased as the acidity was reduced and the reaction time extended. The cresol was formed by trans-esterification of the acetate function and thus the ratio of cresol to acetate increased at lower acidities and consequently longer reaction times.

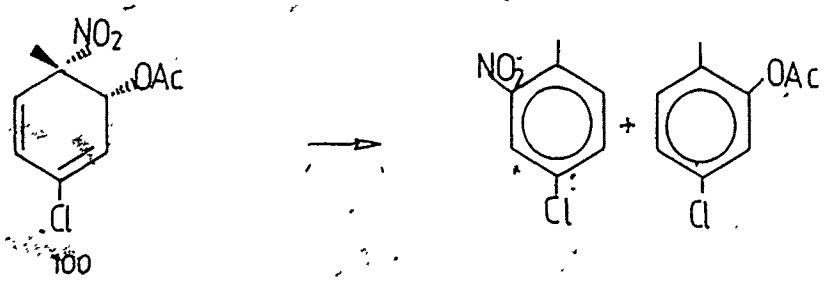
Examples of these reactions are summarized in schemes 4.8 to 4.12.



X=Cl, 100		121	186
	CF_3SO_3H (0°C)	100%	-
	CH_3SO_3H (-20°C)	100%	-
	BF_3(gas)/CD_2Cl_2(-78°C)	100%	-
	CF_3CO_2H (-30°C)	80%	20%
X=Br, 101		123	193
	CF_3SO_3H (0°C)	100%	-
	CH_3SO_3H (0°C)	100%	-
	CH_3SO_3H/CH_2Cl_2	~100%	-
	BF_3(gas)/CD_2Cl_2 (-78°C → ambient, 60min)	75%	25%
	$BF_3.Et_2O$ (-78°C → ambient, 60min)	76%	24%
	$BF_3.Et_2O/CD_2Cl_2$(1:1) (-78°C → ambient, 60min)	76%	24%
	CF_3CO_2H (0°C)	48%	52%

(Examples of Reactions of dienes 100 and 101 in strong acids.)

Scheme 4.8

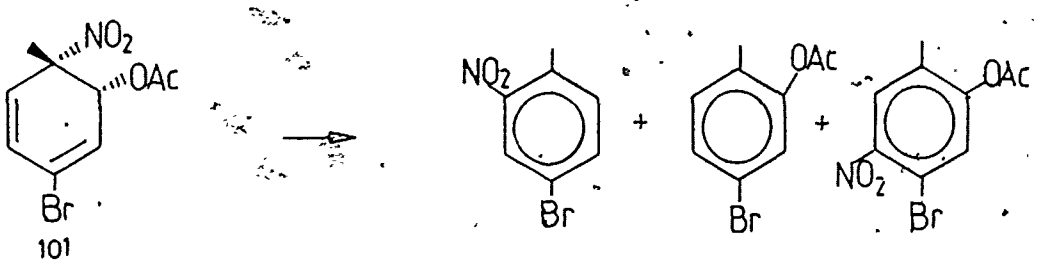


100

Volume of $CDCl_3$:	TFA	$\tau_{1/2}$	121	186
1 :	3	42 min	83%	17%
1 :	1	2.5h	74%	26%
3 :	1	9h	50%	50%
19 :	1	24h	32%	68%

(Reactions of diene 100 with trifluoroacetic acid in chloroform-d)

Scheme 4.9:



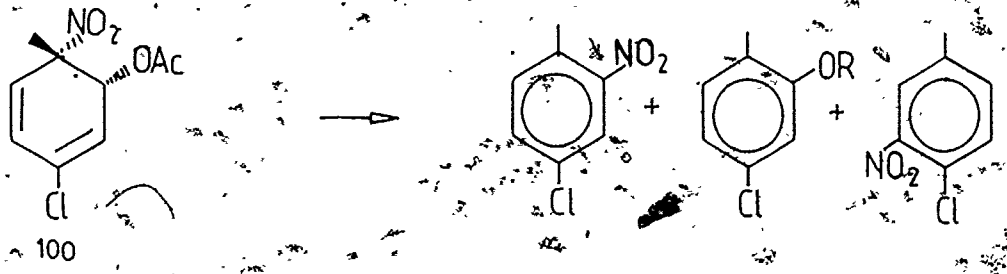
101

Volume of TFA :	$CDCl_3$	time	123	193	254
$^a3$:	1	40min	63%	37%	–
$^b1$:	1	12min	41%	59%	–
$^b1$:	3	30min	22%	70%	8%
$^b1$:	19	>5h	14%	73%	13%

(Reactions of diene 101 with trifluoroacetic acid in chloroform-d)

a: total reaction time ;
b = $T_{1/2}$;

Scheme 4.10

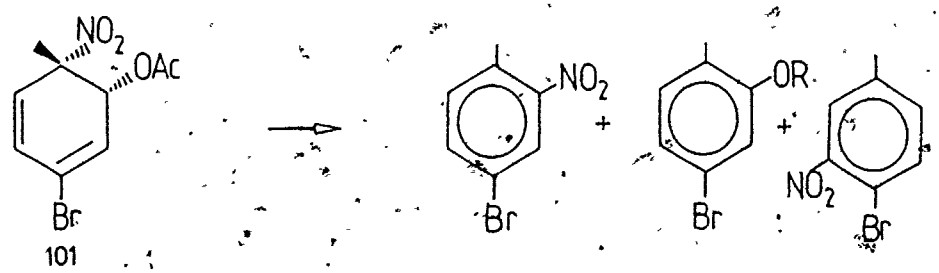


100

Volume of				R=Ac		R=H	
CD_3OD	:	TFA	Time	121	186	213	122
1	:	4	60h	30%	47%	23%	–
1	:	1	17 days	–	9%	72%	19%
9	:	1	32 days	–	–	59%	41%

(Reactions of diene 100 in trifluoroacetic acid and methanol-d_4)

Scheme 4.11



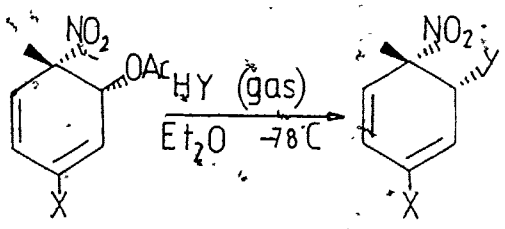
101

Volume of				R=Ac		R=H	
CD_3OD	:	TFA	Time (days)	123	193	215	124
1	:	3	3	40%	50%	–	10%
1	:	1	20	–	–	67%	33%
3	:	1	30	–	–	65%	35%

(Reactions of diene 101 in trifluoroacetic acid and methanol-d_4)

Scheme 4.12

The ^{1}H-NMR spectrum of the reaction mixture obtained by bubbling anhydrous hydrogen chloride gas for 15 min through a solution of diene 100 in ether at -78°C indicated the presence of a new diene. After low temperature work up with aqueous ammonium hydroxide, the mixture contained more than 90% of the new diene 3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl chloride (201) along with 2,4-dichlorotoluene (209) from which the diene 201 was separated by crystallization. Similar reaction of diene 100 with anhydrous hydrogen bromide gas gave 3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl bromide (225) in 76.5% yield. From diene 101 it was possible to prepare 3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl chloride 200, (82%) and bromide 255, (90%) by similar reactions, as shown in scheme 4.13.



100	X=Cl,	Y=Cl:	201	yield ~ 90%
100	X=Cl,	Y=Br:	225	yield ~ 76.5%
101	X=Br,	Y=Cl:	200	yield ~ 82%
101	X=Br,	Y=Br:	255	yield ~ 90%

(Reactions of dienes 100 and 101 with hydrogen halides.)

Scheme 4.13

The elemental analysis of diene 201 indicated the molecular formula was $C_7H_7Cl_2NO_2$. There were no peaks due to an acetate group in the IR, ^{1}H-NMR and ^{13}C-NMR spectra, but the peaks due to the nitro group were present in the IR and the UV spectrum indicated the presence

of conjugated diene system. The diene 201 was assigned the structure 3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl chloride on the basis of the similarity of the ^{1}H-NMR and ^{13}C-NMR spectra of diene 201 with that of diene 100. The major differences in the spectra of 100 and 201 were in the chemical shifts of C-1 (^{13}C-NMR) and 1-H (^{1}H-NMR), both of which were shifted upfield in the case of 201.

The structures of dienes 200, 226 and 255 were established from the spectral properties which were similar to the diene 201. As in the nitration reaction, only a single diastereomer of these dienes was obtained. The splitting patterns of the ring protons were similar to those of dienes 100 and 101 in that $J_{1,6}$ was present, indicating that 1-H was in the pseudo-equatorial position and thus that the halogen substituent was in the pseudo-axial position. (The NMR spectral data of dienes 200 and 201 were listed in Chapter III from which was apparent that they have the (Z)-configuration). The dienes 225 and 255 were also the (Z)-configuration. The stereochemistry of diene 200 was confirmed by single crystal X-ray diffraction studies. The molecular structure of diene 200 is shown in figure 4.1 and the relevant bond lengths and bond angles are given in tables 4.1 and 4.2.

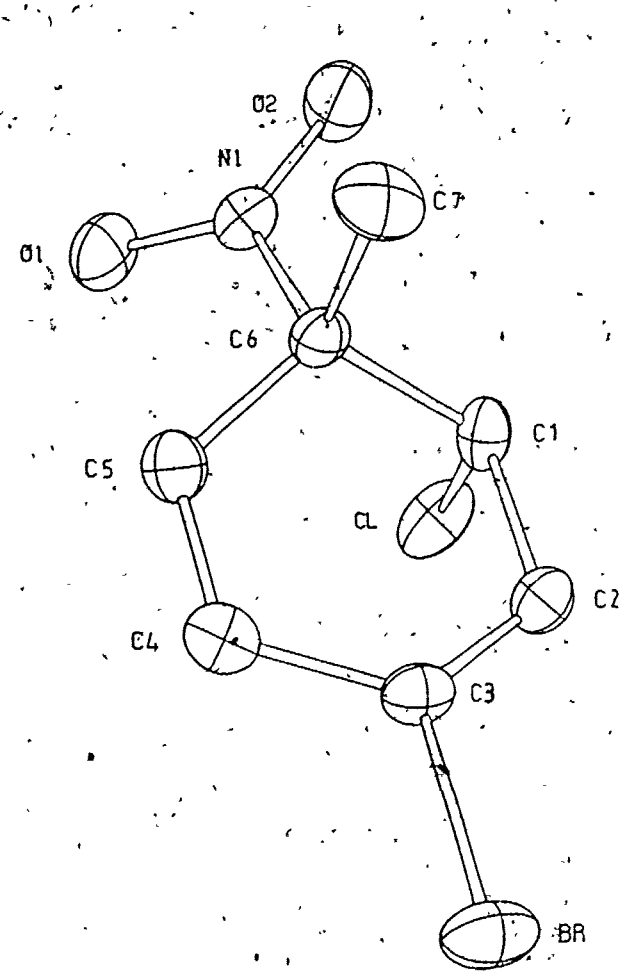


Figure 4.1: Molecular Structure of (Z)-3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl chloride (200).

TABLE 4.1

Interatomic Distances for diene 200.

Atoms	Distance	Atoms	Distance.
C(3) -Br	1.947(8)	C(1) -Cl	1.828(9)
O(1) -N(1)	1.207(10)	O(2) -N(1)	1.207(10)
C(6) -N(1)	1.540(11)	C(7) -C(6)	1.530(13)
C(3) -C(2)	1.325(13)	C(5) -C(4)	1.344(14)
C(1) -C(6)	1.517(12)	C(6) -C(5)	1.480(13)
C(4) -C(3)	1.457(13)	C(1) -C(6)	1.527(12)

Estimated standard deviations are given in parentheses.

TABLE 4.2

Bond Angles (°) for diene 200

Atoms	Angle	Atoms	Angle
O(2) -N(1) -O(1)	123.5(8)	C(5) -C(6) -N(1)	109.7(7)
C(6) -N(1) -O(1)	118.4(7)	C(1) -C(6) -N(1)	106.4(7)
C(6) -N(1) -O(2)	118.1(7)	C(1) -C(6) -C(5)	114.3(7)
C(1) -C(2) -C(3)	118.5(8)	C(7) -C(6) -N(1)	107.5(7)
C(2) -C(3) -Br	118.8(7)	C(7) -C(6) -C(5)	109.3(8)
C(4) -C(3) -Br	117.2(7)	C(7) -C(6) -C(1)	109.3(8)
C(4) -C(3) -C(2)	123.8(8)	C(2) -C(1) -Cl	105.9(7)
C(5) -C(4) -C(3)	119.2(8)	C(6) -C(1) -Cl	111.7(6)
C(6) -C(5) -C(4)	119.2(8)	C(6) -C(1) -C(2)	111.1(7)

Estimated standard deviations are given in parentheses.

The observed stereoselectivity involving retention of configuration in the substitution of acetate by halides is remarkable and this facet of the reaction is discussed in chapter V. The reaction of diene 100 with concentrated hydrochloric acid (6N) in ether at -40°C failed to produce any diene 201 but similar reaction in acetic anhydride at ambient temperature for 4 hours gave 48% of diene 201 along with 121.

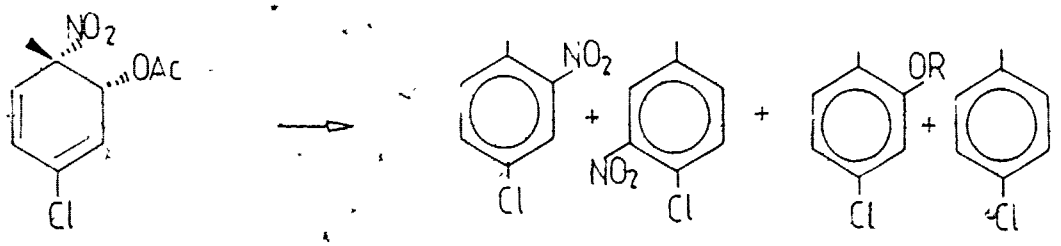
The ^{1}H-NMR spectrum of a reaction mixture containing diene 100 in methanol-d_4 and sulfuric acid (25%, w/w) indicated the formation of an intermediate dienol 204 along with cresol 213. With increase in temperature the diene 100 disappeared at a faster rate and the cresol formation was also increased. Increase in reaction time at lower temperature also resulted in formation of cresol as the predominant product.

Dienol 204 was prepared by stirring diene 100 with a mixture of methanolic sulfuric acid (25%, w/w) at 0°C for eight hours, followed by further storage at -20°C for 12 hours. Under these conditions diene 100 reacted completely and aromatization was at a minimum. After concentration of the reaction mixture on the rotovapour at -40°C, the reaction was worked up with ammonium hydroxide at low temperature to yield a mixture of 60% cresol 213 and 40% dienol 204. The mixture was separated by chromatography on alumina at -78°C and the pure dienol 204 was characterized at low temperature.

Similar reaction of diene 101 gave a mixture containing 77% of a similar dienol 205 along with 23% of cresol 215. This dienol 205 was also obtained pure after chromatography. Some 3-nitrotoluene 124 was isolated during chromatography which was formed by decomposition of the rearranged dienol 214 prior to chromatography.

The ^{1}H and ^{13}C spectra of both dienols 204 and 205 were

similar to those of the corresponding acetates and the differences in chemical shifts could be easily explained on the basis of replacement of acetate by the hydroxyl group. A single diastereomer was obtained in both reactions, as would be expected from an $A_{AC}2$ mechanism leading to retention of configuration. The coupling constants in the ^{1}H-NMR spectrum were also indicative of the (Z)-configuration. The reaction of diene 100 with sulfuric acid in acetone or acetic anhydride yielded complicated product mixtures which are shown in scheme 4.14. Isomerized diene intermediates 187 and 188 were detected in the ^{1}H-NMR spectra of the reaction mixture (reaction b, scheme 4.14).



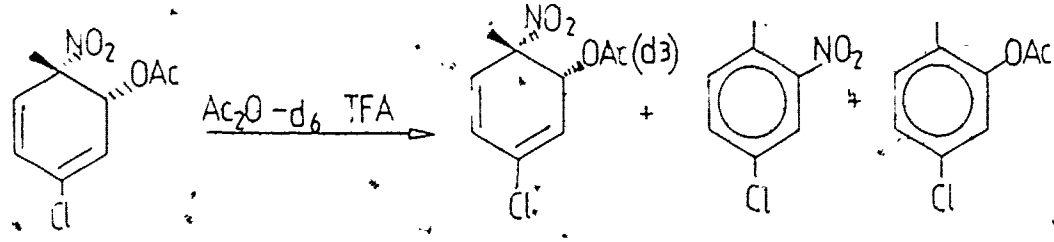
	H_2SO_4	Ac_2O	Time	121	122	186 & 213	11
a)	1	9	-20°C,20min	82%	-	18%	-
b)	0.1	100	22°C,90days	33%	28%	34%	5%
	H_2SO_4	Acetone					
c)	1	9	20min	-	7%	7%	86%

(Reactions of diene 100 with sulfuric acid in acetic anhydride and acetone)

Scheme 4.14

No change occurred in the ^{1}H-NMR spectrum of diene 100 in acetic anhydride containing trifluoroacetic acid (30%, v/v) over 15min at 0°C. On warming the reacting mixture to 22°C, the diene slowly aromatized with a half life of 16 min to a mixture of 121 and 186. Reaction was also carried out in acetic anhydride-d_6 containing trifluoroacetic acid (10%, v/v), and the change in the ^{1}H-NMR spectrum of the methyl region was followed to monitor the course of reaction.

After 4h at -20°C, no change in spectrum was detected. On warming up the reaction mixture to ambient temperature, slow aromatization was detected along with a decrease in intensity of acetate-methyl peak in comparison with the ring methyl which indicated that an exchange of the acetate group with the deuterated solvent counterpart was taking place. The extent of the change taking place with time could be measured from the integration and is given in scheme 4.15.

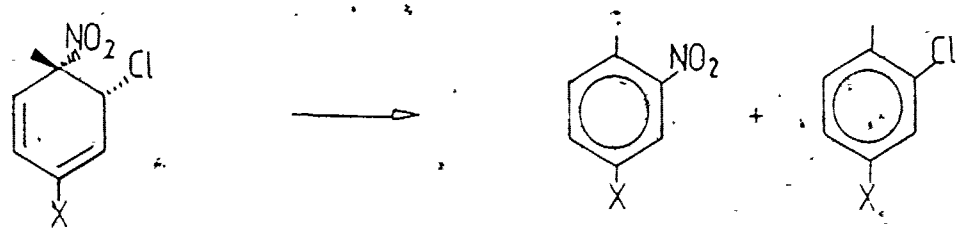


Time	100	100a	121	186
14h	58%	14%	15%	13%
38h	32%	20%	28%	20%
62h	9%	30%	35%	26%
7day (post work-up)		-	53%	47%

(Equilibration and aromatization of diene 100 in acetic anhydride-d_6 and TFA (10%v/v)).

Scheme 4.15

The dienes 200 and 201 aromatized to mixtures of 4-X-2-nitrotoluenes 123 and 121 and dihalotoluenes 207 and 209 in neat trifluoromethanesulfonic acid, and trifluoroacetic acid and in mixtures of equal volumes of chloroform-d and trifluoroacetic acid. The composition of the product mixtures are given in scheme 4.16.



201	X=Cl	CF_3SO_3H, 0°C	121	64%	209	36%
201	X=Cl	CF_3CO_2H, 0°C	121	63%	209	37%
200	X=Br	CF_3SO_3H, 0°C	123	63%	207	37%
200	X=Br	CF_3CO_2H-$CDCl_3$ 1 : 3 (v/v)	123	65%	207	35%

(Reactions of dienes 200 and 201 in strong acids).

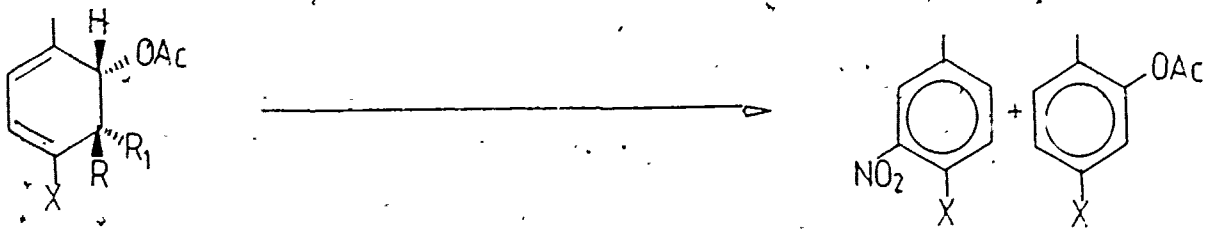
Scheme 4.16

The reaction of diene 201 in a mixture of methanol-d_4 and sulfuric acid at ambient temperature yielded a mixture of 61% 5-chloro-2-methylanisole (256), 26% of nitrocresol 168, 7% 3-nitrotoluene (122) and 6% 2,4-dichlorotoluene (209). The ^{1}H-NMR spectrum of the reaction mixture indicated the formation of an intermediate diene which had a sharp singlet at 1.73ppm and a doublet of doublet at 4.13ppm. The high field proton integrated as three protons when compared to the latter peak as a single proton. No information regarding peaks below 5.4ppm was discernable due to the strong resonance peak of the solvent hydroxyl group. This compound was assigned the structure of 3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl methyl ether 202 by comparison with the ^{1}H-NMR spectrum of the pure ether isolated later on (chapter V). After 3 days at ambient temperature, the mixture contained 3% of 122, 17% of nitrocresol 168, 5% of 209, 27% of 256, 9% of the diene 202 along with 39% unreacted diene 201. The later spectra indicated the amount of the dienes decreased with time, and aromatization increased.

Similar reaction of diene 201 in a mixture containing equal proportions of methanol and trifluoroacetic acid gave 2% of 122, 23% of nitrocresol 168, 20% of 256, 26% of diene 202 and 30% of unreacted diene 201 after 2 days at ambient temperature. The final product mixture after 12 days contained 12% 122, 6% 208, 29% of nitrocresol 168 and 53% of anisole 256.

4.2.2: Reactions of (Z)- and (E)-5-X-2-methyl-6-nitrocyclohexa-2,4-dienyl acetates:

The aromatization of dienes 188, 187, 190 and 191 in trifluoromethanesulfonic acid and in pyridine-d_5 at 0°C yielded the 4-X-3-nitrotoluenes as the only product. The reaction of dienes 186 and 187 with neat trifluoroacetic acid gave almost equal proportions of 122 and 186. In a mixture of methanol-d_4 and trifluoroacetic acid (25% v/v), the only products formed were 4-X-3-nitrotoluenes from all four dienes. In a mixture of chloroform-d and trifluoroacetic acid (25% v/v) the (Z)-diastereomers 187 and 190 gave the acetates 186 and 193 as the major product (<99%) but the (E)-diastereomers 188 and 191 yielded a higher proportion of the 4-X-3-nitrotoluenes along with the acetates as shown in scheme 4.17.



X=Cl or Br; R or R_1 = NO_2 CF_3SO_3H 100%

R_1 or R = H or pyridine-d_5

or CF_3CO_2H-CD_3OD (1:3)

Compound	X	R	R_1		$\tau_{1/2}$		
187	Cl	H	NO_2	CF_3CO_2H		46%	54%
188	Cl	NO_2	H	CF_3CO_2H		50%	50%
187	Cl	H	NO_2	$CDCl_3$-CF_3CO_2H (3:1)	3h	trace	~100%
188	Cl	NO_2	H	$CDCl_3$-CF_3CO_2H (3:1)	60h	30%	70%
190	Br	H	NO_2	$CDCl_3$-CF_3CO_2H (3:1)	~3.5h	1%	99%
191	Br	NO_2	H	$CDCl_3$-CF_3CO_2H (3:1)	~70h	44%	56%

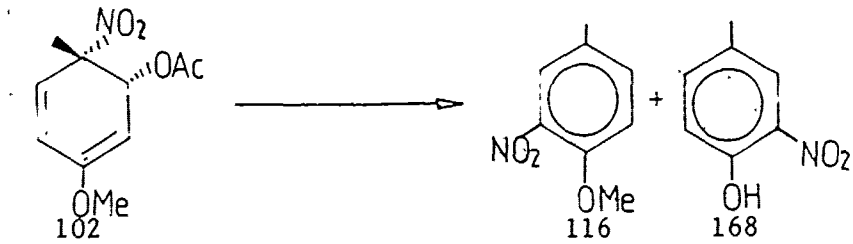
(Reactions of dienes obtained by thermal isomerization).

Scheme 4.17

4.2.3: Reactions of dienes bearing methoxy groups:

The reactions of diene 102 in acidic media proceeded at a faster rate than the reactions of dienes 100 and 101. The predominant products were the nitroanisole 116 and the corresponding cresol 168. The ^{1}H-NMR spectrum of reaction mixture at 0°C or lower temperatures indicated the presence of dienone 56 which decomposed to the nitrocresol 168 during work up at higher temperature. In some reactions the starting anisole 112 was formed. In the reaction with anhydrous hydrogen chl ide gas in ether at -78°C, 23% of p-cresol 219

was detected in the reaction mixture. The results are summarized in scheme 4.18.



	116	168	
CF_3SO_3H (0°C)	85%	15%	
CF_3SO_3H-CH_2Cl_2 (1:3, 0°C)	41%	59%	
TFA[a]	94%	6%	
TFA-$CDCl_3$[a] (1:15)	81%	9%	112, 10%
TFA-CD_3OD (1:15)[a]	-	100%[b]	
BF_3-Et_2O[a]	19%	75%	112, 6%
BF_3 gas ($CHCl_3$)[a]	85%	15%	
BF_3-Et_2O/CH_2Cl_2[a]	4%	86%	112, 10%
HCl (gas) in Et_2O	-	77%[b]	219, 23%

a) -78°C → 0°C (5 min)

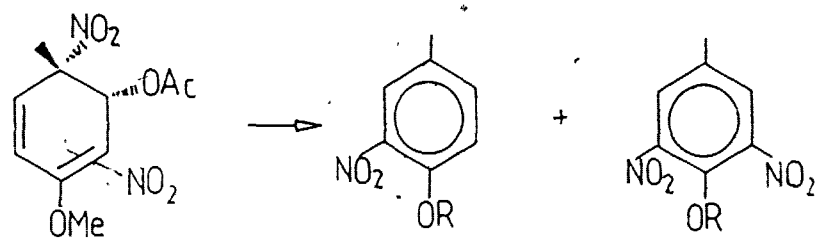
b) complete conversion to dienone 56 in the reaction mixture, detected by ^{1}H-NMR.

(Reactions of (Z)-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (102))

Scheme 4.18

The reactions of dienes 151 and 154 gave almost identical product mixtures under the same reaction conditions. The major products from these dienes were the starting anisole 116 or the corresponding phenol

168 and the 4-methyl-2,6-dinitroanisole (155) or the corresponding phenol 231. Some examples of the reactions of both dienes are summarized in scheme 4.19.



		R=Me	R=H	R=Me	R=H
		116	168	155	231
CF_3SO_3H	154/151	36%	10%	19%	35%
BF_3 (gas)	154	64%	-	36%	-
	151	60%	-	40%	-
CF_3CO_2H	154	24%	-	40%	36%
	151	25%	-	27%	48%
CF_3CO_2H-$CDCl_3$	154	26%	-	13%	61%
(1:1)	151	23%	-	16%	56%
CF_3CO_2H-CD_3OD	154	-	10%	-	90%
	151	-	27%	-	73%
H_2SO_4-CD_3OD	154	-	20%	-	80%
(1:1)	151	-	27%	-	73%

(Reactions of (Z)-2.6-dinitro and 2,4-dinitro-3-methoxy-6-methylcyclohexa-2,4-dienyl acetates (151))

Scheme 4.19

In the reaction of diene 130 with trifluoromethanesulfonic acid a mixture of 19% nitroanisole 136, 39.5% nitrocresol 137 and 41.5%

of 2-chloro-4-methyl-5-nitroanisole 257 was obtained. Reaction with boron trifluoride etherate yielded a similar mixture but the reaction with anhydrous boron trifluoride gas yielded a mixture of 85% anisole 257 and 15% cresol 137. Pure anisole 257 was obtained from this mixture by removing the cresol 137 by washing with sodium hydroxide solution. The reaction with trifluoroacetic acid and with mixtures of trifluoroacetic acid and chloroform-d yielded mixtures of 257, 136 and 137. The amount of anisole 257 decreased with decrease in acid concentration. Reaction with mixtures of trifluoroacetic acid and methanol yielded cresol 137 as the final product. The ^{1}H-NMR spectrum of the reaction mixture indicated the formation of dienone 134. In a mixture containing 75% acid at 0°C, diene 130 was completely converted to dienone 134 within the first 8 minutes, following which the dienone slowly decomposed (half life 33 min) to the cresol 137. With decreasing acid concentration the dimethyl ketal 135 was observed as a precursor to the dienone 134. A similar reaction was observed with methanolic sulfuric acid.

When anhydrous hydrogen chloride gas was bubbled through a solution of diene 130 in ether at -78°C followed by evaporation of the excess acid at 0°C, a mixture of cresol 137,(43%), 119,(6%) and two non-aromatic compounds 258 and 259, (51%) was obtained. The mixture was separated by semi-preparative high pressure liquid chromatography. The early fractions gave cresols 119 and 137. The third fraction contained a mixture of one of the non-aromatic compounds 258, (85%) and cresol 137, (15%). The other compound 259 was obtained in the later fractions along with cresol 137 (<5%). The consistent elution of cresol 137 was probably due to aromatization of 258 and 259. The compound 259 was obtained pure by crystallization but compound 258 could not be

crystallized and it was characterized as a colorless oil after two successive chromatographic separations. The ^{1}H-NMR and ^{13}C-NMR spectra of these two compounds were identical in most respects and thus the compounds were diastereomers. The elemental analysis of 259 corresponded to the formula $C_7H_7Cl_2NO_3$. The peaks due to acetate group were absent in the ^{1}H-NMR, ^{13}C-NMR and IR spectra. There was a strong absorption at 1705 cm^{-1} which indicated the presence of an α,β-unsaturated carbonyl group. The gated ^{13}C-NMR spectrum of both compounds 258 and 259 indicated the presence of sp^3 methyl, methylene, methine and qua-ternary carbons. There were also peaks due to a trisubsti tuted double bond, along with a carbonyl group at 185ppm. The chemical shift of the qua-ternary sp^3 carbon (δ_C≈90ppm) was similar to that of C-6 in diene 130. On the basis of this information, the following two regioisomers are possible:

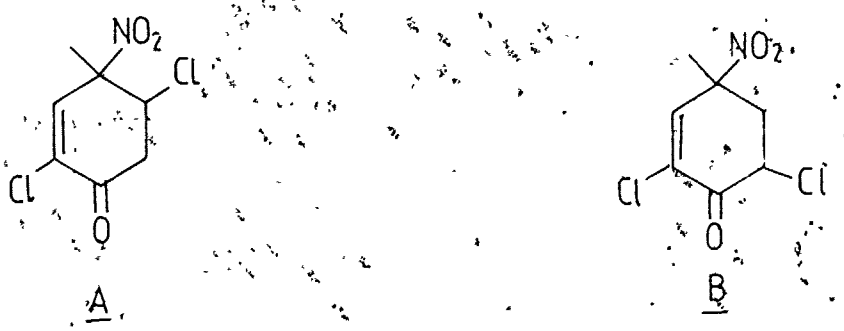
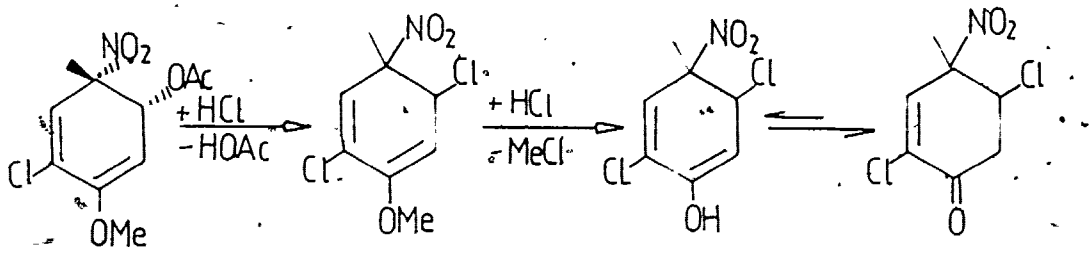


Figure 4.1

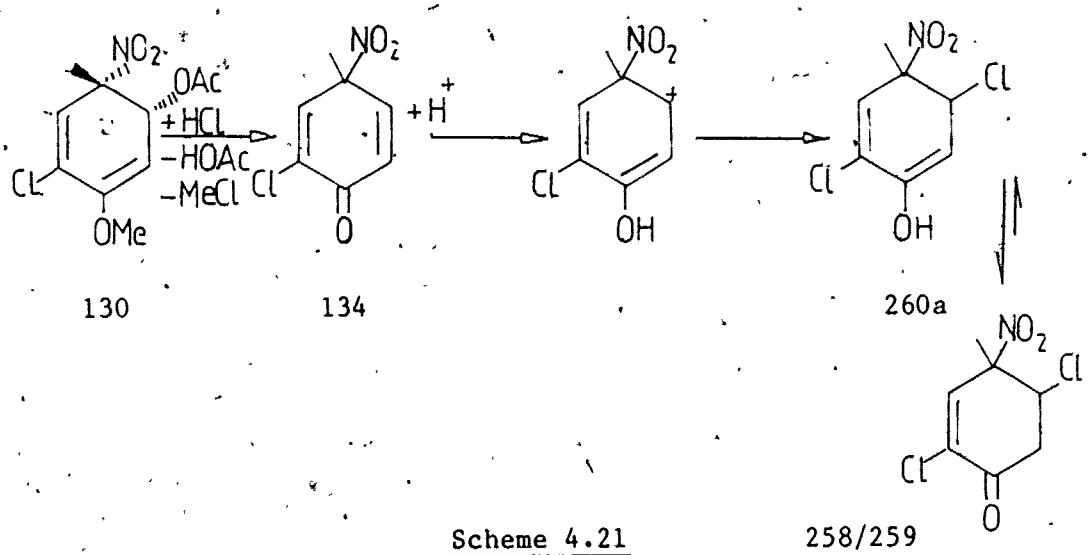
In both 258 and 259 the vinylic proton 3-H is mutually coupled to the methine proton in the same ^{1}H-NMR spectrum, but not with either of the two methylene protons. This is reminiscent of the $^{4}J_{1,5}$ coupling in the starting diene 130 and can be explained by structure A. The absence of any coupling with either of the two methylene protons is not anticipated in structure B. The formation of A can be explained by substitution of the acetoxy group by chloride anion in the starting diene followed by

hydrolysis and tautomerization of the vinyl ether as in scheme 4.20. Alternatively a 1,4-addition of HCl to the dienone 134 as in scheme 4.21 is possible.



130 260 260a 258/259

Scheme 4.20

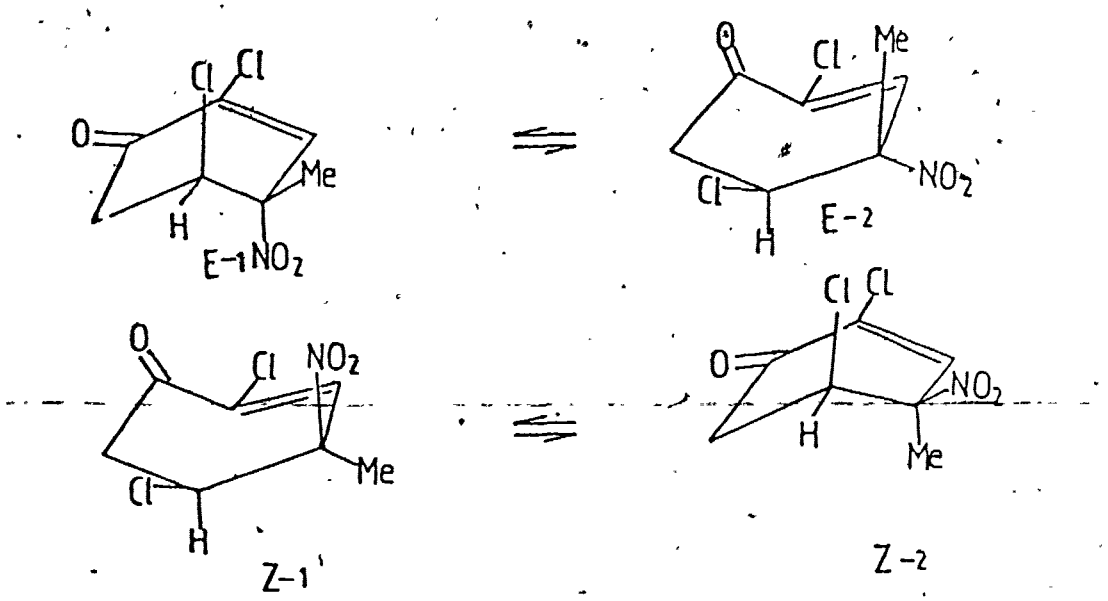


130 134 260a 258/259

Scheme 4.21

When the reaction was repeated and then worked up at -78°C, the products contained 30% dienone 134 and 70% of 259 and 258. The absence of any 260 suggests that the route depicted in scheme 4.21 is the more likely but does not allow us to reject scheme 4.20. The stereochemistry of 258 and 259 was assigned on the basis of the observed γ-gauche effect on the chemical shift of the methyl group due to the chlorine on C-5 in the ^{13}C-NMR spectrum. In either conformer (E-1 & E-2) of the (E)-diastereomer the methyl group is gauche to the chlorine whereas in the (Z)-diastereomer these are anti in the Z-Z

conformer. This conformer (Z-2) has the methyl and chloro groups in the axial and



Scheme 4.22

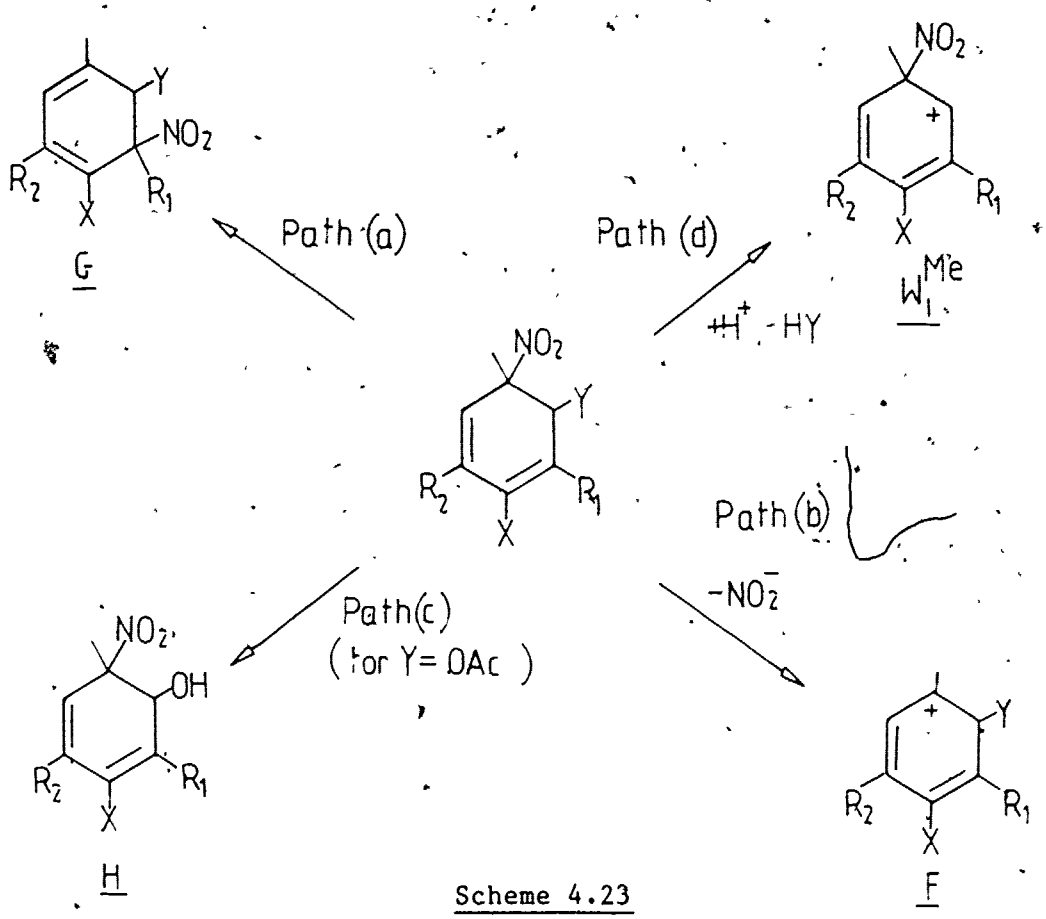
anti orientation and should be preferred over Z-1. Consequently the chemical shift of the methyl group in the (E)-diastereomer should be less than that of the (Z)-diastereomer. In compound 258 the methyl group resonates at 21.6ppm and in 259 it resonates at 24.8ppm, consequently the latter compound is assigned the (Z)-configuration.

4.3: Mechanisms of Acid Catalyzed Reactions of Dienes:

The solvolysis of diene 100 in aqueous sulfuric acid has been investigated by Schofield and his coworkers[129] and the reported results agree well with those obtained in this dissertation.

The reactions of these ipso adducts can be accounted for

by formation of four different intermediates W_1^{Me}, F, G and H as shown in scheme 4.23:



Scheme 4.23

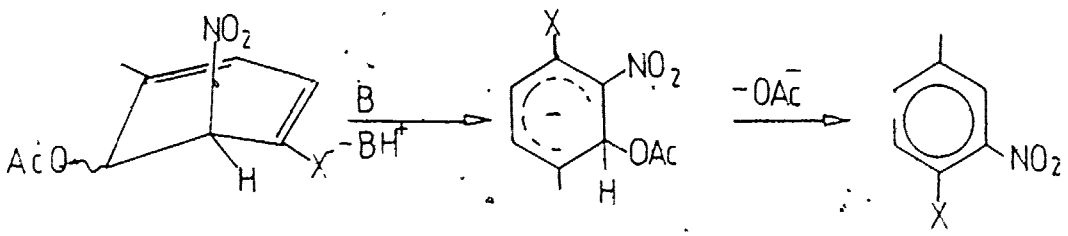
The predominance of any of the four pathways will depend on several factors.

Path (a)

Path (a) is more important in reactions with longer reaction time and/or higher temperatures. Intermediates of type G are detected in the ^{1}H-NMR spectra of the reactions of dienes 100 and 101 carried out

in less acidic nucleophilic solvents (CD_3OD, Ac_2O and acetone). The reactions of the isomerized dienes 187, 188, 190 and 191 have shown that in nucleophilic solvents the major product is the 3-nitrocompound 122 and 124. In non-nucleophilic solvents some cresyl acetates 186 and 193 are formed. However the formation of these acetates in the reactions of dienes 100 and 101 in non-nucleophlic solvents via route (a) only seems unlikely.

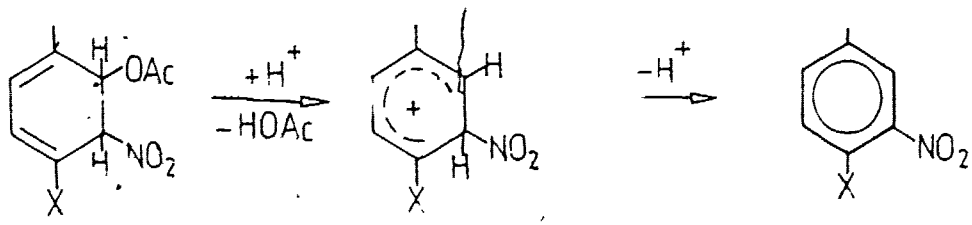
The difference in reactivity of the (Z)- and (E)-diastereomers of these dienes is only reflected in the reactions carried out in trifluoroacetic acid in the absence of a non-nucleophilic solvent. The 6-H of these dienes is the most acidic. An Elcb mechanism favours the elimination of acetic acid as is observed in the reaction with pyridine-d_5 (Scheme 4.24).



122 and 124

Scheme 4.24

Under strongly acidic conditions (CF_3SO_3H) protonation of the acetate group is more extensive than protonation of the nitro group and the cation 261 is formed readily, following which rapid proton loss leads to the 3-nitro compound by an overall E-1 mechanism. (Scheme 4.25).



261 122 and 124

Scheme 4.25

As the acidity of the reaction medium is reduced the nitro group would be expected to ionize as nitrite ion and to compete with the acid catalyzed loss of acetic acid, as happens in the case of dienes 100 and 101. The cation F should be more stable than 261 since the former has methyl group in conjugation with the positive charge. However, although there is some contribution from the unimolecular ionization of nitrite ion, it is evident that a competing bimolecular elimination of nitrous acid is also present. More acetate is formed in the (Z)-diastereomers 187 and 190. This implies that part of the elimination takes place via an E-2 type transition state. The nitro group being antiperiplanar to 1-H is eliminated faster from the (Z) rather than the (E)-diastereomer.

Path (b)

The cresyl acetates 186 and 193 and dihalotoluenes 207 and 208 are formed primarily by route (b), in which the cation aromatizes by a rapid proton loss. Other reactions of this cation are dicussed in the next chapter.

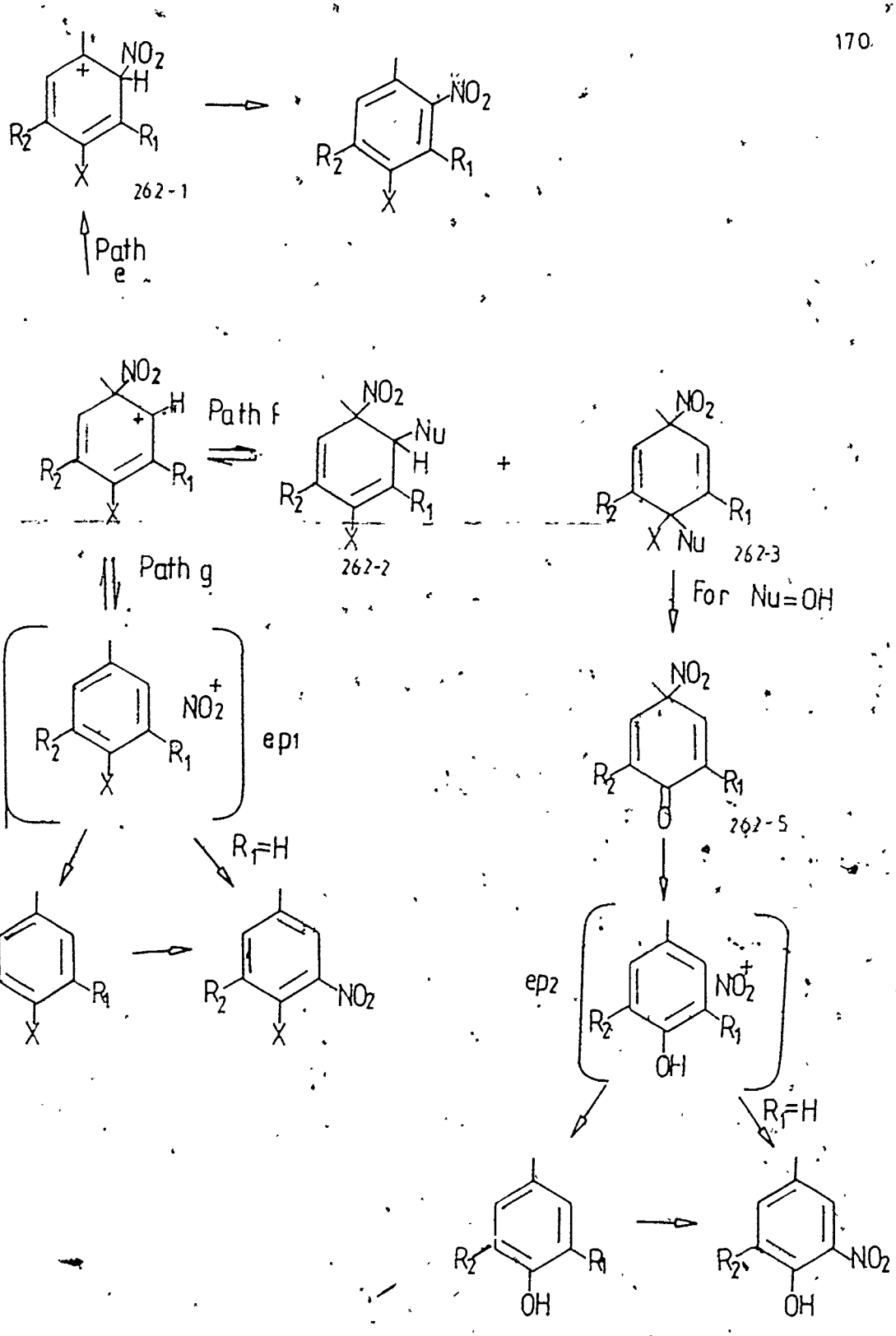
Path (c)

The dienols 204 and 205 are definite intermediates in the formation of cresols 213 and 215 in reactions with sulfuric acid and methanol, and, as mentioned before, these dienols have been isolated from the reaction mixture. This $A_{Ac}2$ mechanism, depicted in scheme 4.23, is important for dienes 100 and 101 in nucleophilic solvents. One source of the cresols which accompany the dienols is by loss of nitrous acid from the dienols. However some of the cresol can also arise from hydrolysis of the aryl acetates 186 and 192 formed by path (b). Schofield and his coworkers[129] have shown that 5-chloro-o-cresyl acetate 186 yields 38.8% of cresol 213 after 30 min hydrolysis in 31.6% aqueous sulfuric acid.

The major factors which allow routes (a), (b) and (c) to predominate over route (d) (scheme 4.23) appear to be lower acidities and higher solvent nucleophilicities. However none of these routes are favoured for dienes bearing a methoxy group.

Path (d)

All products formed in the reactions of the dienes 103, 130, 151 and 154 can be explained by route (d) which involves the formation of W_i^{Me}. Formation of W_i^{Me} is dominant in the case of the methoxy dienes because of the very great stabilizing effect of the methoxyl substituent in the cyclohexadienyl cation. The further chemistry of the W_i^{Me} is relatively complex and its possible modes of reactions are given in scheme 4.26.


NO2
H
R2
R1
X
262-1
Path e
Path f
Nu
262-2
262-3
Path g
For Nu=OH
ep1
ep2
R1=H
OH

Scheme 4 26

In the absence of nucleophiles the partitioning of the W_i^{Me} between (e), (f) and (g) depends primarily on the substituents R_1, R_2 and X. When X=OMe and $R_1=R_2\neq Cl$ the 1,2-nitro shift does not occur. On the other hand when X=Cl or Br, $R_1=R_2=H$, this is the major pathway under strongly acid conditions. In the case of diene 130, where X=OMe, R_2=Cl R_1=H, the W_i^{Me} is partitioned between (e) and (g). In all cases the 1,2-nitro shift generates a tertiary cation centre which is stabilized by the methyl group in the pentadienyl system 262-1. When X=halogen the stabilizing effect of the methyl group in the new pentadienyl system 262-1 is more important than that of X in the original pentadienyl system W_i^{Me} as methyl is the stronger activating group. When X=OMe, this is not the case and the stronger activating power of the methoxy group predominates and the pathway (e) is not favoured. However in the case of X=OMe, R_2=Cl, the new pentadienyl system is also stabilized by the chlorine and the combined stabilizing effects of chloro and methyl groups facilitate the formation of cation 262-1, and a considerable amount of 5-nitro compound is formed. The absence of any 2-chloro-4-methyl-3-nitroanisole in the product mixture probably reflects the greater steric strain attendant on its formation (four adjacent substituents) than exists in the case of the formation of the 5-nitro isomer (with much less buttressing).

The major products in the aromatization of dienes 103, 154 and 151 arise from the encounter pairs ep1 and ep2 via extramolecular migration. The amount of denitration is greater in cases of dienes 151 and 154, as would be expected due to the lower reactivity of the nitroaromatics 116 and 168. The large amount of denitration in the dienes 151 and 154 suggests the use of these dienes as transfer nitrating agents[10]. In order to check the validity of this suggestion,

the aromatization of dienes 103 and 151 with trifluoromethanesulfonic acid was carried out in the presence of an equal proportion of p-chlorophenol 247, a relatively deactivated substrate. With diene 103, a major portion of phenol was recovered unreacted, but with diene 151, 70% of the phenol 247 was converted to the 4-chloro-2-nitrophenol 246, and negligible amounts of dinitroanisole 155 and/or cresol 231 were obtained. These latter observations suggest that a major portion of the products 155 and 231 formed in the absence of phenol 247 is formed via intermolecular rather than extramolecular migration of the nitro group.

The amount of cresols 168, 187 and 231 formed in the reaction of the corresponding dienes increases with increasing nucleophilicity of the solvent (methanol-d_4) as the path (f) becomes more dominant. The amount of these cresols formed cannot however be taken as a direct measure of this process as the anisoles are susceptible to hydrolytic damage of the ether group; the anisole 154, when stirred in a solution of trifluoromethanesulfonic acid at 0°C for 30 minutes formed cresol 231. The ^{1}H-NMR spectrum of the dienes 103, 151 and 154 in methanol-acid reaction mixtures however indicated the formation of almost quantitative amounts of dienone, in which case the process (f) (scheme 4.26) is the obvious route to the cresols.

The dimethylketals obtained in the nitration reaction of 112, 115 and 116 are examples of intermediate 262-3, which precedes the formation of dienones of the type 262-5. These ketals were isolated under milder conditions (described in the next chapter) and the ketal 226, on treatment with boron trifluoride etherate, yielded a mixture of cresol 168 (40%) and anisole 116 (60%); with methanol-d_4 and chloroform-d (1:9, v/v) it slowly aromatized to cresol 168.

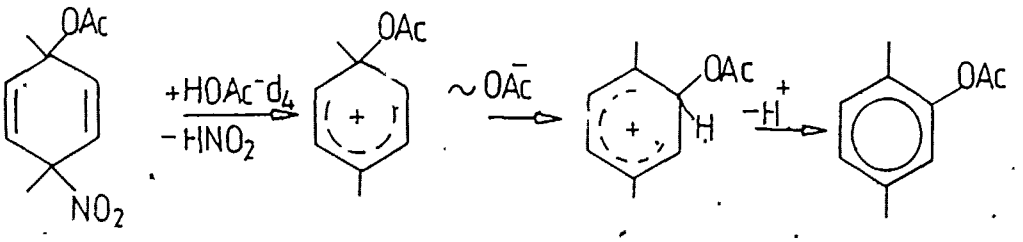
The Wheland intermediates from 100 and 101 are quantitatively formed on treatment with strong acids and in the presence of excess nucleophiles, as in the reactions with hydrogen halides, these intermediates are quantitatively trapped. The substituent Y has a considerable effect in controlling the ratio of reactions proceeding via path (b) and (d) in scheme 4.23. Under very acidic conditions the chlorides 200 and 201 have a higher proportion of reaction via path (b) as the chlorine (Y) is less basic than acetate group. The path (c) is closed for chlorides and under nucleophilic conditions solvolysis of the chloride [path (d)] is evident.

CHAPTER V: REACTIONS OF IPSO-ADDUCTS WITH NUCLEOPHILES IN NEUTRAL OR WEAKLY ACIDIC MEDIA:

5.1 Introduction:

Aromatic compounds were one of the earliest classes of compounds available to chemists, but still today it is difficult to access some appropriately functionalized arenes. The unique feature in the overall transformation induced by adduct formation on **ipso** nitration is the introduction of two functionalized sp^3 carbons in a single step into commonly available aromatic compounds. Such a transformation sets the stage to allow further manipulation of these functional groups and develop routes to other cyclohexadienyl derivatives and functionalized aromatic compounds in a regioselective manner. Previous work[69] in this area gives clear indications regarding the synthetic potential of **ipso**-nitrocyclohexadienes.

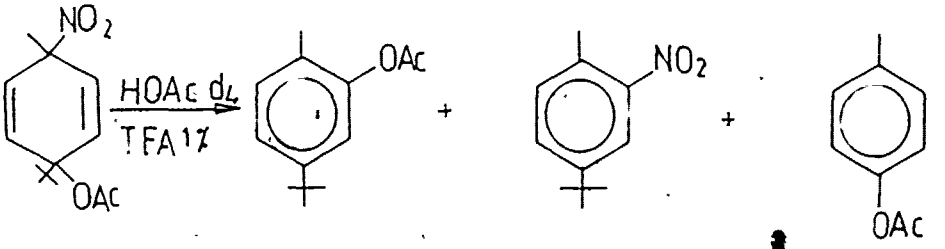
The work described in Chapter IV deals primarily with reactions under acidic conditions, whereby it is established that **ipso**-nitrocyclohexadienyl cations can be regenerated and used for the preparation of other dienes and aromatic compounds. However with decrease in acidity reactions proceeding with retention of the acetate group become more important. There is a wide body of evidence consistent with the proposition that the reactions proceed via an acetoxycyclohexadienyl cation. Solvolysis of the nitro group has been observed in weakly acidic or neutral conditions when the adduct is a tertiary acetate 77, the acetate group migrates intramolecularly to the adjacent carbon, which after proton loss gives the aromatic acetate (scheme 5.1)[82].



77 77a 77b 263

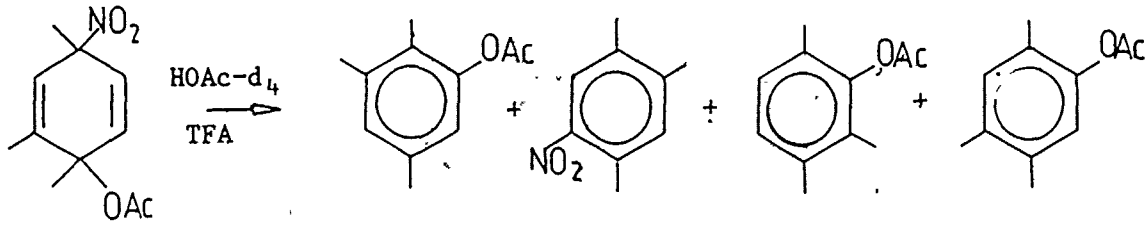
Scheme 5.1 Ref 82.

The intramolecularity of the process was established when it was shown that no exchange with other nucleophiles such as acetic acid-d_4 or propionic acid occurred. A few examples of 1,3-acetate migration in tertiary acetates are also known. Aromatization of 1-t-butyl-4-methyl-4-nitrocyclohexa-2,5-dienyl acetate 83 in acetic acid-d_4 in the presence of trifluoroacetic acid gave 5-t-butyl -2-methylphenyl acetate (264) in 87% yield (scheme 5.2). No exchange of the acetoxy group was noted in the aromatization of 1,2,4-trimethyl-4-nitrocyclohexa-2,5-dienyl acetate (scheme 5.3).



83 264 265 265a

Scheme 5.2 Ref 84

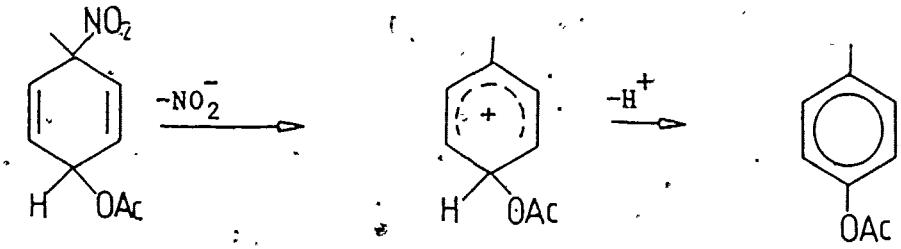


78 266 267 268 269

Scheme 5.3 Ref 130

Either recombination of the ipsocyclohexadienyl cations and acetate anion within the solvent cage to the isomeric secondary acetates, or a concerted process involving 1,3-acetate bridging, in each case followed by aromatization involving loss of nitrous acid, could account for the formation of the products 264, 268 and 269.

When the adduct is a secondary acetate, aromatization via direct proton loss in the cation is the only process identified (scheme 5.4), as exemplified for the adduct 76 from toluene.

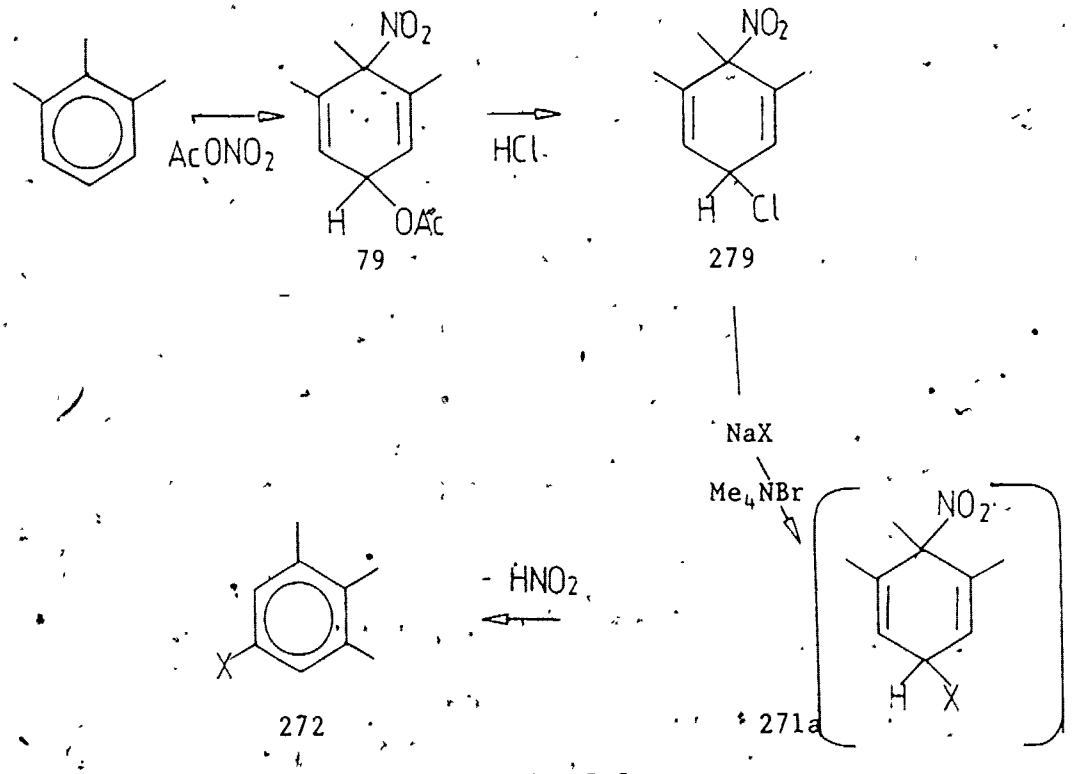


76 76a 265a

Scheme 5.4 Ref 82

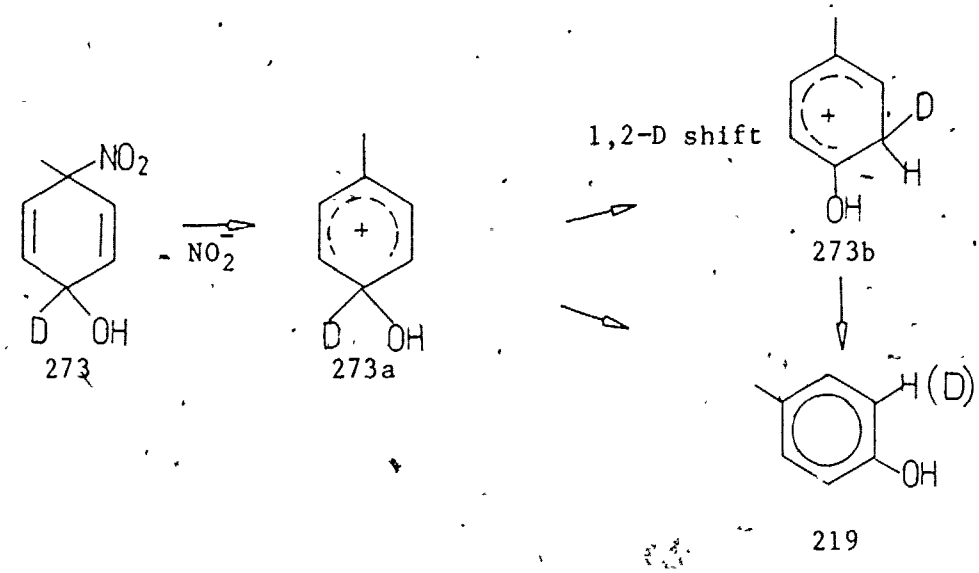
On changing the acetate group to other functional groups a

similar reaction can occur. This process has been elegantly utilized by Myhre[131] to develop a regioselective route to the synthesis of 5-X-hemimelitenes. The 3,4,5-trimethyl-4-nitro-cyclohexa-2,5-dienyl-chloride (279) obtained from the corresponding acetate 79 underwent substitution by various nucleophiles in the presence of tetramethylammonium bromide in methylene chloride, followed by aromatization via solvolysis of the nitro group, to yield the required arenes (scheme 5.5).



Scheme 5.5

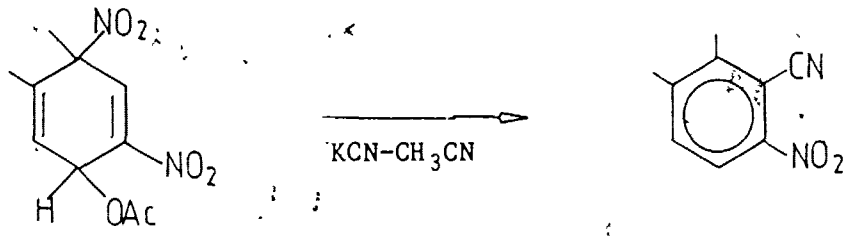
The behaviour of secondary nitrodienols is somewhat different from that of the acetates. In the solvolysis of the nitrodienols a major portion of the aromatization reaction is preceded by an intramolecular hydrogen shift (NIH shift)[132]. Reactions using labelled dienols have shown that about 25-30% of the product arises from such a process (scheme 5.6).



Scheme 5.6

The hydroxy group strongly stabilizes the rearranged cation 273b and this favours the rearrangement process. Similar isotopic studies[132] with acetates indicate that only 0.3% of the reaction in this case occurs via an NIH shift.

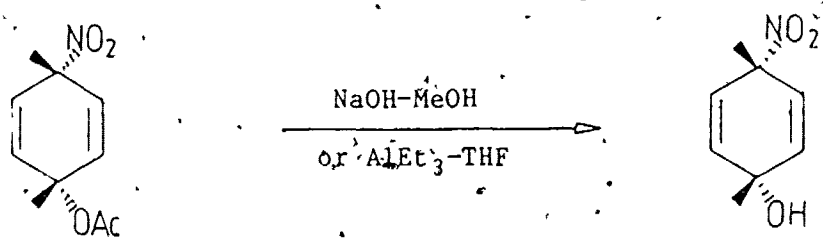
The reactions shown in scheme 5.5 resemble direct nucleophilic substitution of a secondary acetate. Examples of allylic substitution (S_N') are also known. Nucleophilic substitution on the 1,4-diene 93 obtained by nitration of 4-nitro-o-xylene yields 3-X-4-nitro-o-xylene derivatives 274 by allylic substitution of acetate group (scheme 5.7)[65]. The greater reactivity of the double bond bearing the nitro group makes this process faster than direct replacement.



93 274

Scheme 5.7

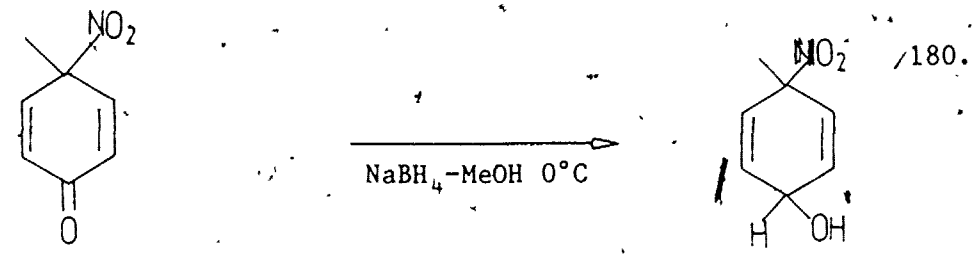
Apart from nucleophilic displacement of acetate groups, other routes to the synthesis of nitrodienyl derivatives bearing oxygenated functional groups have been developed. Alkaline hydrolysis (B_{Ac}) [279] or reductive cleavage by aluminium hydride [133] of acetates allow synthesis of the nitrodienols in a stereospecific manner (scheme 5.8).



Z-80 275

Scheme 5.8

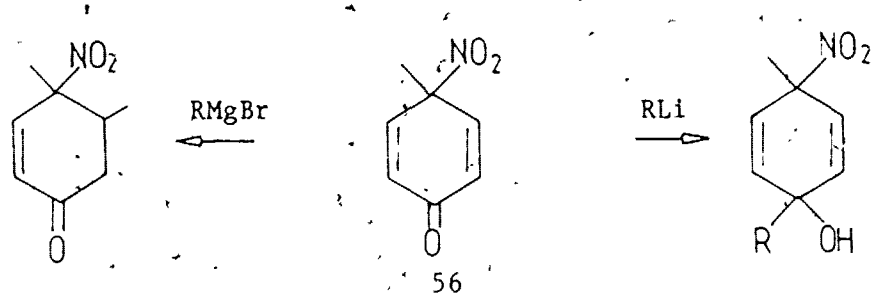
Reduction of nitrodienones by mild reducing agents like sodium borohydride has been shown by Myhre [132] to be an efficient route to the synthesis of the corresponding secondary nitrodienols (scheme 5.9).



56 273

Scheme 5.9

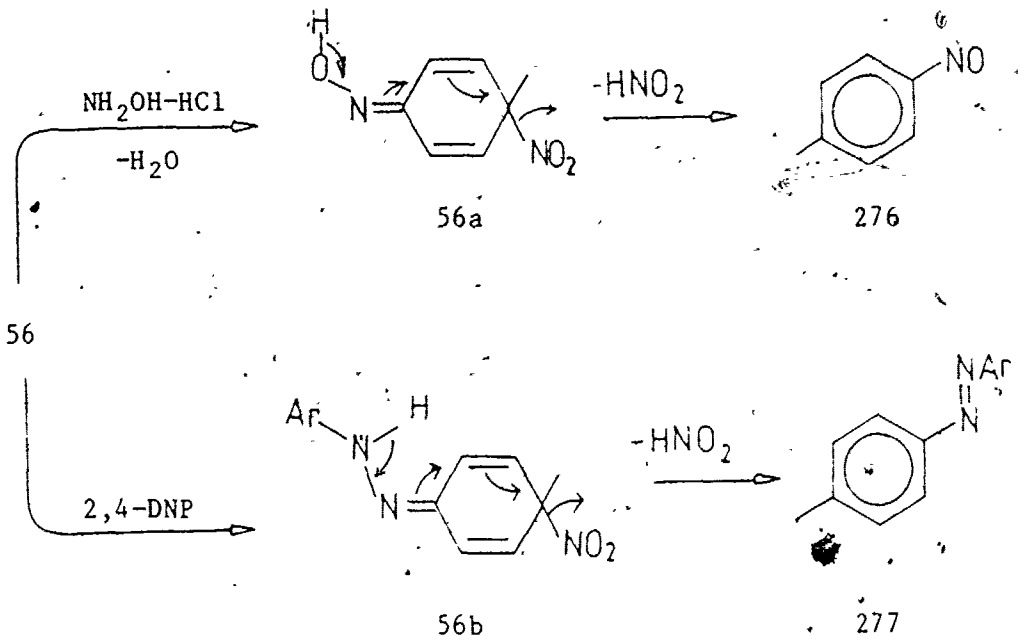
The reactivity of the carbonyl group towards nucleophiles to develop the synthesis of a large number of functionalized 1-R-4-alkyl-4-nitrocyclohexa-2,5-dienols by using alkyllithium reagents as nucleophiles have been exploited by several workers (G.N.Henderson and S.Sankararaman[134]). This route also allows the synthesis of **ipso**-adducts not obtainable by direct nitration. Grignard reagents add in a 1,4-manner (scheme 5.10).



56

Scheme 5.10

Attack by nitrogen nucleophiles on the carbonyl group of dienone 56 has also been investigated and shown to be a viable synthetic route to replace the hydroxy group of cresols by various nitrogen-bearing functional groups (scheme 5.11)[69].



Scheme 5.11

Dienones are unstable and isolation and purification can be complicated. A potential alternate route to dienones is via dienes obtained from anisole derivatives. The dienes obtained from the nitration of anisoles are easily isolated as pure solids and are relatively stable. During the acid catalyzed reactions of these dienes, intermediate dienone formation was observed in high yields, when nucleophilic solvents were used (MeOH). Consequently these dienes would serve as synthons for the corresponding dienones. This has been investigated in this chapter.

The reactions of these dienes resemble those of other secondary acetates in that these allow ready exchange (by halides) and modification (by acid hydrolysis) of the acetate group. The possibilities of a) extending the solvolytic displacement under nucleophilic conditions and b) of other modifications (e.g. by AlH_3 reduction) of the acetate group exist. The results obtained from

investigations of these reactions are discussed in the following section.

5.2 Results and discussion:

The reactions described in this section can be classified broadly on the basis or the reagents used viz:

1) Common nucleophiles

2) Metal hydrides.

The reactions of dienes 100 and 101, obtained from 4-chloro- and 4-bromotoluene with common nucleophiles, were found to differ from the behaviour of the dienes from anisole and shall be discussed separately. The reactions of metal hydrides with dienes have been discussed in the third part of this section.

5.2.1: Reactions of Dienes from 4-chloro- and 4-bromotoluene.:

After overnight stirring of an aqueous methanolic solution of diene 100 at ambient temperature, 30% of unreacted diene was recovered, along with 61% 5-chloro-o-cresyl acetate (186) and 9% 4-chloro-3-nitrotoluene (122). When the reaction was repeated in the presence of added sodium acetate (2 mol proportions) after 2 days at ambient temperature, a mixture of compounds 186, (88%) and 122, (12%) was obtained. The mixture was separated by chromatography on silica gel. Early fractions using 2% ether-petroleum ether mixtures gave compound 122. Compound 186 was eluted with 5% ether-petroleum ether mixtures. Both compounds had spectral and physical characteristics similar to those reported in the literature. When diene 100 was stirred with a mixture of potassium cyanide 18-crown-6 in acetonitrile-d_3 the

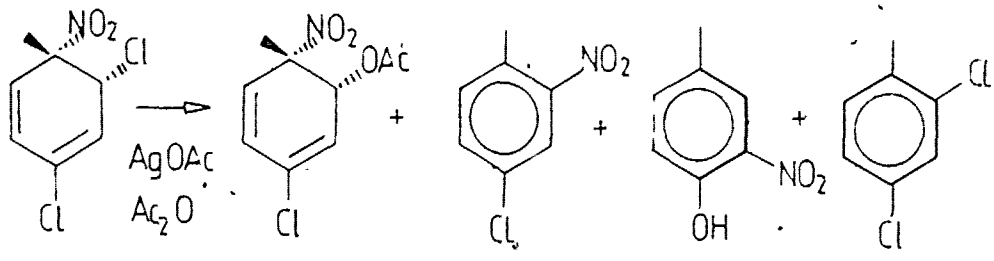
major product was cresol 213. Similar results were obtained when a heterogenous mixture of aqueous potassium cyanide and tetramethylammonium bromide and a methylene chloride solution of diene 100 was stirred 24h. When a sodium thiophenoxide solution in acetonitrile containing diene 100 was stirred for 15h the major product was acetate 186 and diphenyl disulfide.

After stirring diene 101 in an aqueous methanol solution at ambient temperature for three days, a mixture of cresyl acetate 193, (66%), toluene 124, (24%) and unreacted diene 101, (10%) was obtained. In the presence of sodium acetate the diene 101 aromatized completely over a period of 6 days to a mixture of cresyl acetate 193, (80%) and toluene 124, (20%). Both compounds were obtained pure after separation by chromatography on a silica column.

Reactions of (Z)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl chloride (201) with potassium cyanide led to the formation of 2,4-dichlorotoluene (209) and 5-chloro-o-cresol (213) as the major products. In the GCMS of the product mixture, the peaks due to p-chlorotoluene (111), 2-nitro-p-cresol (168) and another compound having a molecular ion m/e=153,151 corresponding to chlorotoluonitrile (278) were found. When the reaction was repeated in the presence of added 18-crown-6 the only product was 209. Similar results were obtained when the reaction was repeated in heterogeneous mixture (methylene chloride - water) containing added tetramethylammonium iodide. On stirring a solution of diene 201 in aqueous methanol for 12 hours a mixture of cresol 213, (20%), 5-chloro-o-cresyl methyl ether (256), (38%), 2-nitro-p-cresol (168), (26%), p-chlorotoluene (111), (12%) and the 3-nitro- compound 122, (4%) was obtained. The products obtained from the reactions of dienes 100, 101 and 201 described here indicate that under nucleophilic and weakly acidic conditions the

reactions proceed predominantly via elimination of nitrous acid. The prospect of generating W_i^{Me} for nucleophilic trapping under solvolytic conditions thus appears to be limited. Increasing the nucleophilicity by addition of 18-crown-6 increases the rate of elimination and fails to produce any noticeable substitution. However it is possible to generate the W_i^{Me} in such solvolytic conditions from the halides 200 and 201 by the addition of silver salts.

When diene 201 was stirred at ambient temperature for 15h with silver acetate in acetic anhydride a mixture containing 18% of acetate diene 100 was obtained as shown in scheme 5.12.



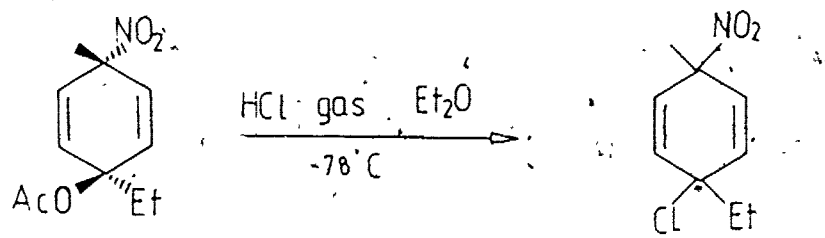
201 100, 18% 121, 68% 168, 9% 209, 5%

Scheme 5.12

The mechanism involved in the formation of 121 and 168 via W_i^{Me} was discussed in chapter IV (scheme 4.18). Reaction with silver nitrate in methanol at 0°C for ninety minutes yielded a mixture of 63% dienone 56 and 36% of a single diastereomer of 3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl methyl ether (202). Pure diene 202 was obtained after chromatography on an alumina column at -78°C. Similar reaction with the diene 101 also yielded 37% dienone 56 and 63% of a single diastereomer of 3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl methyl ether (203). The ^{1}H-NMR and ^{13}C-NMR spectra of these dienes were similar to those of the starting dienes 100 and 101 and could be

explained on the basis of the assigned structures. The splitting pattern in these dienes also indicated these had the Z-configuration as in the starting diene. The Z-stereochemistry of diene 202 was confirmed by methylation of the dienol 204 formed by $A_{Ac}2$ solvolysis of the Z-acetate 100. In the latter reaction the dienyl C–O bond is not broken and thus the Z-stereochemistry is preserved in the dienyl methyl ether 202.

At this point it is useful to review the stereochemical course of the reactions leading to 1,2-adduct formation. All the 1,2-adducts from **ipso**-nitration hitherto known have been isolated as a single diastereomer. The work described in this dissertation has shown that the nitration reaction leads to (Z)-diastereomers and this (Z)-configuration is retained in the reactions where the acetate is replaced by halide, or in reactions with HCl and HBr. The (Z)-configuration is again retained on conversion of the halide to methyl ether. Such stereoselectivity is in contrast to that observed in the 1,4-adducts (as in scheme 2.5) where almost equal proportions of both diastereomers are formed in the initial nitration and on substitution of the acetate by halides, both diastereomers are again obtained[135].

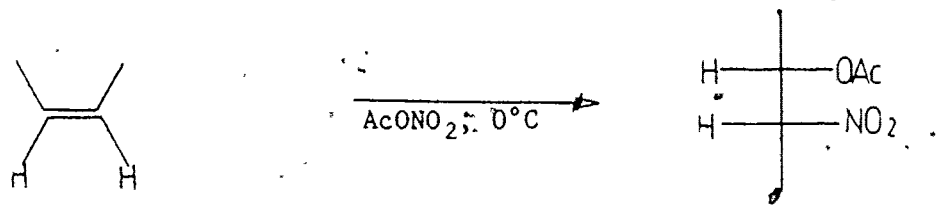


(E)-81 279 (Z and E)

Scheme 5.13

The stereochemistry of acetyl nitrate addition to olefins has

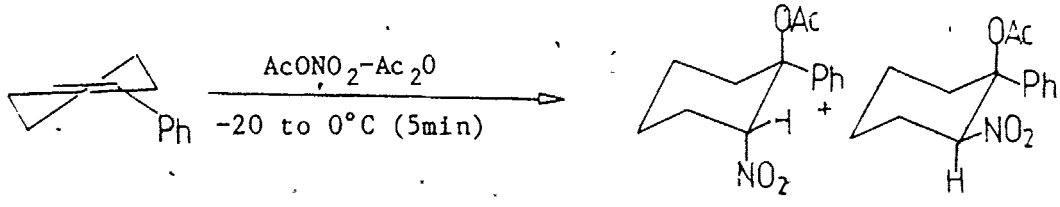
invoked considerable interest. Initial studies by Garbisch and Bordwell showed that a major portion of this reaction proceeds as cis-addition[136a]. In later studies with substrates capable of producing stable carbocations, predominantly anti addition was observed[137] as shown in scheme 5.14.



cis-2-butene — Erythro (70%)

trans-2-butene — Threo (65%)

Ref 136



3

Ref 137

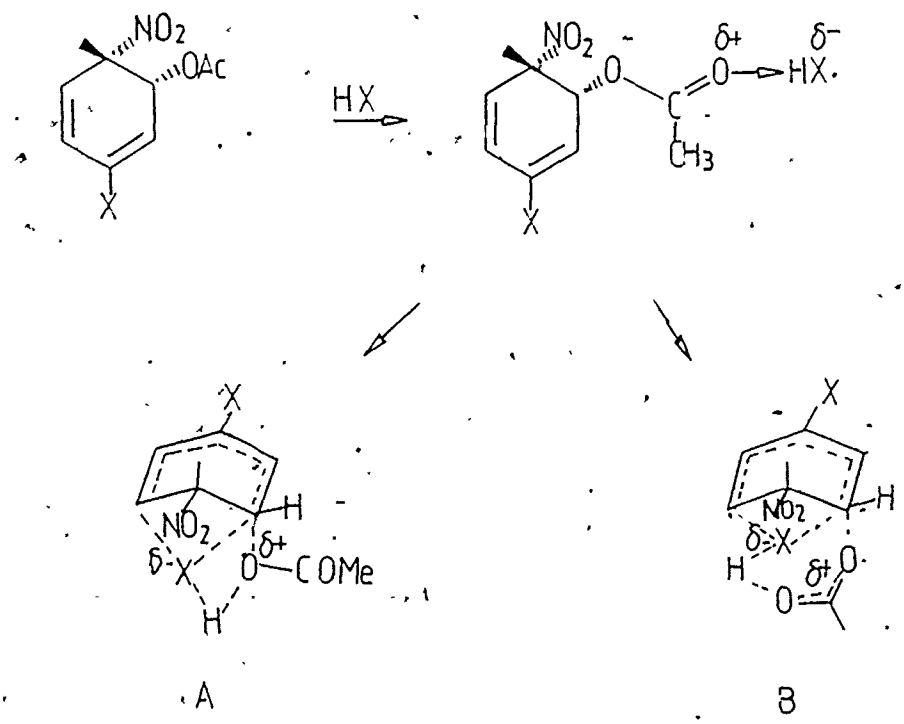
Scheme 5.14

It has been proposed that in the formation of 1,2-adducts the acetic acid remains closely associated with the W_i^{Me} within the encounter pair and attaches to the same face of the W_i^{Me} as the NO_2^+ leading to the Z-isomer[76]. This proposal fails to explain why the subsequent substitution reactions proceed with retention of configuration. It also does not explain why no (E)-diastereomer is formed under equilibrating conditions. The reaction of diene 100 with $Ac_2O(d_6)$+TFA leading to

exchange of acetate with the deuterated analog in acetic anhydride only produces the (Z)-diastereomer.

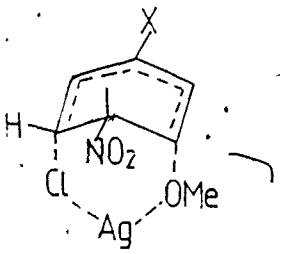
The (E)-diastereomers 189, 192 and 196 have been detected and characterized during thermal reactions, and were found to survive treatment with ammonia followed by ambient temperature work up. This shows that if these dienes were formed in the nitration reaction in isolable yields they would have been isolated and detected. Thus the (Z)-diastereomer appears to be formed selectively under both kinetic and thermodynamic conditions.

Retention of configuration on reaction of the acetate with hydrogen halides would occur if the reaction proceeds via an S_Ni mechanism as shown in scheme 5.15.



Scheme 5.15

The two highly organized transition states A and B shown in scheme 5.15 can arise after coordination of HX with either of the two ester oxygens followed by delivery of the nucleophile on the same face which bears the acetate. A similar transition state could explain the retention of configuration in the substitution of halides catalyzed by silver salts as shown in scheme 5.16.



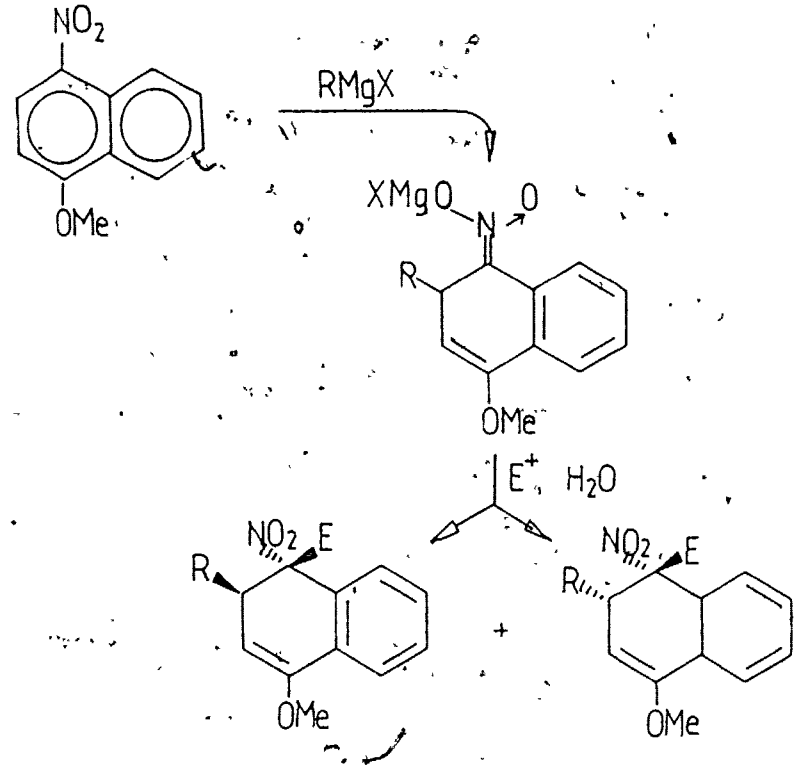
Scheme 5.16

It is not possible to distinguish between the attack at C-5 and C-1 with the present body of evidence.

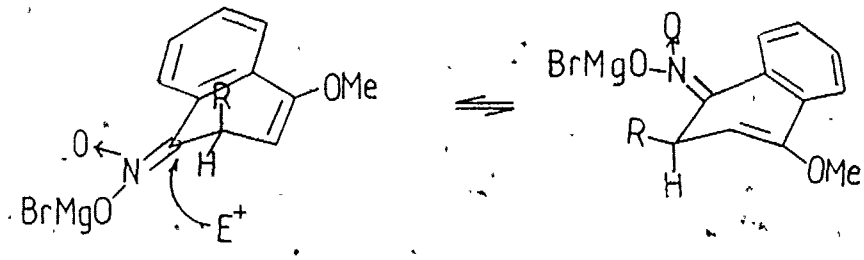
The reaction of hydrogen chloride with the 1,4-adduct 81 yielded a mixture of diastereomeric chlorides Z-279 and E-279 as shown in scheme 5.13. These were not isolated and it is difficult to predict whether the reaction proceeded via partial retention or inversion, but the result does indicate that at least part of the reaction proceeds via a free cation.

The tertiary acetates Z-83 and E-83 obtained by 1,4-addition of acetyl nitrate to p-t-butyl toluene, when treated with HCl gave both diastereomers of the 1,4-chloronitro-adducts Z-280 and E-280 along with one diastereomer of 1,2-adduct 281. A similar product mixture was obtained when the secondary acetate 104 was treated with HCl[84]. The 1,4-chloronitro-adducts (Z) and (E)-280 on treatment with silver acetate

in acetic acid gave a mixture of both diastereomers of 1,4-acetate 83 and one diastereomer of 1,2-acetate 104. If an S_Ni mechanism was involved in these reactions, then the (E)-diastereomer of 104 would have been formed from the (E)-1,4-adduct, E-280. Diene 104, the only 1,2-adduct obtained has been shown to have the (Z)-configuration, and its formation from (E)-1,4-adduct E-280 would necessarily involve a cationic intermediate with some factor controlling the approach of the nucleophile to the cation leading to preferential formation of Z-diastereomer. Such stereoselectivity could arise from steric approach control of the reagent. An example for such steric approach control is reported by Bartolli and his coworkers[121] in the formation of the nitronate adducts from 4-methoxy-1-nitronaphthalene and RMgX as shown in scheme 5.17. In the intermediate 282 the alkyl group prefers an axial orientation 283A to relieve the steric interaction with the adjacent nitro group which would be present in the other conformer 283B. The axial alkyl group hinders the axial approach of the proton from the same face. The major adduct is thus the one with (Z)-configuration formed by protonation from the face anti to the methyl group. The stereoselectivity increased when bulkier alkyl groups and electrophiles (halogens from hypohalites) were used.



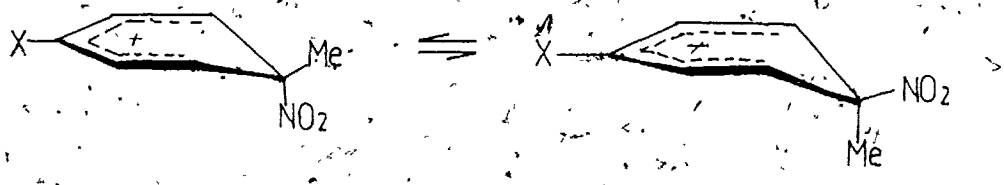
E	R	282B	282A
H	Me	15%	61%
H	$PhCH_2$	9%	60%
Br	Me	0%	100%
Cl	Me	0%	100%



283A 283B

Scheme 5.17

In the W_i^{Me} from any of these aromatics studied in this dissertation, two limiting conformations are possible as shown in AA and BB.

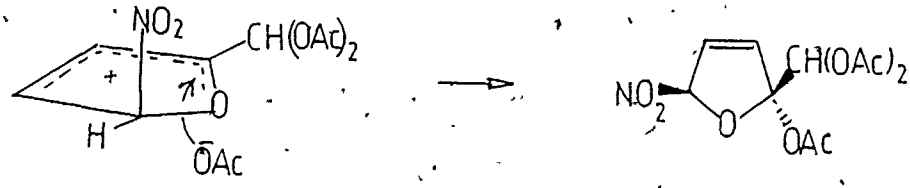


BB AA

Scheme 5.18

The axial methyl group in the conformer AA could stabilize the cation by overlap of bonding pair between (C-CH_3). This would allow partial development of the aromatic sextet. This axial orientation of the methyl group would hinder attack of the nucleophile from the same side and lead to predominant formation of (Z)-1,2-adducts. In contrast the attack at C-4 would not be affected by the axial methyl group at C-1 and both diastereomers of 1,4-adducts would be obtained.

This explanation can also explain the retention of the (Z)-stereochemistry on conversion of the acetate to the chlorides and in turn to the methyl ethers. A related explanation accounts for the preferential anti addition of acetyl nitrate in furfural diacetate (284); where the axial nitro prevents syn addition, due to steric interactions and leads to the formation of E-284 selectively (88%) (scheme 5.19).



284A E-284

Scheme 5.19 Ref '138

The presence of electron withdrawing groups on the cation should make the cation more reactive and nucleophilic trapping via either of the two conformers AA and BB prior to any equilibration between the two becomes likely. This is reflected in the nitration of nitroanisole 116 where nucleophilic attack at C-3 is faster than at C-5 and in the presence of trifluoroacetic anhydride the (E)-diastereomer 152 is formed. This could also arise from the equilibration of the Z-diastereomer 151 in the reaction media, as in the (E)-diastereomer the acetoxy group is axial and removed from the plane of the nitro group on C-2.

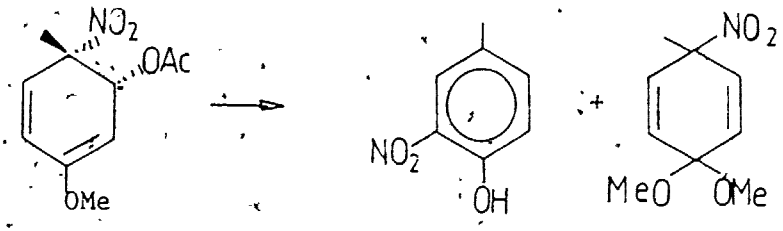
Similarly in the reaction of 2-carbomethoxyfuran with acetyl nitrate equal proportions of both (Z-) and (E-) adducts are formed. In both cases the cation is destablized and therefore made more reactive due to the presence of electron withdrawing groups on the ring.

5.2.2: Reactions of Dienes bearing Methoxy Groups:

Unlike the dienes from 4-halotoluenes, the methoxy analog 102 generated the W_i^{Me} readily by loss of acetic acid under solvolytic

conditions and this could be trapped by several nucleophiles.

The diene 102 in neat methanol-d_4 at 0°C for 30 mins yielded a mixture of dienone 56, (20%) and unreacted diene 102, (80%). On warming the reaction mixture to ambient temperature the dienone 56 decomposed to the cresol 168. During the course of this reaction, the ^{1}H-NMR spectrum of the reaction mixture indicated the presence of an intermediate diene (226) with an AA'BB' pattern in the vinylic region. When diene 102 was stirred at ambient temperature in aqueous methanol the nitrocresol 168 was obtained as the major product along with traces of p-cresol (219). A similar reaction in the presence of sodium acetate (2 mol proportions) gave a mixture of cresol 168, and diene 226. The yield of the diene 226 increased and that of the nitrocresol decreased in the absence of added water, and also on substituting sodium acetate with tris(hydroxymethyl)aminomethane. In the presence of N,N-diisopropylethylamine (NNDIPEA) the diene 226 was obtained as the major product, but in the presence of sodium perchlorate only cresol 168 was obtained. The reactions are summarized in scheme 5.20.



102	168	226	
CH_3OH	~100%	-	
$CH_3OH + H_2O$	~90%	-	~10% p-cresol
$CH_3OH + H_2O$ + NaOAc(2eq)	45%	49%	6%
CH_3OH + NaOAc	40%	60%	
CH_3OH + TRIZMA	20%	80%	
CH_3OH + NNDIPEA	-	~100%	
$CH_3OH + NaClO_4$	~100%	-	

Scheme 5.20

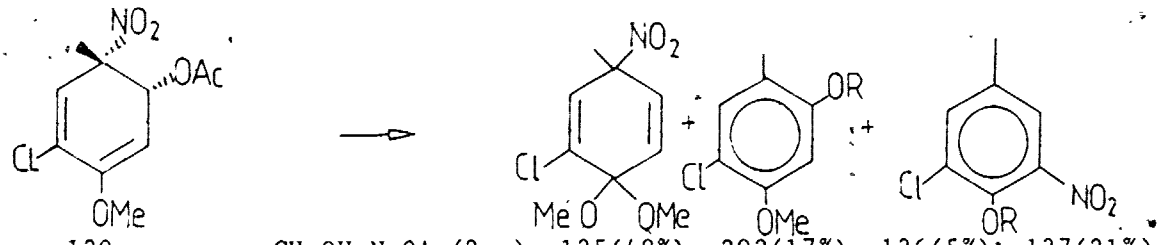
The results suggest that 168 is formed from 226 via the dienone and that as would be expected the conversion of the ketal to a dienone is inhibited by the absence of acid and reduction of the amount of water present.

The reaction with potassium cyanide in acetonitrile and water produced a mixture of (Z)- and (E)-1-methoxy-4-methyl-4-nitrocyclohexa-2,5- dienylcarbonitrile 286, (30%) and 287, (58%), respectively, along with 12% of aromatic compounds. After overnight stirring at ambient temperature in the presence of NNDIPEA the mixture was separated by semi preparative-HPLC on a CN-10 column and the dienes 286 and 287 were obtained pure. The later fraction eluted with 100% methylene chloride contained 3-cyano-p-cresol (288). In the absence of water in the reaction mixture unreacted diene 102 was recovered. Reactions with

potassium thiocyanate and potassium iodide gave predominantly cresol 168 along with p-cresol, while with potassium fluoride in the presence of 18-crown-6 unreacted diene 102 was recovered. Reaction with isopropanol in presence of NNDIPEA gave predominantly the cresols 168 and 219 along with 24% of a mixture of (Z) and (E)-4-methyl-4--nitrocyclohexa-2,5-dienone isopropyl methyl ketals 289Z and 289E. No attempts were made to separate these dienes. Reaction with sodium nitrite in a mixture of acetonitrile and water gave 4-methyl-3-nitroanisole (118) as the major product in the presence of either sodium acetate or NNDIPEA. The cresol 168 was present in both reactions as a minor product.

The reaction of diene 102 with NN-diisobutylamine gave unreacted diene when stirred for 4 hours in acetonitrile at ambient temperature, but yielded a mixture containing N,N-diisobutyl-p-toluidine (290) and its 3-nitroderivative 291 as the major products when water was added. The pure toluidine 290 was obtained from the mixture by extraction with aqueous hydrochloric acid, followed by basification of the extract and extraction with ether. Attempts to purify the nitrotoluidine by chromatography or crystallization failed and it was characterized from its spectral properties.

The diene 130 gave, when stirred in aqueous methanol in the presence of sodium acetate, 2-chloro-4-methyl-4-nitrocyclohexa--2,5-dienone dimethyl ketal (135) along with 4-chloro-5-methoxy-o-cresyl acetate 292, nitrocresol 137 and anisole 136 as shown in scheme 5.21. The nitrocresol 137 was removed from the mixture by washing with sodium hydroxide and the remaining mixture was separated by semi-preparative HPLC on a CN-10 column.



130	CH_3OH-NaOAc(2eq)	135(48%)	292(17%)	136(5%)	137(21%)
			R=OAc	R=Me	R=H
130	CH_3OH-H_2O-NNDIPEA(2eq)	135(41%)	293(41%)	136(6%)	137(11%)
			R=H		

Scheme 5.21

When the reaction was repeated by substituting sodium acetate with NNDIPEA, no acetate 292 was formed, instead the corresponding cresol 293 was obtained along with other products 137, 136 and 135 (scheme 5.21).

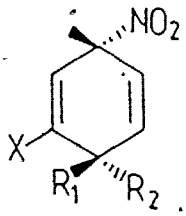
A mixture of anisole 292, cresol 137 and the (Z) and (E)-diastereomers of 2-chloro-1-methoxy-4-methyl-4-nitrocyclohexa-2,5-dienylcarbonitrile (294) and (295) was obtained from the reaction of diene (130) with potassium cyanide in acetonitrile and water in the presence of NNDIPEA. The major diastereomer 294 and cresol 137 were each obtained pure after semi-preparative HPLC and crystallization. The other diastereomer 295 was characterized in mixtures containing traces of an unknown compound.

Both dienes 151 and 154 yielded the dimethyl ketal 156 when stirred with aqueous methanol in presence of sodium acetate. The nitrocresols, which were probably formed in the reaction mixture, were removed during aqueous extraction. There were also traces of some unknown compounds (formed by addition of methanol across a double bond)

in these reactions. On substituting sodium acetate with NNDIPEA the major product was the nitrocresol 231. No ketal 156 was detected in the product mixture. Attempts to prepare the cyano adducts also failed and the cresols 231 and 168 were the major products.

The vinylic region of the ^{1}H-NMR spectra of the 1,4-adducts were similar to that of the corresponding dienones. The change in chemical shift of the protons could be attributed to the absence of the carbonyl group. The ketals 226, 135 and 156 had two signals in the methoxyl region in the ^{1}H and ^{13}C-NMR spectrum. The IR spectra indicated the absence of a carbonyl group. The ^{13}C-NMR spectra of dienes 286, 287, 294 and 295 had absorptions due to the cyano group demonstrating its presence in these compounds in spite of the absence of any strong absorption around 2200cm^{-1} in the IR spectrum.

The stereochemistry of dienes 286, 287, 294 and 295 was assigned on the basis of chemical shifts of the methyl and the methoxyl group in the ^{1}H- and ^{13}C-NMR spectra. The methyl group (**ipso** to NO_2) in the 1,4-adducts from p-xylene, 80 and 250, is shielded in the (Z)-diastereomer and has a higher field chemical shift in the ^{1}H and ^{13}C-NMR spectrum, whereas the methoxyl group is shielded in the (E)-diastereomer. The stereochemistry of diene (Z)-250 was established by X-ray diffraction studies on the corresponding dienol (Z)-275. The relevant values for dienes 286, 287, 294 and 295 are given in table 5.1 from which the dienes (286 and 295) are assigned (Z) and dienes (287 and 294) are assigned (E)-configuration.



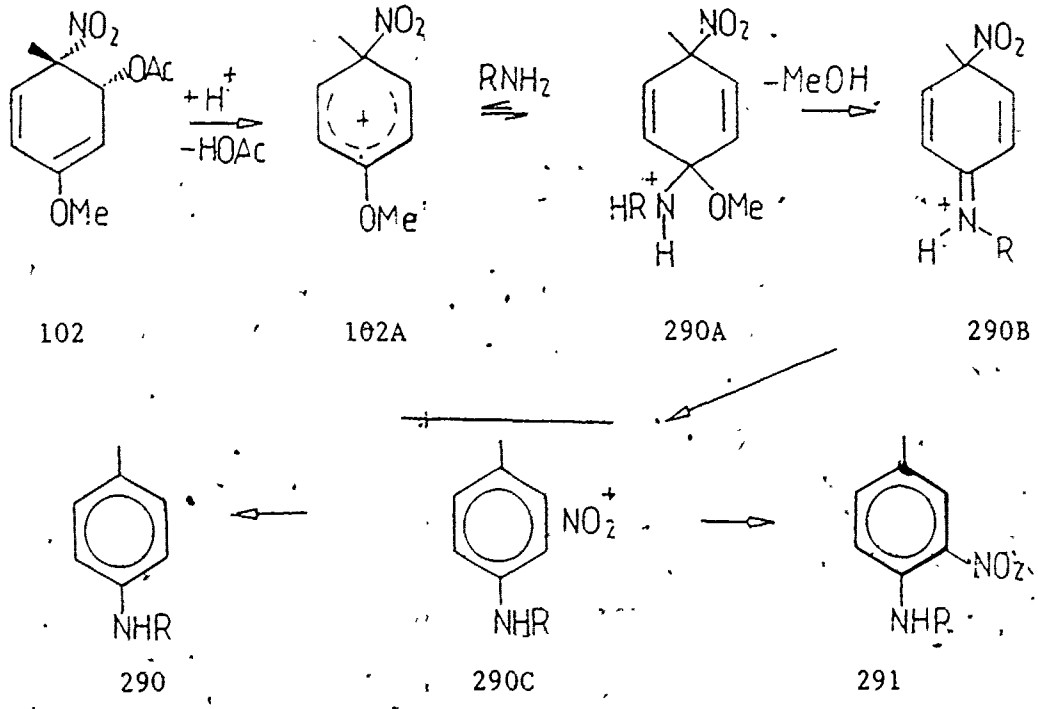
X	R_1	R_2	Compound	Chemical Shifts ^1H		Chemical Shifts ^{13}C	
				CH_3	OCH_3	CH_3	OCH_3
H	OMe	Me	E-250	1.74	3.03	a	52.0
H	Me	OMe	Z-250	1.70	3.08	a	52.4
H	OAc	Me	E-80	1.79	-	26.4	-
H	Me	OAc	Z-80	1.71	-	27.8	-
H	OMe	CN	E-287	1.81	3.34	26.9	52.6
H	CN	OMe	Z-286	1.80	3.41	26.7	52.7
Cl	OMe	CN	E-294	1.86	3.23	26.6	52.0
Cl	CN	OMe	Z-295	1.83	3.28	26.5	52.1

a: The ^{13}C-chemical shifts of the two CH_3 groups in the compounds were not distinguishable.

Table 5.1: Chemical Shifts (^1H and ^{13}C) of CH_3 and OCH_3 groups in (Z)- and (E)-2-X-4-methyl-4-nitrocyclohexa-2,5-dienyl derivatives.

The formation of the major products in these reactions can be explained via nucleophilic trapping of the Wheland intermediate. The formation of the intermediate (an S_N' type reaction), however, requires ionizing conditions and a protic solvent and the reaction does not proceed in the absence of any protic solvent. The fate of the intial adduct depends on the nature of the nucleophile and the reaction media.

The acetic acid liberated in the reaction can catalyze the formation of dienone intermediates from the ketals. The addition of NNDIPEA reduces the acid concetration and decreases the rate of dienone formation (table 5.20). When isobutylamine is used as a nucleophile the intermediate adduct is not isolated but the toluidine derivatives 290 and 291 are formed via an iminium intermediate as shown in scheme 5.23.



Scheme 5.23

The large extent of denitration could be due to the presence of base (ArNHR) within the encounter pair and in the bulk solvent (RNH_2). Similar iminium intermediates could also be formed by attack of amines on the intermediate dienone. Addition of diene 102 to a solution of 2,4-dinitrophenylhydrazine in ethanol and sulphuric acid led to the precipitation of 2,4-dinitrophenyl-4'-methylazobenzene (277). Under the

reaction conditions the dienone 56 is formed readily and is trapped almost quantitatively by the hydrazine (scheme 5.11).

5.2.3: Reactions with aluminium hydrides:

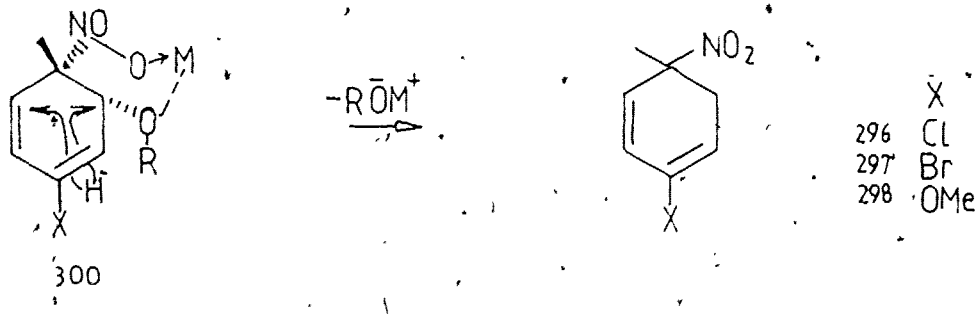
Reduction of the acetate group in dienes 100, 101 and 102 with aluminium hydride did not yield any dienols, in contrast to what is observed in the reactions of 1,4-dienes. The ^{1}H-NMR spectra of the product mixtures after careful low temperature work up indicated in each case the presence of a diene which decomposed to the respective 4-X-toluene on warming the mixture. These dienes [(X=Cl, 296), (X=Br, 297), (X=OMe, 298)] were characterized in mixture from the NMR spectral characteristics observed after accounting for the aromatic products (toluenes and cresols) also present in the mixture.

The absorptions due to the acetate group were absent in the ^{1}H and ^{13}C-NMR spectra, and the methine sp^3-carbon (bearing the acetate group) in the ^{13}C-NMR spectra of the starting diene was also absent; instead a sp^3-methylene (triplet in the gated spectrum) was present at a higher chemical shift. In the ^{1}H-NMR spectra, there were signals due to a pair of geminal protons with a large mutual coupling constant (~18Hz). Apart from these differences the spectra resembled those of the starting dienes. Based on these observations these dienes were assigned the structure 4-X-1-methyl-1-nitrocyclohexa-2,4-diene (X=Cl, 296), (X=Br, 297) and (X=OMe, 298).

The cresols formed in these reactions could result either from the aromatization of an intermediate dienol or via the cresyl acetate formed via loss of nitrous acid. However there was no evidence

regarding the formation of cresyl acetates in these reactions and the former process is the more likely. The proportion of cresols increased when lithium aluminium hydride was used for the reduction. Reaction with diisobutylaluminium hydride was slow and yielded unreacted diene and cresols. Brown and Yoon[140a] have shown that the reduction of nitro groups is slower with aluminium hydride than with LAH. This was probably one of the reasons that prompted earlier workers[141] to use the former reagent to selectively reduce acetates in the presence of nitro groups. However the dienol 275 was obtained in quantitative yield when (Z)-4-dimethyl-4-nitrocyclohexa-2,5-dienyl acetate (Z-80) was reacted with lithium aluminium hydride.

Hydrogenolysis of alcohols by metal hydrides has been reported in the literature[140b] and the reaction appears to proceed via nucleophilic displacement of the oxygen functionality which remains complexed to the aluminium. Such a mechanism would account for the formation of dienes 296, 297 and 298. The absence of any hydrogenolysis in the reaction of 1,4-adducts is puzzling. It is possible that a stable six membered complex 300 involving the nitro and the adjacent hydroxyl group is formed in these 1,2-adducts, which then undergoes nucleophilic displacement as shown in scheme 5.24.



Scheme 5.24

Alternatively, the displacement of the oxygen (bonded to an aluminium) by hydride could be accelerated due to the accompanying relief of steric strain which is present between adjacent substituents in the 1,2-adducts.

CHAPTER VI: CONCLUSIONS

The observations and discussions presented in the preceding chapters of the dissertation lead to a number of conclusions regarding **ipso**-attack - the formation of **ipso**-adducts and their fate - in nitration of appropriate aromatic substrates. In this chapter some of these conclusions are highlighted and possibilities for future investigation are presented.

The nitration of 4-X-tolyl derivatives 110-113 and 2-X-4-methylanisole derivatives 114-116 have been shown to yield **ipso**-adducts in high yields. The reactivity of the aromatics can be explained in terms of substituent effects. The isomer proportions obtained in the nitration of the 4-X-tolyl derivatives agreed well with those calculated from the principle of additivity. It has been mentioned in the literature[116b] that "with the recognition of the phenomena accompanying **ipso**-attack, they (partial rate factors) have in many cases lost their simple significance." The present work shows that, for a large number of substituents (X), the assumption that **ipso**-position has a reactivity equal to that of the meta position holds good and hence a reasonable estimate of the true isomer proportions on reaction can be obtained from the partial rate factors quoted in the literature. Steric effects predominate in the reactions of the tri-substituted compounds 114-116 apart from which the results parallel those expected from the principle of additivity.

The 1-Y-3-X-6-methyl-6-nitrocyclohexa-2,4-dienes isomerize under thermal conditions via a [1,5]-nitro shift, which has contributions from a concerted [1,5]-sigmatropic shift and a

stereorandom yet regioselective radical chain process. These are the first known examples of a radical chain process leading to carbon to carbon [1,5]-nitro shift in a regioselective manner. When Y=Cl, OMe, these reactions are also stereoselective and proceed via inversion of configuration. Kinetic investigations have shown that when Y=OAc the sigmatropic shift is faster than the radical process. It should be pointed out that it is necessary to determine the percentage versus time plots for the isomerization of dienes 187 and 190 in the absence of p-cresol to obtain similar information and substantiate this observation.

These isomerization reactions have led to the synthesis of several novel adducts bearing secondary nitro groups. Such adducts have never been obtained by direct nitration. Reactions of these dienes in turn have demonstrated the various routes via which these can contribute towards the formation of 3-nitrotolyl derivatives and 5-X-o-cresyl acetates under various conditions. Use of these dienes in Diels-Alder reaction with suitable dienophiles may be investigated in the future.

Different intermediates involved in the reactions of the **ipso**-adducts at different acidities have been identified. For dienes bearing the methoxyl group, the major portion of the reactions proceed via the W_1^{Me}, which can be trapped by other nucleophiles at lower acidities but collapse to dienones at higher acidities. From dienes not bearing a methoxyl group the W_1^{Me} can be regenerated at high acidities only but at lower acidities reactions via other intermediates become important. A large number of 1,2-dienes have been prepared from these dienes (100 and 101) by

a) nucleophilic trapping of W_i^{Me} at high acidities

b) by modification of the substituent Y (OAc→OH).

The dienols 204 and 205 are intermediates proposed[129] to be formed in the nitration reaction with mixed acid. Reactions of these dienols at various acidities should provide more precise information regarding the role of **ipso**-substitution in mixed acid rather than relying on predictions based on the behaviour of the dienyl acetates.

The nucleophilic trapping of W_i^{Me} to yield 1,2-adducts is stereoselective and the adducts have the (Z)-configuration. A mechanism involving steric approach control of the nucleophile on the W_i^{Me} can explain the observations. The crystal structures for dienes 101, 190 and 200 are the first to be determined for cyclohexa-1,3-dienyl derivatives formed by **ipso**-nitration. These structures contribute significantly to the knowledge of structural features of cyclohexa-1,3-dienes. In spite of the fact that the conformation of the dienes in solution may vary from what is observed in the solid state, the NMR spectral features of these dienes can be explained on the basis of the conformation obtained from the crystal structures.

Apart from the preparation of large numbers of dienes, the work described in this dissertation also contributes towards the regiospecific synthesis of several aromatic compounds:

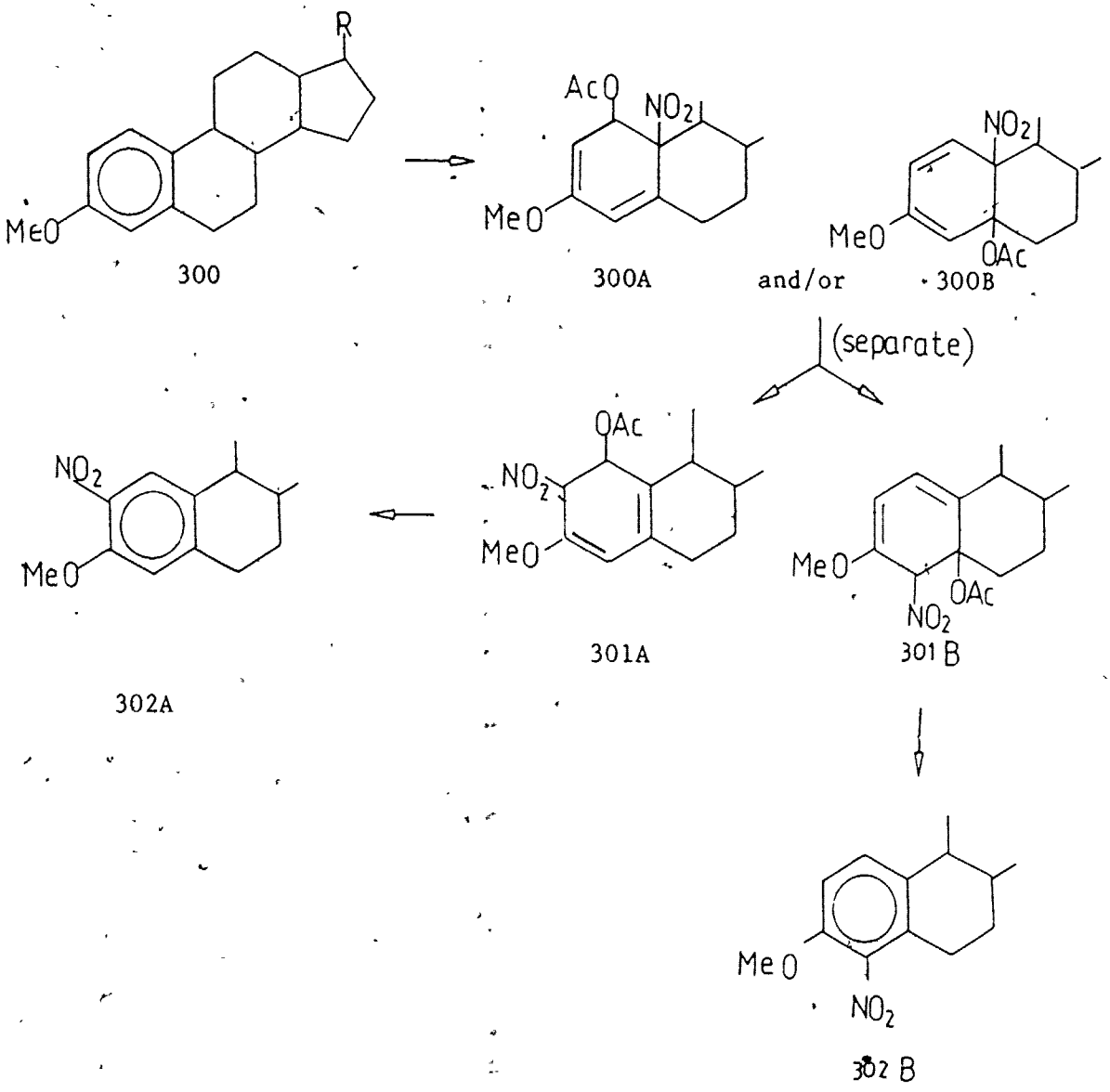
a) 4-X-2-nitrotoluenes (X=Cl, Br, OMe);

b) 4-X-3-nitrotoluenes (X=Cl, Br, OMe);

c) 4-X-2-Y-tolyl derivatives (X=Cl, Br, OMe; Y=OH, OAc, OMe, Cl, Br).

Some of these compounds are well known synthetic intermediates and have been previously[142] obtained via multi-step synthesis, e.g. 5-chloro-4-methoxy-2-nitrotoluene (251), prepared from diene 130 by reaction with strong acid, is an important intermediate in the synthesis of 1,4-benzodiazepin-2-ones and the present 2 step synthesis replaces the earlier 5 step sequence from 3-amino-4-methoxytoluene.

It may be possible to design the regioselective synthesis of nitroestrone derivatives 301 and/or 302 by combining the nitration reaction and aromatization following the thermal isomerization as shown in scheme 6.1.



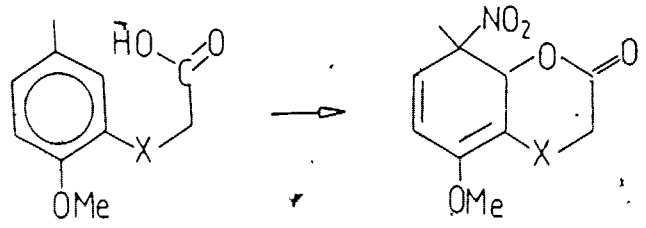
300 300A and/or 300B

301A 301B

302A 302B

Scheme 6.1

The scope of the nitration reaction can be extended to substrates of the type 303 as internal nucleophilic trapping of the W_i^{Me} can lead to the preparation of functionalized coumarins as shown in scheme 6.2.



303 303A

X=C=O, CH_2, CRH, CRR'

Scheme 6.2

CHAPTER VII: EXPERIMENTAL PROCEDURE.

7.1 Instrumentation:

Melting points are uncorrected and were determined on Buchi SMP-20 melting point apparatus. Infrared spectra, calibrated with polystyrene, were recorded on a Perkin Elmer 283 spectrometer. Observations were made on potassium bromide discs for solids and on thin films between sodium chloride plates for liquids. The absorptions are reported in wave numbers (cm^{-1}). Proton nuclear magnetic resonance spectra of solutions in carbon tetrachloride, chloroform-d, methylene chloride-d_2, acetone-d_6, acetic acid-d_4, nitromethane-d_3, pyridine-d_5, methanol-d_4, or benzene-d_6 were recorded on Perkin Elmer R-12B (60MHz), Perkin Elmer R-32 (90MHz) or Bruker WM 250 (250MHz) spectrometers. Tetramethylsilane was used as an internal standard. NMR spectra of nitration reaction mixtures were recorded with the acetic anhydride peak at δ 2.15ppm as the lock signal. Substitution reactions with hydrogen halides were followed using the ether peak at δ 1.85ppm as lock signal. For all other solutions tetramethylsilane (90MHz) or the solvent deuterium signal (250MHz) was used as the lock signal. Carbon-13 nuclear magnetic resonance spectra were recorded on a Bruker WM 250 (62.9MHz) spectrometer using solutions in $CDCl_3$ with TMS as the internal standard. In some cases the $CDCl_3$ peak (δ_C 77.0ppm) was used for calibration. Normally the data point resolution (SW, 01) was sufficient to achieve the number of significant figures for $\delta(^1H$ & $^{13}C)$ and J. In some cases resolution enhancement was used to improve on the values reported. The composition of reaction mixtures reported earlier in this dissertation, was obtained directly from the integrated ^1H-NMR spectra of the reaction mixture prior to work up. In most cases these values remained unchanged after work up. Ultraviolet spectra were recorded on a Beckman DU-8 spectrophotometer using methanol or methylene chloride as solvent.

Mass spectra were recorded on a Perkin Elmer Hitachi RMU-7 spectrometer with 70eV electron impact ionization, or on a Finnigan 3300 gas chromatography - mass spectrometry system using methane as the carrier gas for chemical ionization. Gas chromatography was performed on a Varian-3700 gas chromatograph, using a SE 30 glass capillary column. A standard experiment or analysis involved injection of 1 microlitre of a methylene chloride solution (1mg sample in $2cm^3$ of solvent) with the splitter closed. The temperature was held at 50°C for 3min then increased to 250°C over 40min and held for 15min. The splitter (1:400) was opened after 3min. For high perfo=rmance liquid chromatography a Varian 5000 liquid chromatography or a Waters Prep LC system was used. Elemental analysis was performed by Microanalytical Services, Vancouver, British Columbia. X-ray diffraction studies (crystallography) were performed by Dr. G. Bushnell on Picker 4-circle diffractometer automated with a PDP 11/10 computer.

7.2 Reagents:

The following chemicals were used without further purification: 4-bromotoluene (Baker), 4-chlorotoluene (Eastman), 4-methylanisole, 2-bromo-p-cresol, 2-nitro-p-cresol, 3-nitro-p-cresol, mesitylene (all Aldrich) and p-cresol (Aldrich Gold label). Acetic anhydride was certified ACS from Fisher. Trifluoroacetic acid, trifluoroacetic anhydride and dimethyl sulfate were Aldrich gold label (99+%). Fuming nitric acid (Fisher, $300cm^3$) was purified by distilling from urea (10g) and sulfuric acid ($500cm^3$) at 100Pa and stored at -25°C.

Solvents for chromatography inluding pentane (reagent, Fisher), ether (Fisher) and petroleum ether (reagent, Fisher) were dried over sodium and distilled before use. Methylene chloride and methanol (Carelton) were used without further purification. Tetrahydrofuran

(BDH) for hydride reductions was distilled under argon from potassium metal and benzophenone and stored under argon. Solvents for high performance liquid chromatography were methylene chloride and hexane (both Burdick and Jackson). Non-deuterated solvents for spectroscopy were certified ACS (Eastman Kodak). Deuterated solvents used for NMR spectroscopy were chloroform-d (Aldrich Gold Label), methylene chloride-d_2, acetonitrile-d_3, nitromethane-d_3, acetic acid-d_3, methanol-d_4, pyridine-d_5, acetone-d_6, aceticanhydride-d_6, benzene-d_6, and tetrahydrofuran-d_8 (Merk Sharp and Dohme.)

Silica gel (60-200 mesh, Davison Commercial grade H), neutral alumina (Brockman Activity I) and alumina (80-200 mesh, Fisher) deactivated with 3% (v/v) distilled water were used for chromatography. Anhydrous magnesium sulfate was used to dry solutions in organic solvents.

The following compounds were prepared in the laboratory: 4-methylacetanilide, (D. L. Fyles), (Z)-4-t-butyl-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (Dr. G. S. Bapat), 3-chloro-4-methyl-4-nitrocyclohexa-2,5-dienone (Dr. G. N. Henderson, R.G.Clewley). Donation of samples of these compounds is gratefully acknowledged.

7.3 Preparation of Starting Materials and Authentic Samples:

7.3.1 Preparation of 2-chloro-p-cresol (119)[143a]:

A mixture of sulfuryl chloride (22cm^3, d=1.68, 0.275mol) and p-cresol 219 (27g, 0.25mol) in a 100cm^3 round bottom flask fitted with a reflux condenser connected through a $CaCl_2$ drying tube to a trap containing NaOH solution was heated in a water bath thermostated at 55°C for 1h. Excess sulfuryl chloride was removed on the water aspirator and the pure cresol 119 (24g, 68% yield) was obtained by distillation bp:

194-198°C (lit[143b] 195-196°C); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.26 (3H, s, CH_3), 5.40 (1H, br s, OH), 6.89 (1H, d, J=8.23Hz, 6-H), 6.97 (1H, dd, J=1.60 and 8.23Hz, 5-H), 7.12 (1H, d, J=1.60Hz, 3-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 20.2 (CH_3), 116.1 (C-6), 119.5 (C-2), 128.9 and 129.3 (C-3 and C-5), 131.0 (C-4), 149.1 (C-1)ppm.

7.3.2 Preparation of 3-chloro-p-cresol (120)[99]:

Trifluoromethanesulfonic acid (5cm^3) was added to 4-chloro-4-methylcyclohexa-2,5-dienone (143) (2g, 0.016mmol) at -78°C. The mixture was allowed to warm up to 0°C and stirred for 20min in an ice bath. The mixture was neutralised with sodium bicarbonate, diluted to 150cm^3 with water, then extracted with ether (3x50cm^3). The ether solutions were combined, washed with water (2x50cm^3) and dried over anhydrous $MgSO_4$. Removal of ether gave cresol 120 (1.6g, 69% yield) as a brown oil. A part of this cresol was purified by crystallization from pentane to yield off white crystals mp: 53-4°C (lit[99] 55°C); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.28 (3H, s, CH_3), 4.75 (1H, br s, OH), 6.64 (1H, dd, J=8.20 and 2.60Hz, 6-H), 6.86 (1H, d, J=2.6Hz, 2-H), 7.06 (1H, d, J=8.20Hz, 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 19.0 (CH_3), 114.0 (C-6), 116.2 (C-2), 128.5 (C-4), 131.5 (C-5), 134.6 (C-3), 153.6 (C-1)ppm.

7.3.3 Preparation of anisoles:

In a typical experiment, the phenol was dissolved in 10% aqueous NaOH (1:1 mol proportion) solution. The mixture was cooled in an ice bath and dimethylsulfate (1:1 mol proportion) was slowly added to it. The resulting mixture was refluxed for 3h. The mixture was extracted with ether and the combined ether solution was washed with dilute $NaHCO_3$ solution and with water, and then dried over anhydrous $MgSO_4$. After removal of ether, the crude anisole was purified by distillation.

Using this method, the following anisoles were prepared:

(a) 2-chloro-4-methylanisole (115) (94% yield):

Bp: 214-8°C (lit[144] 215-8°C); IR (neat): 1255 and 1062 ($ArOCH_3$); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.20 (3H, s, CH_3), 3.79 (3H, s, OCH_3), 6.74 (1H, d, J=8.40Hz, 6-H), 6.95 (1H, dd, J=8.40 and 2.03Hz, 5-H), 7.11 (1H, d, J=2.03Hz, 3-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 20.3 (CH_3), 56.3 (OCH_3), 112.3 (C-6), 122.2 (C-2), 128.3 (C-5), 130.9 (C-3), 131.1 (C-4), 153.1 (C-1)ppm.

(b) 3-chloro-4-methylanisole (117) (95% yield):

Bp: 210-3°C (lit[144] 212°C); IR (neat): 1240 and 1045cm^{-1} ($ArOCH_3$); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.29 (3H, s, CH_3), 3.76 (3H, s, OCH_3), 6.70 (1H, dd, J=2.50 and 8.40Hz, 6-H), 6.90 (1H, d, J=2.50Hz, 2-H), 7.99 (1H, d, J=8.40Hz, 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 18.9 (CH_3), 55.5 (OCH_3), 112.8 (C-6), 114.6 (C-2), 127.9 (C-4), 131.2 (C-5), 134.3 (C-3), 158.4 (C-1)ppm.

(c) 2-bromo-4-methylanisole (114) (85% yield):

Bp: 125-6°C (lit[145] 125-7°C,25mm); IR (neat): 1255 and 1050 ($ArOCH_3$): ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.20 (3H, s, CH_3), 3.79 (3H, s, OCH_3), 6.72 (1H, d, J=8.30Hz, 6-H), 6.98 (1H, dd, J=8.30 and 1.50Hz, 5-H), 7.29 (1H, d, J=1.50Hz, 3-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 19.9 (CH_3), 56.1 (OCH_3), 111.1 (C-2), 111.7 (C-6), 128.7 (C-5), 131.2 (C-4), 133.5 (C-3), 153.6 (C-1)ppm.

(d) 4-methyl-2-nitroanisole (116) (76% yield):

Bp: 272-4°C (lit[146] 274°C); IR (neat): 1530 and 1350 (NO_2), 1260 and 1020 ($ArOCH_3$); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.33 (3H, s, CH_3), 3.92 (3H, s, OCH_3), 6.98 (1H, d, J=8.55Hz, 6-H), 7.34 (1H, dd, J=8.55 and 2.10Hz, 5-H), 7.64 (1H, d, J=2.10Hz, 3-H)ppm; ^{13}C-NMR (62.9MHz,

$CDCl_3$): δ_C 19.8 (CH_3), 56.3 (OCH_3), 113.3 (C-6), 125.4 (C-3), 129.9 (C-4), 134.6 (C-5), 139.0 (C-2), 150.7 (C-1)ppm.

(e) 4-methyl-3-nitroanisole (118) (76% yield):

Bp: 263-9°C (lit[146] 266-7°C); IR (neat) 1527 and 1345 (NO_2), 1250 and 1035 ($ArOCH_3$); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.21 (3H, s, CH_3), 3.79 (3H, s, OCH_3), 6.72 (1H, d, J=8.35Hz, 5-H), 6.98 (1H, dd, J=8.35 and 1.40Hz, 6-H), 7.30 (1H, d, J=1.40Hz, 2-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 19.3 (CH_3), 55.5 (OCH_3), 108.9 (C-2), 119.6 (C-6), 125.2 (C-4), 133.2 (C-5), 149.2 (C-3), 157.9 (C-1)ppm.

7.3.4 Preparation of 2-bromo-6-nitro-p-cresol (149):

Pure cresol 149 was prepared by nitrating 2-bromo-p-cresol (150) (1.87g, 10mmol). The cresol 150 was added to a mixture of nitric acid (0.69g, 11mmol) and CH_2Cl_2 (5cm^3) at 0°C and the mixture was stirred for 30min during which time the temperature was allowed to rise to 25°C. The mixture was poured on crushed ice (25g) when the cresol 149 precipitated as a yellow solid. After filtration the residue was dissolved in CH_2Cl_2(25cm^3), washed with water (2x10cm^3) and evaporated to dryness to yield a yellow residue (2.1g, 90.5% yield) of cresol 149. Crystallization from methanol-water mixture gave yellow flakes of cresol 149. mp: 69°C (lit[147] 69°C); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.35 (3H, d, J=0.78Hz, CH_3), 7.70 (1H, d, J=1.00Hz, 3-H), 7.89 (1H, dd, J=1.00 and 0.78Hz, 5-H), 10.97 (1H, br s, OH)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 20.0 (CH_3), 112.8 (C-2), 124.0 (C-5), 130.6 (C-4), 133.8 (C-6), 141.7 (C-3), 150.0 (C-1)ppm.

7.3.5 Preparation of 2-bromo-4-methyl-6-nitroanisole (147);

Cresol 149 (1g, 4.3mmol) was methylated by the procedure described above using dimethyl sulfate (0.595g; 4.7mmol). Pure anisole

(0.92g, 87% yield) was obtained after crystallization from methanol-water mixtures. mp: 45°C; ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.37 (3H, d, J=0.54Hz, CH_3), 3.98 (3H, s, OCH_3), 7.52 (1H, dd, J=0.55 and 2.05Hz, 3-H), 7.60 (1H, d, J=2.05Hz, 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 20.3, (CH_3), 62.5 (OCH_3), 119.2 (C-2), 124.5 (C-5), 135.6 (C-4), 138.1 (C-3), 144.9 (C-6), 148.5 (C-1)ppm.

7.4 Nitration Reactions:

(a) Nitration of 4-chlorotoluene (111):

A nitrating mixture was prepared by the careful addition of acetic anhydride (75g, 0.75mmol) with stirring to freshly distilled nitric acid (18.9g, 0.3mmol) at -78°C. After the completion of addition, the mixture was warmed to 0°C, stirred for 15min at 0°C and cooled to -40°C. Trifluoroacetic anhydride (20.8g, 0.15mmol) was then slowly added to the mixture at -40°C. A solution of 111 (18.99g, 0.15mol) in acetic anhydride (15g, 0.15mol) was added dropwise over 30min to the nitrating mixture at -40°C. After the addition, the reaction mixture was stirred for 1h, at -40°C, cooled to -78°C and poured into ether (80cm^3) at -78°C contained in a 3dm^3, three necked round bottomed flask fitted with a mechanical stirrer. Ammonium hydroxide (6.5mol, 450cm^3) was added in small portions to the stirred mixture. After the addition was complete, stirring was continued for 1h, during which the mixture warmed to room temperature. The ether layer was separated and the residue was washed with ether (400cm^3). The combined ether solution was washed with cold water (4x300cm^3) and dried. Removal of ether on the rotorvapor at 15°C yielded a brown oil (31g). The ^{1}H-NMR spectrum of the crude mixture indicated the presence of 70% (Z)-3-chloro-6-methyl-6-nitrocyclohexa

-2,4-dienyl acetate (100), 13% 4-chloro-3-nitrotoluene (122) and 17% 4-chloro-2-nitrotoluene (121).

Crystallization from ether pentane (500cm^3, 1:4) at -20°C afforded crude diene 100 (12g), which on recrystallization gave colorless crystals, mp 49-50°C; IR (KBr) 1740 and 1230 ($OCOCH_3$), 1555 and 1375 (NO_2); UV (CH_3OH):-263nm (ε=390 $m^2 mol^{-1}$); ^{1}H-NMR (250MHz, $CDCl_3$):δ 1.78 (3H, s, CH_3), 1.99 (3H, s, $OCOCH_3$), 5.53 (1H, dd, J=6.13 and 1.65Hz, 1-H), 6.03 (1H, dd, J=10.20 and 1.97Hz, 4-H), 6.12 (1H, ddd, J=6.13, 1.97 and 0.61Hz, 2-H), 6.55 (1H, ddd, J=10.20, 1.65 and 0.61Hz, 5-H)ppm; ^{13}C-NMR ($CDCl_3$, 62.9MHz): δ_C 20.6 ($OCOCH_3$), 23.2 (6-CH_3), 70.2 (C-1), 87.2 (C-6), 118.1 (C-2), 126.1 (C-4), 129.4 (C-5), 133.6 (C-3), 169.5 ($OCOCH_3$); analysis: C 46.67%, H 4.35%, N 6.05% (calculated for $C_9H_{10}NO_4Cl$: C 46.61%, H 4.29%, N 5.92%).

(b) Nitration of 4-bromotoluene (110):

A solution of 110 (17.07g, 0.1mol) in acetic anhydride (10.21g, 0.1mol) was added dropwise with stirring over 30min to a nitrating mixture at -40°C, prepared in the same way as described above from nitric acid (12.64g, 0.2mol), acetic anhydride (51.1g, 0.5mol) and trifluroacetic anhydride (21.05g, 0.1mol). After complete addition the reaction mixture was stirred for an additional 90min at -40°C and then worked up with NH_4OH as described before to yield a reddish-brown oil (25.51g). The ^{1}H-NMR spectrum of the crude mixture indicated the composition was 64% (Z)-3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (101), 8% 4-bromo-3-nitrotoluene (124) and 28% 4-bromo-2-nitrotoluene (123).

Crystallization from ether-pentane mixture at -20°C afforded crude diene 101 (9g) as pale yellow crystals, which was purified by recrystallization. mp: 48-49°C; IR (KBr): 1745 and 1230 ($OCOCH_3$), 1555

and 1365 (NO_2); UV (CH_2Cl_2): 266.4nm (ε=350 $m^2 mol^{-1}$); ^{1}H-NMR ($CDCl_3$, 250MHz): δ 1.77 (3H, s, CH_3), 1.98 (3H, s, $OCOCH_3$), 5.45 (1H, dd, J=6.15 and 1.76Hz, 1-H), 6.13 (1H, dd, J=10.23 and 1.80Hz, 4-H), 6.37 (1H, ddd, J=6.15, 1.80 and 0.55Hz, 2-H), 6.45 (1H, ddd, J=10.23, 1.76 and 0.55Hz, 5-H)ppm; ^{13}C-NMR ($CDCl_3$, 62.9MHz): δ_C 20.6 ($OCOCH_3$), 23.1 (6-CH_3), 70.4 (C-1), 86.8 (C-6); 122.0 (C-2), 122.6 (C-3), 127.8 (C-4), 128.5 (C-5), 169.0 ($OCOCH_3$); analysis: C 39.36%, H 3.52%, N 5.04% (calculated for $C_9H_{10}NO_4Br$: C 39.15%, H 3.65%, N 5.07%).

(c) Nitration of 4-methylanisole (112):

A solution of 112 (54.6g, 0.445mol) in acetic anhydride (45.4g, 0.445mol) was added dropwise with stirring at -40°C over 30min to a nitrating mixture prepared from nitric acid (56g, 0.89mol) and acetic anhydride (181.55g, 1.78mol). After complete addition, the mixture was stirred for 30min at -40°C, then transferred into a three necked 3dm^3 round bottom flask fitted with a mechanical stirrer, a low temperature thermometer, an ammonia condenser, and containing 1.5dm^3 ether at -78°C. Ammonia was condensed into the mixture until the temperature which had risen to -60°C fell again to -78°C. At this point the mixture was alkaline to litmus. Excess NH_3 was removed on the aspirator. During the removal, the temperature was allowed to rise to 0°C over a period of 60min, after which time the mixture was neutral to litmus. The ether layer was decanted into a separating funnel and the residue was washed with more ether (750cm^3). The combined ether solution was washed with cold distilled water (4x500cm^3) and dried. Removal of the ether at 15°C yielded a reddish brown oil (80g). The ^{1}H-NMR spectrum of this mixture indicated the composition was 30% (Z)-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (102), and

70% 4-methyl-2-nitroanisole (116).

Crystallization from ether-pentane mixture at -20°C afforded in three successive crops crude diene 102 (26g), which on recrystallization yielded colorless crystals of diene 102, mp: 101.5-103.5 °C ; IR (KBr): 1735 and 1235 ($OCOCH_3$), 1545 and 1370 (NO_2), 1450 (OCH_3); UV (CH_2Cl_2): 271.3nm (ε=290m mol); ^{1}H-NMR ($CDCl_3$, 250MHz): δ 1.77 (3H, s, CH_3), 1.95 (3H, s, $OCOCH_3$), 3.60 (3H, s, OCH_3), 4.97 (1H, dd, J=6.57 and 1.75Hz, 2-H), 5.62 (1H, dd, J=6.57 and 1.52Hz, 1-H), 5.93 (1H, dd, J=10.20 and 1.75Hz, 4-H), 6.56 (1H, dd, J=10.20 and 1.52Hz, 5-H)ppm; ^{13}C-NMR ($CDCl_3$, 62.9MHz): δ_C 19.6 ($OCOCH_3$), 22.6 (CH_3), 53.8 (OCH_3), 70.8 (C-1), 87.3 (C-6), 87.8 (C-2), 122.7 (C-4), 128.4 (C-5), 155.2 (C-3), 168.6 ($OCOCH_3$)ppm; Analysis C 53.00%, H 5.94%, N 6.14%; (calculated for $C_{10}H_{13}NO_5$: C 52.86%, H 5.77%, N 6.16%).

(d) Nitration of 4-acetamidotoluene (113):

Finely powdered 113 (1.49g, 10mmol) was added to a nitrating mixture prepared from nitric acid (3.15g, 50mmol), acetic anhydride (15g, 150mmol) and trifluoroacetic anhydride (2.1g, 10mmol) at -40°C. The mixture was stirred at -40°C for 2h, cooled to -78°C and added to ether (500cm^3) at -78°C. Ammonium hydroxide (100cm^3, 1.4mol) was slowly added with stirring and the mixture was stirred for an additional 2h at -78°C. The ether layer was decanted and stored at -78°C. The residue was dissolved in cold water (250cm^3) in a separating funnel previously cooled to -20°C. The combined solution was quickly washed with cold brine (4x250cm^3), dried at -78°C and filtered through a jacketed filtering funnel (-78°C) into a 1dm^3 round bottom flask, cooled to -78°C.

The ether was removed on a rotovapor connected to a high vacuum pump via a dry ice condenser followed by three liquid nitrogen traps. The evaporation flask was maintained at -40°C. The ^{1}H-NMR spectrum of the yellow residue (2g) obtained, taken at -40°C, indicated the presence of 35% (Z)-3-acetamido-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (103), and 65% 4-methyl-2-nitroacetanilide (125). The mixture was chromatographed on activated silica gel (mesh size 60-200, 75g) contained in a jacketed filtering funnel (4x15cm^{3}) cooled to -78°C. Solvent used as eluent was cooled, in a jacketed dropping funnel, to -78°C under nitrogen. All fractions were collected in flasks cooled to -78°C, and evaporated below -40°C. Elution first with 60% ether-petroleum ether and with 80% ether-petroleum ether gave pure 125 mp: 95-96°C (lit[148] 96°C); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.22 (3H, s, CH_3), 2.32 (3H, s, $NHCOCH_3$), 7.38 (1H, dd, J=1.85 and 8.70Hz, 5-H), 7.92 (1H, d, J=1.85Hz, 3-H), 8.54 (1H, d, J=8.70Hz, 6-H), 10.12 (1H, s, NH)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 20.5 (CH_3), 25.5 ($NHCOCH_3$), 122.2 (C-6), 125.5 (C-3), 132.5 (C-4); 133.5 (C-1), 136.4 (C-2), 136.8 (C-5), 168.9 ($NHCOCH_3$). The 90% ether-petroleum ether fraction contained 30% of 125 and 70% of diene 103.

The mixture of 125 and 103 (~500mg) was rechromatographed on silica gel (75g) under the same conditions. Pure diene 103 was eluted with 100% ether fraction and was used for characterization without further purification. ^{1}H-NMR ($CDCl_3$, 250MHz, -32°C): δ 1.78 (3H, s, CH_3), 1.95 (3H, s, $OCOCH_3$), 2.10 (3H, s, $NHCOCH_3$), 5.62 (1H, dd, J=6.55 and 1.53Hz, 1-H), 6.09 (1H, dd, J=10.30 and 1.70Hz, 4-H), 6.49 (1H, m, 2-H), 6.61 (1H, dd, J=10.30 and 1.53Hz, 5-H), 7.64 (1H, m, NH)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$-32°C): δ_C 20.7 ($OCOCH_3$), 23.3 (CH_3), 24.5

($NHCOCH_3$), 70.3 (C-1), 87.7 (C-6), 102.6 (C-2), 122.7 (C-4), 129.1 (C-5), 134.3 (C-3), 169.2 and 170.0 ($OCCOCH_3$ and $NHCOCH_3$)ppm.

(e) Nitration of 2-chloro-4-methylansiole (115):

Anisole 115 (7.8g, 0.05mol) was added to a nitrating mixture prepared from nitric acid (6.3g, 0.1mol) and acetic anhydride (25.5g, 0.25mol) at -40°C, over a period of 2min. After stirring for 1h at -40°C the mixture was cooled to -78°C. At this stage the ^{1}H-NMR spectrum showed that the composition was 49% (Z)-4-chloro-3-methoxy--6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (130), 18% 2-chloro-4-methyl-4-nitrocyclohexa-2,5-dienone (134) and 33% 2-chloro-4-methyl-6-nitroanisole (136). The mixture was poured into ether (500cm^3) at -78°C.

Ammonium hydroxide (75cm^3, 1.1mol) was slowly added to this mixture and stirring was continued for 1h. The ether layer was separated and the residue was dissolved in water (200cm^3) and extracted with ether (2x100cm^3). The combined ether solution was washed with water (4x150cm^3), dried and concentrated on the rotovapor at 15°C to yield a heterogenous mixture. Crude (Z)-4-chloro-3-methoxy-6-methyl--6-nitrocyclohexa-2,4-dienyl acetate 130 (5.2g) was obtained on filtration. Removal of ether from the filtrate gave a yellow oil (6g). The ^{1}H-NMR spectrum of this oil indicated the presence of 10.5% unchanged anisole 115, 56.5% of 136, 22.5% of 137, 5.5% 2-chloro-4-methyl-4-nitrocyclohexa-2,5-dienyl dimethyl ketal (135) and 4% diene 130.

Pure diene 130 was obtained as white crystals after recrystallization from ether-petroleum ether mixture at -20°C. It had mp 82°C; IR (KBr): 1735 and 1230 ($OCOCH_3$), 1540 and 1360 (NO_2), 1235

(OCH_3), 665 (C-Cl); UV (CH_2Cl_2): 275.6nm (ε=123.7 $m^2 mol^{-1}$); ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.80 (3H, s, CH_3), 1.97 (3H, s, $OCOCH_3$), 3.68 (3H, s, OCH_3), 5.12 (1H, d, J=6.45Hz, 2-H), 5.60 (1H, dd, J=6.45 and 1.85Hz, 1-H), 6.73 (1H, d, J=1.85Hz, 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 20.7 ($OCOCH_3$), 23.5 (CH_3), 55.8 (OCH_3), 71.2 (C-1), 88.7 (C-6), 91.1 (C-2), 126.2 (C-5), 127.6 (C-4), 152.4 (C-3), 169.6 ($OCOCH_3$)ppm; analysis: C 45.70%, H 4.55%, N 5.22%; (calculated for $C_{10}H_{12}NO_5Cl$: C 45.90%, H 4.62%, N 5.35%).

(f) Nitration of 2-chloro-p-cresol (119):

A nitrating mixture was prepared from nitric acid (1.89g, 0.03mol) and acetic anhydride and cooled to -45°C. To this mixture cresol 119 (1.42g, 0.01mol) was added and stirred for 10min then cooled to -78°C. The ^{1}H-NMR spectrum of this mixture at this stage indicated the presence of 58% 2-chloro-6-nitro-p-cresol (137) and 42% of 2-chloro-4-methyl-4-nitrocyclohexa-2,5-dienone (134).

The reaction mixture was poured into ether (200cm^3) at -78°C, and neutralized with excess NH_4OH (35cm^3, 0.5mol). After stirring the mixture for 1h at -78°C, the ether layer was separated and the residue diluted with water (100cm^3) was extracted with cold ether (2x50cm^3). The combined ether solution was washed with water (4x75cm^3), dried and filtered through a jacketed filtering funnel cooled to -78°C. The ether was removed from the filtrate at -40°C. The ^{1}H-NMR spectrum of the remaining residue indicated the presence of 12% cresol 137 and 88% dienone 134.

The mixture was dissolved in 80% ether-petroleum ether (30:60) (250cm^3) and filtered through basic alumina (150g) contained in a jacketed filtering funnel cooled to -78°C. The alumina was washed with 80% ether - 20% petroleum ether (250cm^3) followed by 100% ether

($250cm^3$). After removal of the ether at -50°C, the filtrate and the washings yielded pure dienone 134: ^{1}H-NMR (250MHz, $CDCl_3$, -40°C): δ 2.04 (3H, s, CH_3), 6.52 (1H, d, J=10.12Hz, 6-H), 7.20 (1H, dd, J=10.12 and 2.80Hz, 5-H), 7.34 (1H, d, J=2.80Hz, 3-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$, -40°C): δ_C 25.1 (CH_3), 84.6 (C-4), 128.4 (C-6), 137.5 (C-3), 142.0 (C-5), 142.2 (C-2), 198.5 (C-1)ppm.

(g) Nitration of 3-chloro-4-methylanisole (117):

Anisole 117 (78mg, 0.5mmol) was added to a nitrating mixture prepared from nitric acid (63mg, 1mmol) and acetic anhydride (510mg, 5mmol) at -45°C. After 3min at -45°C a ^{1}H-NMR sample was withdrawn and the reaction at -40°C in the probe was followed by ^{1}H-NMR. After 35min the reaction was complete and there was present 26% 3-chloro-4-methyl-2-nitroanisole (138), 51% 5-chloro-4-methyl-2-nitroanisole (139) and 23% 3-chloro-4-methyl-4-nitrocyclohexa-2,5-dienone (140).

Similar product mixtures were obtained from different reaction mixtures using: (a) 1.5 mol proportion of nitric acid and 10 mol proportion of acetic anhydride at -40°C and (b) 2 mol proportion of nitric acid, 10 mol proportion of acetic anhydride together with a 1mol proportion of trifluoroacetic anhydride at -60°C.

(h) Nitration of 3-chloro-p-cresol (120):

Cresol 120 (490mg, 3.4mmol) was added dropwise over a period of 5min to a nitrating mixture prepared from nitric acid (270mg, 4.28mmol) and $CHCl_3$ ($4cm^3$) at -60°C. The mixture was stirred for 30min during which the temperature was allowed to rise to -40°C. The ^{1}H-NMR spectrum of the mixture at this stage indicated the composition as 22% 3-chloro-4-methyl-4-nitrocyclohexa-2,5-dienone (140), 25% 3-chloro-2-nitro-p-cresol (142), and 53% 5-chloro-2-nitro-p-cresol (141). It was then cooled to -78°C and transferred onto an alumina

(basic, 30g) column cooled to -78°C, and kept under argon. The column was eluted with ether ($50cm^3$) followed by CH_2Cl_2 ($200cm^3$). The eluents were collected in a receiving flask cooled to -78°C, and evaporated at -50°C to yield pure dienone 140 (70mg) as a colourless liquid. ^{1}H-NMR (250MHz, $CDCl_3$, -50°C): δ 2.01 (3H, s, CH_3), 6.50 (1H, dd, J=9.95 and 1.47Hz, 6-H), 6.69 (1H, d, J=1.47Hz, 2-H), 6.95 (1H, d, J=9.95Hz, 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$, -50°C): δ_C 22.3 (CH_3), 87.4 (C-4), 129.1 (C-2), 130.0 (C-6), 141.4 (C-5), 148.0 (C-3), 181.7 (C-1)ppm; The dienone decomposed to an equimolar mixture of cresols 141 and 142 at 0°C over a period of 10min. The alumina after isolation of the dienone was stirred with concentrated HCl acid in methanol (1:9 v/v) ($200cm^3$). The filtrate was evaporated to dryness to yield a mixture of cresols 120, 141 and 142.

The mixture was separated by chromatography on a silica gel column (80g) using ether-petroleum ether mixtures as eluents. The fractions eluted with 5% to 10% ether solutions contained pure cresol 142. Mixtures of cresols 142 and 120 were obtained on elution with 20% ether solutions. Pure cresol 120 was eluted in later 20% ether fractions. Elution with 40% to 80% ether solution gave pure cresol 141. Cresol 142 crystallized from ether-petroleum ether mixtures as yellow flakes. It had mp 69-70°C; IR (KBr): 3500 (OH), 1569 and 1320 (NO_2); UV (CH_2Cl_2): λ_{max} 361nm (ε=580 $m^2 mol^{-1}$), 291nm (ε=1167 $m^2 mol^{-1}$); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.35 (3H, s, CH_3), 7.18 (1H, s, 6-H), 7.97 (1H, s, 3-H), 10.43 (1H, s, exchanges with D_2O, OH)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$) δ_C19.1 (CH_3), 120.1 (C-6), 120.4 (C-4), 126.0 (C-3), 128.8 (C-2), 144.2 (C-5), 153.4 (C-1)ppm; MS (70ev, EI), m/e (relative intensity): 189(16), 187(48), 157(20), 129(23), 90(16), 77(100); exact mass: found 187.003

(calculated for $C_7H_6NO_3^{35}Cl$ 187.003).

Cresol 141 was obtained as brown crystals: mp 68.5°C; IR (KBr) 3360 (OH), 1530 and 1390 (NO_2); UV (CH_2Cl_2): λ_{max} 365nm (ε=219 $m^2 mol^{-1}$), 286nm (ε=403 $m^2 mol^{-1}$); ^{1}H-NMR (250MHz, $CDCl_3$):δ 2.37 (3H, s, CH_3), 6.97 (1H, d, J=8.70Hz, 6-H), 7.33 (1H, d, J=8.70Hz, 5-H), 8.80 (1H, brs, OH)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$):δ_C 18.9 (CH_3), 116.1 (C-6), 126.7 (C-3), 129.5 (C-4), 134.7 (C-2 and C-5), 151.0 (C-1)ppm; MS (70ev, EI), m/e (relative intensity): 189(14), 187(41), 157(17), 105(13), 93(10), 77(100); exact mass: found 187.003 (calculated for $C_7H_6NO_3^{35}Cl$: 187.003).

The composition of the reaction mixture prior to chromatography was determined from a separate reaction using cresol 120 (71mg, 0.5mmol) and nitric acid (47.5mg, 0.75mmol) in $CDCl_3$ ($0.5cm^3$). The ^{1}H-NMR spectrum of the reaction mixture indicated the presence of 39% dienone 140, 32% cresol 141 and 29% cresol 142.

(i) Nitration of 2-bromo-4-methylanisole (114):

Anisole 114 (8g, 0.05mol) was added over a period of 2min to a nitrating mixture prepared with nitric acid (7.56g, 0.12mol) and acetic anhydride (204g, 0.2mol) at -40°C. The ^{1}H-NMR spectrum of the reaction mixture indicated the presence of 30% Z-4-bromo-2-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (146), 27% 2-bromo-4-methyl-4-nitrocyclohexa-2,5-dienone (148) and 43% 2-bromo-4-methyl-6-nitroanisole (147). The mixture was stirred for 40min, cooled to -78°C and poured into ether ($450cm^3$) at -78°C. The ^{1}H-NMR spectrum of the crude mixture (8.6g) after low temperature work up with NH_4OH indicated the presence of 16% 2-bromo-6-nitro-p-cresol 149, 38% (Z)-4-bromo-3-methoxy-6-methyl-

6-nitrocyclohexa-2,4-dienyl acetate (146) and 46% anisole 147.

Crystallization of the mixture from ether-petroleum ether mixture yielded pure diene 146 (1.05g) as pale yellow crystals. mp: 85°C; IR (KBr): 1749 ($OCOCH_3$), 1550 and 1320 (NO_2); UV (CH_2Cl_2): 280.5nm (ε=232 $m^2 mol^{-1}$), 235.6nm (ε=288 $m^2 mol^{-1}$); ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.80 (3H, s, CH_3), 1.98 (3H, s, $OCO\underline{CH_3}$), 3.67 (3H, s, OCH_3), 5.09 (1H, d, J=6.62Hz, 2-H), 5.59 (1H, dd, J=6.62 and 1.91Hz, 1-H), 6.99 (1H, d, J=1.91Hz, 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 20.7 ($OCO\underline{CH_3}$), 23.2 (CH_3), 55.8 (OCH_3), 71.1 (C-1), 89.3 (C-6), 90.5 (C-2), 117.3 (C-4), 130.4 (C-5), 152.5 (C-3), 169.6 ($O\underline{C}OCH_3$)ppm; Analysis: C 39.20%, H 3.70%, N 4.69%; (calculated for $C_{10}H_{12}NO_5Br$ C 39.23%, H 3.95%, N 4.57%).

(j) Nitration of 4-methyl-2-nitroanisole (116) in the presence of trifluoroacetic anhydride:

A mixture of anisole 116 (4.4g, 0.028mol) and acetic anhydride (7g, 0.068mol) was added to a nitrating mixture prepared from nitric acid (8.8g, 0.14mol), acetic anhydride (35g, 0.34mol) and trifluoroacetic anhydride (5.88g, 0.028mol) at -20°C. The mixture was stirred for 30min, cooled to -78°C and poured into a mixture of aqueous sodium bicarbonate (160g, 2mol in 750cm^3) and ether (1dm^3). The mixture was stirred for 2h (pH=8) and the ether layer was separated. The aqueous layer was extracted with ether (2x500cm^3). The combined ether solution was washed with saturated brine (4x500cm^3), dried and then evaporated to dryness on the rotorvapor at ambient temperature. The ^{1}H-NMR spectrum of the yellow residue (5.5g) indicated that it was 88% of a mixture of dienes and 12% 4-methyl-2,6-dinitroanisole (155).

The residue was triturated with ether (250cm^3). The residue (1.1g) obtained on filtration contained 80% (Z)-3-methoxy-6-methyl-

2,6-dinitrocyclohexa-2,4-dienyl acetate (151) and 20% of the (E) isomer (152). Fractional crystallization of the residue from CH_2Cl_2 at -20°C gave 152 (88mg) as the first crop, followed by a mixture of 18% 152, and 82% 151 in the second crop (200mg). Pure diene 151 (200mg) was obtained in the third crop.

Crystallization from the filtrate gave pure diene 151 (500mg). Only mixtures were obtained on further crystallization from the mother liquor and the remaining mixture was therefore chromatographed on a silica gel (125g) column at -40°C. Mixtures (10, 20, 25, 30, 40, 50, 75 and 100)% of ether and petroleum ether were used as eluents. Pure 1-methoxy-4-methyl-2,4,6-trinitrocyclohex-2--enyl-1,5-diacetate (153) was obtained in the 10% ether fraction. Anisole 155 was obtained in the 20-25% ether fractions. Pure (Z)-3-methoxy-6-methyl-4,6-dinitrocyclohexa-2,4-dienyl acetate (154) was obtained after crystallization of the residue from the 30% ether fractions. Later fractions contained mainly mixtures of anisole 155 and 4-methyl-2,4-dinitrocyclohexa-2,5-dienyl dimethyl ketal (156) which could not be separated. All dienes were purified by recrystallization from ether-petroleum ether mixtures at -20°C. Diene 152 had mp 138°C; IR (KBr): 1755 ($OCOCH_3$), 1586 and 1565 (NO_2), 1210 (OCH_3); UV (CH_2Cl_2): λ_{max} 336.4nm (ε=800 $m^2 mol^{-1}$); ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.79 (3H, s, CH_3), 2.10 (3H, s, $OCOCH_3$), 4.04 (3H, s, OCH_3), 6.36 (1H, dd, J=10.20 and 1.61Hz, 5-H), 6.71 (1H, d, J=10.20Hz, 4-H), 7.04 (1H, d, J=1.61Hz, 1-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 20.5 ($OCO\underline{C}H_3$), 21.8 (CH_3), 58.1 (OCH_3), 68.2 (C-1), 86.3 (C-6), 122.4 (C-4), 124.3 (C-2), 135.6 (C-5), 156.5 (C-3), 169.2 ($O\underline{C}OCH_3$)ppm; Analysis: C 43.93%, H 4.23%, N 10.09%; (calculated for $C_{10}H_{12}N_2O_7$: C 44.12%, H 4.44%, N 10.29%).

Diene 151 had mp 112-4°C; UV (CH_2Cl_2): 335.6nm (ε=812

m^2mol^{-1}), 238.9nm (ε=239 m^2mol^{-1}); IR (KBr): 1755 ($OCOCH_3$), 1586 and 1565 (NO_2), 1210 (OCH_3); ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.88 (3H, s, CH_3), 1.97 (3H, s, $OCO\underline{CH_3}$), 4.03 (3H, s, OCH_3), 6.47 (1H, d, J=10.60Hz, 4-H), 6.57 (1H, d, J=2.06Hz, 1-H), 7.09 (1H, dd, J=10.60 and 2.06Hz, 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 20.4 ($OCO\underline{CH_3}$), 22.8 (CH_3), 58.0 (OCH_3), 70.4 (C-1), 88.9 (C-6), 117.2 (C-4), 123.7 (C-2), 138.3 (C-5), 155.9 (C-3), 168.4 ($O\underline{C}OCH_3$)ppm; Analysis: C 44.11%, H 4.10%, N 10.02% (calculated for $C_{10}H_{12}N_2O_7$, C 44.12%, H 4.44%, N 10.29%).

Compound 153 had mp 134°C; UV (CH_2Cl_2): 244.3nm (ε=257 m^2mol^{-1}); IR (KBr) 1790 and 1755 ($OCOCH_3$), 1545 and 1560 (NO_2), 1190 OCH_3); ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.88 (3H, s, CH_3), 2.07 (3H, s, $OCOCH_3$), 2.21 (3H, s, C_1-$OCO\underline{CH_3}$), 3.66 (3H, s, OCH_3), 5.72 (1H, d, J=11.80Hz, 6-H), 6.33 (1H, d, J=11.8Hz, 5-H), 6.96 (1H, s, 3-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 20.1 ($OCO\underline{CH_3}$), 20.9 ($OCO\underline{CH_3}$), 22.2 (CH_3), 53.4 (OCH_3), 68.0 (C-5), 87.3 (C-4), 87.6 (C-6), 95.1 (C-1), 130.1 (C-3), 148.5 (C-2), 168.1 ($O\underline{C}OCH_3$), 168.7 ($O\underline{C}OCH_3$)ppm; Analysis: C 37.95%, H 3.87%, N 10.70%; (calculated for $C_{12}H_{15}N_3O_{11}$, C 38.20%, H 4.00%, N 11.10%).

Diene 154 had mp: 99-100°C; UV (CH_2Cl_2): 248.9nm (ε=204 m^2mol^{-1}); IR (KBr): 1745 and 1010 ($OCOCH_3$), 1545 and 1360 (NO_2), 1060 (OCH_3); ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.88 (3H, s, CH_3), 1.99 (3H, s, $OCOCH_3$), 3.71 (3H, s, OCH_3), 5.27 (1H, d, J=6.70Hz, 2-H), 5.64 (1H, dd, J=6.70 and 2.02Hz, 1-H), 7.29 (1H, d, J=2.02Hz, 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 20.6 ($OCO\underline{CH_3}$), 22.5 (CH_3), 56.1 (OCH_3), 70.7 (C-1), 87.5 (C-6), 93.5 (C-2), 127.3 (C-5), 145.4 (C-4), 149.3 (C-3), 169.4

($OCOCH_3$)ppm; Analysis: C 44.12%, H 4.44%, N 10.20%; (calculated for $C_{10}H_{12}N_2O_7$, C 44.12%, H 4.44%, N 10.20%).

The anisole 155 had mp 122 °C (lit[146] 122 °C); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.48 (3H, s, CH_3), 4.04 (3H, s, OCH_3), 7.85 (2H, s, 3-H and 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 20.3 (CH_3), 64.5 (OCH_3), 129.2 (C-3 and C-5), 134.9 (C-4), 144.8 (C-2 and C-6), 145.1 (C-1)ppm.

(k) Nitration of 4-methyl-2-nitro anisole (116) at 0°C in the absence of trifluoroacetic anhydride:

Anisole 116 (8.35g, 0.05mol) was added dropwise over 2min to a nitrating mixture, prepared from nitric acid (9.45g, 0.15mol) and acetic anhydride (51g, 0.5mol), at -40°C. The reaction mixture was warmed to 0°C and stirred on an ice bath for 1h, then poured into cold ether (500cm^3, -78°C). The precipitate which formed was filtered off in a jacketed filtering funnel (-78°C). The residue was dissolved in CH_2Cl_2 (500cm^3) and washed with 10% aqueous $NaHCO_3$ (3x150cm^3). This solution was dried and evaporated to dryness. The residue after crystallization from ether-petroleum ether mixture at -20°C yielded pure diene 151 (3.5g).

The original filtrate was placed in a 2dm^3 three necked round bottom flask fitted with a mechanical stirrer and cooled to -78°C. Ammonium hydroxide (200cm^3, 3mol) was slowly added and the mixture was stirred for 2h. The organic layer was decanted, washed with water (3x250cm^3), dried and evaporated to dryness to yield a yellow residue (2.05g). The ^{1}H-NMR spectrum of this mixture indicated the presence of 75% diene 154 and 25% anisole 155. Crystallization from ether-petroleum ether mixture gave pure diene 154 (550mg). The ammonia solution after separation of the organic layer was diluted with water (250cm^3) and

extracted with ether ($2x250cm^3$). The ether layer was washed with saturated brine ($2x200cm^3$), dried and evaporated to dryness to yield a brown residue (3g). The ^{1}H-NMR spectrum of this mixture indicated the composition as 75% anisole 155 and 25% diene 154.

(1) Nitration of 4-methyl-3-nitroanisole (118):

Anisole 118 (1.169mg, 7mmol) was added to a nitrating mixture prepared from nitric acid (2.205g, 35mmol), acetic anhydride (7g, 70mmol) and trifluroacetic anhydride (2.94g, 14mmol), at -40°C. The resulting slurry was stirred for 30min at -40°C and then poured into ether at -78°C. The ^{1}H-NMR spectrum of the red solid residue (1.38g) after NH_4OH work up indicated the presence of 29% 4-methyl-2,5-dinitro anisole (158) and 71% of 4-methyl-2,3-dinitroanisole (157). Crystallization of the residue from ether-petroleum ether mixture gave anisole 157 (300mg), which was purified by recrystallization. It had mp: 132°C (lit[149] 132-133°C); ^{1}H-NMR (250MHz, $CDCl_3$): δ 7.17 (1H, d, J=8.80Hz, 6-H), 7.43 (1H, d, J=8.80Hz, 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C17.2 (CH_3), 57.1 (OCH_3), 115.9 (C-6), 122.6 (C-4), 134.5 (C-5 and C-2), 143.3 (C-3), 150.0 (C-1)ppm.

The remaining residue was separated by chromatography on a silica gel column. Anisole 157 was eluted with 10% ether - 90% petroleum ether mixtures, and the anisole 158 eluted with 60% ether - 40% petroleum ether mixtures. After crystallization pure anisole 158 was obtained as pale yellow flakes. mp: 122°C (lit[149] 123-124°C); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.58 (3H, s, CH_3), 4.03 (3H, s, OCH_3), 7.68 (1H, s,

6-H), 7.79 (1H, s, 3-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 19.4 (CH_3), 57.3 (OCH_3), 110.2 (C-6), 125.8 (C-4), 129.3 (C-3), 141.7 (C-2), 151.2 (C-1), 161.3 (C-5)ppm.

Other attempts were made to obtain diene intermediates from reaction of 40, with little success. When a mixture of $CDCl_3$ and acetic anhydride was used as a solvent, solid products separated out from the reaction solution. In one attempt the reaction mixture was filtered at -78°C after pouring into cold 50% ether-petroleum ether mixture. The ^{1}H-NMR spectrum of the residue indicated the presence of aromatic products and no dienes. The ^{1}H-NMR spectrum of the residue, obtained after removing the solvent from the filtrate at -40°C, indicated that it was a mixture of anisole 157 and 158 together with ~10% 3-methoxy--6-methyl-5,6-dinitrocyclohexa-2,4-dienyl acetate 159 [^{1}H-NMR (90MHz, Ac_2O, lock 2.15, -45°C): δ 5.32 (1H, dd, 2-H), 5.58 (1H, d, 1-H), 7.13 (1H, d, 4-H), $J_{1,2}$=6Hz, $J_{2,4}$=1.5Hz] and some 4-methyl-3,4--dinitrocyclohexa-2,5-dienone (160) [^{1}H-NMR (90MHz, Ac_2O, lock 2.15, -45°C): δ 6.50 (1H, dd, 6-H), 7.07 (1H, d, 5-H), 7.42 (1H, d, 2-H)ppm, $J_{2,6}$=2Hz, $J_{5,6}$=10Hz].

The peaks corresponding to the diene 159 and dienone 160 disappeared on raising the temperature of the probe to -30°C. Attempts to isolate the dienes after low temperature work up of the filtrate with NH_4OH also failed in repeated experiments.

7.5 Large Scale Isomerization of Dienes leading to Characterization of New Dienes:

(a) (Z)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (100):

A solution of diene 100 (10g, 43mmol) in C_6H_6 (25cm^3) was

heated in a water bath thermostated at 76°C for 2h. Removal of C_6H_6 on the rotovapor at 25°C yielded a reddish brown oil. The ^{1}H-NMR spectrum of the product indicated the presence of 11% acetate 186, 75% of a mixture of (E)- and (Z)-5-chloro-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate (188 and 187 respectively) and (E)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (198), along with 14% of unreacted diene 100.

Fractional crystallization from an ether-pentane (1:1) mixture at -20°C first yielded diene 188 (1.2g). Further crystallization of the mother liquor from an ether-pentane (1:2.5) solution yielded a mixtures of dienes 188 and 187 (1:3, 2.4g) as second crop. Three more crops of diene 188 (1.1g) were obtained from the mother liquor solution in ether-pentane (1:4, -20°C).

Recrystallization of the first crop (1g) from ether-pentane (1:2, -20°C) gave pure diene 188 (0.91g) as colorless crystals: mp: 75-77°C; IR (KBr) 1740 and 1220 ($OCOCH_3$), 1550 and 1380 (NO_2); uv (CH_3OH) λ_{max} 283nm (ε=219 $m^2 mol^{-1}$); ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.85 (3H, d, J=1.45Hz, CH_3), 2.15 (3H, s, $OCOCH_3$), 5.15 (1H, d, J=3.31Hz, 6-H), 5.94 (1H, dq, J=6.43 and 1.45Hz, 3-H), 5.96 (1H, d, J=3.31Hz, H-1), 6.44 (1H, d, J=6.43Hz, 4-H)ppm. ^{13}C-NMR (62.9MHz, $CDCl_3$, -20°C) δ_C 19.9 (CH_3), 20.7 ($OCOCH_3$), 70.7 (C-1), 88.8 (C-6), 120.7 (C-5), 122.0 (C-3), 127.9 (C-4), 131.9 (C-2), 169.8 ($OCOCH_3$)ppm; Analysis C 46.80%, H 4.26%, N 6.07% (Calculated for $C_9H_{10}NO_4Cl$, C 46.67%, H 4.35%, N 6.05%).

Pure diene 187 (1.4g) was obtained from recrystallization of the second crop as colorless crystals: mp 78°C; IR

(KBr) 1745 and 1225 ($OCOCH_3$), 1560 and 1360 (NO_2); UV (CH_3OH) λ_{max} 281.4nm (ε=240 $m^2 mol^{-1}$); ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.84 (3H, br dd, J=1.86 and ~1.5Hz, CH_3), 2.19 (3H, s, $OCOCH_3$), 5.26 (1H, d, J=8.74Hz, 6-H), 5.85 (1H, ddq, J=6.22, 2.46, 1.86 Hz, 3-H), 5.91 (1H, ddq, J=8.74, 2.46 and ~1.5Hz, 1-H), 6.46 (1H, d, J=6.22Hz, H-4)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 17.8 ($6-CH_3$), 20.5 ($OCOCH_3$), 71.0 (C-1), 86.5 (C-6), 119.0 (C-3), 122.1 (C-5), 129.9 (C-4), 134.8 (C-2), 169.8 ($OCOCH_3$)ppm; Analysis C 46.51%, H 4.38%, N 6.09% (calculated for $C_9H_{10}O_4NCl$ C 46.67%, H 4.35%, N 6.05%).

The ^{1}H-NMR of the reaction mixture after crystallization of dienes 187 and 188 indicated diene 189 was enriched to about 10%. For isolation of diene 189, the number of components in the mixture was reduced by selectively aromatizing dienes 187 and 188. A solution of the mixture (2.5g) in ether (100cm^3) was stirred with 5% aqueous ammonia (10cm^3) in an ice bath for 15min. The ether layer was separated, washed with saturated brine (2x25cm^3) and dried. Removal of the ether on the rotovapor at 15°C yielded a reddish oil (2.25g). The ^{1}H-NMR of the oil indicated the presence of 10% diene 189, 30% diene 100 and 60% mixture of toluene 122 and acetate 186, along with traces of dinitrochlorotoluene.

The mixture was separated by column chromatography on silica gel (650g) at -40°C using mixtures of ether-petroleum ether as eluent. Elution up to 3% ether gave toluene 122 as the principle product. The 6% ether fractions (4L) gave mixtures of toluene 122 and the acetate 186.

The 10% ether-petroleum ether fractions gave mixtures containing diene 189 as the principle component (<95%). Attempts to crystallize did not succeed, so diene 189 was characterized in the

mixture. It had ^{1}H-NMR (250MHz, $CDCl_3$, -20°C): δ 1.72 (3H, s, 6-CH_3), 2.08 (3H, s, $OCOCH_3$), 5.92 (1H, dd, J=3.99 and 1.73Hz, 2-H), 5.96 (1H, d, J=9.93Hz, 5-H), 6.07 (1H, dd, J=9.93 and 1.73Hz, 4-H), 6.26 (1H, d, J=3.99Hz, 1-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$, -20°C), δ_C: 19.5 ($OCO\underline{C}H_3$), 20.7 (6-CH_3), 128.4 and 128.7 (C-4 and C-5), 134.1 (C-3), 169.5 ($O\underline{C}OCH_3$)ppm;

(b) (Z)-3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (101):

A solution of diene 101 (10g, 36mmol) in C_6H_6 (20cm^3) was heated in a water bath thermostatted at 74°C for 1h. Removal of C_6H_6 on the rotovapor at 25°C yielded a reddish brown oil. The ^{1}H-NMR spectrum of the mixture indicated the presence of 74% of a mixture of (E)- and (Z)-5-bromo-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate (191) and (190) respectively and (E)-3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (192) with traces of toluene 124, acetate 193 and 26% of unreacted diene 101.

Fractional crystallization from ether-pentane (1:1, -20°C) gave diene 190 (2.56g) in the first two crops. The third crop (0.96g) from the mother liquor contained a mixture of dienes 191 and 190 (1:1). Further crystallization from ether-pentane (1:2) solution yielded a mixture of diene 191 (95%) and diene 190 as the fourth crop (700mg). Finally from a (1:3) mixture of ether-petroleum ether (30:60), diene 190 was obtained as the fifth crop (600mg).

Recrystallization of the first crop (300mg) from ether-petroleum ether (1:1) gave pure diene 190 (240mg) as pale yellow crystals: mp 93-5°C; IR: (KBr) 1735 and 1230 ($OCOCH_3$), 1560 and 1370 (NO_2); UV (CH_2Cl_2): λ_{max} 260 nm (ε=721 m^2 mol^{-1}); ^{1}H-NMR (250MHz, $CDCl_3$), δ: 1.82 (3H, br dd, J=1.63 and 1.00Hz, CH_3), 2.17 (3H, s, $OCO\underline{C}H_3$), 5.35 (1H, d, J=8.7Hz, 6-H), 5.79 (1H, dd, q, J=6.25, 2.65 and 1.63Hz, 3-H), 5.91 (1H, ddq, J=8.7, 2.65 and 1.00Hz, 1-H), 6.69 (1H, d,

J=6.25Hz, 4-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$) δ_C: 18.0 (CH_3), 20.5 ($OCO\underline{C}H_3$), 70.9 (C-1), 87.5 (C-6), 109.5 (C-5), 119.5 (C-3), 134.1 (C-4), 135.1 (C-2), 169.8 ($O\underline{C}OCH_3$)ppm; Analysis C 39.08%, H 3.67%, N 5.07% (Calculated for $C_9H_{10}NO_4Br$, C 39.15%, H 3.65%, N 5.07%).

Recrystallization of the fourth crop (500mg) from ether-petroleum ether mixture (1:1) at -20°C gave pure diene 191 as pale yellow crystals (420mg) mp: 63-64°C; IR (KBr) 1745 and 1210 ($OCOCH_3$), 1558 and 1360 (NO_2); UV (CH_2Cl_2):280 nm (ε=820 $m^2 mol^{-1}$); ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.83 (3H, d, J=1.04Hz, CH_3), 2.15 (3H, s, $OCOCH_3$), 5.24 (1H, d, J=3.47Hz, 6-H), 5.86 (1H, dq, J=6.32 and 1.04Hz, 3-H), 5.93 (1H, d, J=3.47Hz, 1-H), 6.66 (1H, d, J=6.32Hz, 4-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 19.9 (CH_3), 20.7 ($OCOCH_3$), 70.8 (C-1), 90.1 (C-6), 109.1 (C-5), 122.4 (C-3), 132.2 (C-4), 132.5 (C-2), 169.8 ($O\underline{C}OCH_3$)ppm; Analysis C 39.3%, H 3.54%, N 5.18% (Calculated for $C_9H_{10}NO_4Br$, C 39.15%, H 3.65%, N 5.07%).

The ^{1}H-NMR spectrum of the mother liquor at this stage indicated the presence of 37% dienes 190 and 191, 37% diene 101, 5% diene 192 and 21% acetate 193 and toluene 124. In order to isolate diene 192, dienes 190 and 191 were selectively aromatized. A solution of the reaction mixture (2g) in ether (10cm^3) was stirred in an ice bath with ammonium hydroxide (5cm^3, 58%) for 15min. The mixture was diluted with ether (80cm^3), washed with cold brine (4x20cm^3) and dried over anhydrous magnesium sulfate. ^{1}H-NMR of the residual oil, obtained after removal of solvent at 15°C, indicated the presence of 37% toluene 124, 21% acetate 193, 37% diene 101 and 5% diene 192.

The mixture (1.3g) was separated by column chromatography on silica gel (180g) using a mixture of ether-petroleum ether (30:60) as eluent at -40°C. Initial fractions with 3% ether gave toluene 124.

Mixtures of acetate 193, toluene 124 and diene 101 were eluted next with 6% ether.

Further elution with 10% ether gave mixtures containing diene 192 (95%) and toluene 124 (5%). Diene 192 could not be crystallized from mixtures of ether-petroleum ether solutions, and was characterized in solution. ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.74 (3H, s, CH_3), 2.13 (3H, s, $OCOCH_3$), 5.94 (1H, m, 2-H), 6.23 (3H, m, 1-H, 4-H and 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$, -15°C): δ_C 18.2 ($\underline{C}H_3$-6), 19.6 ($OCO\underline{C}H_3$), 70.8 (C-1), 87.0 (C-6), 117.1 (C-3), 126.5 (C-2), 127.2 (C-4), 129.1 (C-5), 169.5 ($O\underline{C}OCH_3$).

(c) (Z)-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (102):

A solution of diene 102 (5g, 22mmol) in C_6H_6 (50cm^3) was heated for 4h in a water bath thermostatted at -78°C. Removal of solvent on the rotovapor yielded a dark red oil. The ^{1}H-NMR of this oil indicated the presence of 48% of (E)- (Z)-5-methoxy-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate (195) and (194) (E)-3-methoxy-6-methyl-6- nitrocyclohexa-2,4-dienyl acetate (196), 15% of 5-methoxy-o-cresyl acetate (197) and 37% unreacted diene 102.

Crystallization from ether-petroleum ether mixture (1:1) at -20°C gave a single crop of diene 102 (0.45g).

The reaction mixture (3.5g) was separated by column chromatography on silica gel (325g) using mixtures of petroleum ether (30:60) and ether as eluent at -40°C.

The 6% ether fractions contained predominantly 168. The first fraction with 12% ether contained acetate 197 as a red oil: IR (neat): 1755 ($OCOCH_3$), 1210 and 1030 (Ar-OMe); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.09 (3H, s, $OCO\underline{C}H_3$), 2.30 (3H, s, CH_3), 3.76 (3H, s, OCH_3),

6.58 (1H, d, J=2.60Hz, 6-H), 6.71 (1H, dd, J=8.40 and 2.60Hz, 4-H), 7.11 (1H, d, J=8.40Hz, 3-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 15.3 (CH_3), 20.8 ($OCO\underline{CH_3}$), 55.5 (OCH_3), 107.9 (C-6), 111.9 (C-4), 121.9 (C-2), 131.3 (C-3), 149.9 (C-1), 158.7 (C-5), 169.0 ($O\underline{C}OCH_3$); MS (70ev) 180(13), 138(100), 137(39), 109(18), 107(25), 79(25), 78(28), 77(57); Analysis C, 64.06%, H 6.56%; (calculated for $C_{10}H_{12}O_3$, C 64.05%, H 6.70%).

The subsequent fraction contained a mixture (400mg) of 30% acetate 197, 50% diene 194 and 20% unreacted diene 102. The mixture could not be further separated by chromatography over silica gel using 8% ether-petroleum ether mixture as eluent at -40°C. Diene 194 was characterized in solution by NMR: ^{1}H-NMR (250MHz, $CDCl_3$) δ: 1.78 (3H, br d, J=1.70Hz, CH_3), 2.17 (3H, s, $OCOC\underline{H_3}$), 3.64 (3H, s, $OC\underline{H_3}$), 5.14 (1H, d, J=8.50Hz, 4-H), 5.36 (1H, d, J=6.80Hz, 6-H), 5.82 (2H, m, 1-H and 3-H)ppm. The chemical shifts of H-1 and H-3 were obtained after irradiation of the signal at 1.78ppm which led to the collapse of the multiplet at 5.28 to a set of overlapping doublets 5.83 (1H, 1-H) and 5.81 (1H, 3-H); ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 16.4 (CH_3, $OCO\underline{C}H_3$), 54.63 (OMe), 70.2 (C-1), 83.4 (C-6), 99.1 (C-4), 117.8 (C-3), 125.6 (C-2), 148.3 (C-5), 169.1 ($O\underline{C}OCH_3$)ppm.

Further elution with 12% ether-petroleum ether mixture gave a mixture of 50% diene 195, 20% ketal 226, 20% anisole 116 and 10% unreacted diene 102.

The 35% ether fraction contained 95% diene 195 which was characterized without further purification. ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.79 (3H, br d, J=1.05Hz, CH_3), 2.12 (3H, s, $OCOC\underline{H_3}$), 3.67 (3H, s, OCH_3), 5.09 (1H, d, J=4.32Hz, 6-H), 5.29 (1H, d, J=6.57Hz, 4-H), 5.89 (1H, dq, J=6.57 and 1.05Hz, 3-H), 5.94 (1H, d, J=4.32Hz, 1-H)ppm.

Irradiation of the signal at 1.79ppm reduced the signal at 5.89 to a doublet (J=6.52Hz). ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 19.31 (CH_3), 20.53 ($OCO\underline{C}H_3$), 55.7 (OCH_3), 71.96 (C-1), 87.1 (C-6), 97.9 (C-4), 122.1 (C-3), 124.8 (C-2), 147.9 (C-5), 169.9 ($O\underline{C}OCH_3$)ppm.

The 100% ether fraction gave a mixture (90mg) of 20% cresol 168 and 80% diene 196 which was characterized without further purification. ^{1}H-NMR (250MHz, $CDCl_3$, -15°C): δ 1.72 (3H, s, CH_3), 2.15 (3H, s, $OCOCH_3$), 3.61 (3H, s, OCH_3), 4.79 (1H, d, J=5.65Hz, 2-H), 5.17 (1H, d, J=5.65Hz, 1-H), 5.57 (1H, d, J=10.1Hz, 4-H), 6.12 (1H, d, J=10.1Hz, 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C68.6 (C-1), 87.3 (C-6), 99.1 (C-2), 119.0 (C-4), 124.3 (C-5), 156.4 (C-3), 169.7 ($O\underline{C}OCH_3$)ppm.

(d) (Z)-3-Acetamido-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (103):

A solution of diene 103 in $CDCl_3$ was heated for 30min in the NMR probe (Perkin Elmer R-32) at 35°C. The ^{1}H-NMR spectrum of the mixture indicated the composition as 11% of 4-methylacetanilide (113) 22% of 4-methyl-2-nitroacetanilide(125), 23% (Z)-5-acetamido-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate (198) along with 44% unreacted diene 103. Diene 198 was characterized in solution. ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.86 (3H, d, J=1.57Hz, CH_3), 2.08 and 2.09 (3H, s, $NHCOCH_3$ and $OCOCH_3$), 5.51 (1H, dd, J=2.05 and 1.04Hz, 6-H), 5.91 (1H, dd, J=2.05Hz, 1-H), 6.13 (1H, dq, J=6.73 and 1.57Hz, 3-H), 6.49 (1H, dd, J=6.73 and 1.04Hz, 4-H).

On heating the reaction mixture for a further 10min at 60°C, the dienes 198 and 103 partially decomposed. After 1h at 60°C, the ^{1}H-NMR spectrum of the mixture contained 32% acetanilide 113, 35% nitroacetanilide 125 and 12% 4-methyl-2,6-dinitroacetanilide 199.

^{1}H-NMR (250MHz, $CDCl_3$): δ 2.36 (3H, s, $NHCOCH_3$), 2.38 (3H, s, $OCOCH_3$), 8.07 (2H, s, 3-H and 5-H); GCMS confirmed the presence of these compounds, 113 (m/e 149), 125 (m/e 194) and 199 (m/e 239).

(e) (Z)-3-Bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl chloride (200):

A solution of diene 200 (195mg, 0.77 mmol) in C_6D_6 was heated for 2h in a water bath thermostatted at 75°C. The ^{1}H-NMR spectrum of the mixture indicated the presence of 50% (E)-5-bromo-2-methyl-6-nitrocyclohexa-2,4-dienyl chloride (206) and 50% of a mixture of aromatic compounds including 4-bromotoluene (110) and 4-bromo-2-chlorotoluene (207). Attempts to crystallize diene 206 from mixtures of ether and pentane after removal of C_6D_6 failed. Filtration of a representative sample through silica gel at -20°C with ether led to decomposition of a major portion of the diene 206 to toluene 124. However aromatic compounds could be partially removed from the mixture on the vacuum pump at ambient temperature and diene 206 was characterized in the mixture containing ~80% diene. It had ^{1}H-NMR (250MHz, $CDCl_3$) δ: 1.96 (3H, d, J=1.20Hz, CH_3), 4.96 (1H, d, J=1.79Hz, 1-H), 5.28 (1H, d, J=1.79Hz, 6-H), 5.88 (1H, dq, J=1.20 and 6.38Hz, 3-H), 6.81 (1H, d, J=6.38Hz, 4-H)ppm. Irradiation of the signal at 1.96ppm reduced the signal at 5.88ppm to a doublet (J=6.38Hz); ^{13}C-NMR (62.9MHz, $CDCl_3$) δ_C: 20.1 (CH_3), 56.7 (C-1), 91.1 (C-6), 109.1 (C-5), 122.2 (C-3), 127.3 (C-2), 132.7 (C-4)ppm.

(f) (Z)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl chloride (201):

A solution of diene 201 (300mg, 1.2 mmol) in C_6D_6 was heated for 2h in a water bath thermostatted at 75°C, to yield a mixture of 52% (E)-5-chloro-2-methyl-6-nitrocyclohexa-2,4-dienyl chloride (208) along with 9% unreacted diene 201 and 39% of a mixture of 2,4-dichlorotoluene (209) and 4-chlorotoluene (111). On keeping the reaction mixture on the vacuum pump for 12h, the aromatic compounds were partially removed and diene 208, enriched to ~90%, was characterized in solution. ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.95 (3H, d, J=1.47Hz, CH_3), 4.96 (1H, d, J=1.84Hz, 1-H), 5.14 (1H, d, J=1.84Hz, 6-H), 5.91 (1H, dq, J=6.30 and 1.47Hz, 3-H), 6.40 (1H, d, J=6.30Hz, 4-H)ppm. On irradiating the doublet at 1.95ppm, the signal at 5.91ppm collapsed to a doublet (J=6.3Hz); ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 19.9 (CH_3), 56.3 (C-1), 89.1 (C-6), 120.8 (C-5), 121.5 (C-3), 128.4 (C-4), 133.9 (C-2)ppm.

(g) (Z)-3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl methyl ether (203):

A solution of diene 203 (60mg, 0.24 mmol) in $CDCl_3$ ($1cm^3$) was kept at ambient temperature. After 18h, the ^{1}H-NMR spectrum indicated the presence of 44% (E)-5-bromo-2-methyl-6-nitrocyclohexa-2,4-dienyl methyl ether (211) and 56.5% unreacted diene 203. There was no change in the composition on further heating of the mixture for 2h in a water bath thermostated to 40°C. After 7h at 55°C the composition was 55% of diene 211 and 45% of a mixture of toluene 124 and 5-bromo-o-cresoxy methyl ether 214. Diene 210 could not be separated by crystallization

and was characterized in solution. ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.90 (3H, d, J=1.00Hz, CH_3), 3.48 (3H, s, OCH_3), 4.16 (1H, d, J=2.4Hz, 1-H), 5.24 (1H, d, J=2.40Hz, 6-H), 5.75 (1H, dq, J=6.20 and 1.00Hz, 3-H), 6.58 (1H, d, J=6.20Hz, 4-H)ppm. On irradiating the centre of the doublet at 1.90ppm, then signal at 5.75ppm collapsed to a doublet (J=6.20Hz); ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 19.2 (CH_3), 55.7 (OCH_3), 79.9 (C-1), 89.8 (C-6), 112.6 (C-5), 120.3 (C-3), 131.9 (C-4), 137.7 (C-2)ppm.

(h) (Z)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl methyl ether (202):

A solution of diene 202 (20mg, 0.08 mmol) in $CDCl_3$ (0.5cm^3) was heated for 4h in a water bath thermostatted at 50°C. The ^{1}H-NMR of the mixture indicated the presence of 61% (E)-5-chloro-2-methyl-6-nitrocyclohexa-2,4-dienyl methyl ether (210), along with 40% unreacted diene 202 and traces of aromatics.

Diene 210 was characterized in solution. ^{1}H-NMR (90MHz, $CDCl_3$): δ 1.9 (3H, d, J=1.75Hz, CH_3), 3.43 (3H, s, OCH_3), 4.23 (1H, d, J=2.50Hz, 1-H), 5.19 (1H, d, J=2.50Hz, 6-H), 5.87 (1H, dq, J=6.00 and 1.70Hz, 3-H), 6.48 (1H, d, J=6.00Hz, 4-H).

(i) (Z)-3-Bromo-6-methyl-6-nitrocyclohexa-2,4-dienol (205):

A solution of diene 205 (75%) and cresol 215 (25%) in $CDCl_3$ was kept at ambient temperature and the ^{1}H-NMR was recorded at regular intervals. After 18.5h there was a mixture of 35% diene 205 and 40% (Z)-5-bromo-2-methyl-6-nitrocyclohexa-2,4-dienol (214) along with 25% cresol 215. At this stage the diene 214 was characterized by ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.91 (3H, dd, J=1.77 and 1.50Hz, CH_3), 3.0 (1H, br m, OH), 4.90 (1H, m, 1-H), 5.10 (1H, d, J=7.40Hz, 6-H), 5.68 (1H, ddq, J=6.10, 2.58 and 1.50Hz, 3-H), 6.60 (1H, d, J=6.10Hz, 4-H)ppm. On irradiation of the signal at 1.91ppm, the signal at 5.68ppm reduced to a

dd (J=6.10 and 2.58Hz). On irradiation of the multiplet at 4.90ppm, the signal at 5.10ppm reduced to a singlet, the multiplet at 5.68ppm collapsed to a dq (J=6.10 and 1.50Hz) and the dd at 1.9ppm collapsed to a d (J=1.77Hz).

The reaction mixture was kept at ambient temperature and ^{1}H-NMR spectrum recorded over a period of 7 days indicated no change in the ratio of dienes, but aromatization to toluene 124 and cresol 215 had increased.

(j) (Z)-3-Chloro-6-methyl-6-nitrocyclohexa-2,4-dienol (204):

A solution of diene 204 (20mg, 0.09 mmol) in $CDCl_3$ (0.5cm^3) was kept in the probe of the NMR (Bruker WM-250) instrument at 25°C and the spectrum was recorded at regular intervals. After 21h there was 45 % (Z)-5-chloro-2-methyl-6-nitrocyclohexa-2,4-dienol (212) along with 55% unreacted diene 204 and traces of cresol 213. Diene 212 was characterized in solution: ^{1}H-NMR (250MHz, $CDCl_3$); δ 1.87 (3H, br dd, CH_3), 2.80 (1H, br s, OH), 4.84 (1H, m, H-1), 4.95 (1H, d, J=7.40Hz, H-6), 5.61 (1H, ddq, J=6.20, 2.50 and 1.64Hz, H-3), 6.31 (1H, d, J=6.20Hz, H-4)ppm. Irradiation of the signal at 1.87ppm led to the collapse of the multiplet at 5.61ppm to a dd (J=6.26 and 2.50Hz). Similar irradiation of the signal at 4.84ppm led to the collapse of 'm' at 5.61ppm to a dq (J=6.26 and 1.64Hz) and reduced dd at 1.87ppm to a d (J=1.64Hz).

7.6 Kinetic Studies on the Thermal Reactions of Dienes:

Solutions of the dienes in $CDCl_3$ ($0.5cm^3$) were heated in a water bath, thermostatted at 58.5°C. The reactions were monitored by FT-^{1}H-NMR spectroscopy on WM-250 (250MHz). The compositions of the mixtures were obtained by integration of the diene region (5.1ppm to 5.5ppm and 5.7ppm to <7.0ppm) and the methyl region (1.5ppm to 2.6ppm) from expanded plots. During the time period the diene solutions were not being heated the solutions were stored in an ice bath.

[As an aid to understanding the tables, the following symbols have been used:

ZS= (Z) diastereomer of 3-X-6-methyl-6-nitrocyclohexa-2,4-dienyl derivatives;

ES= (E) diastereomer of above diene

ZI= (Z) isomer of 5-X-2-methyl-6-nirtocyclohexa-2,4-dienyl derivatives

EI= (E) diastereomer of above diene

CA= 5-X-o-cresyl acetates

3N= 4-X-3-nitrotoluene]

The rate constants, computed from the equilibrium constants ($K_{eqm} = k_1/k_{-1}$) and the slopes ($k_1 + k_{-1}$), obtained from the graphs are shown in chapter III. A standard linear regression programme was used to obtain the best fit straight line using the mehtod of least squares. The reported rate constants are estimated as reliable to ±10% as assessed from the reproducibility of the experiments using different concentrations and sampling times. This error estimate is indicative of the inherent errors in the NMR technique and the time measurements.

Table 7.1 Isomerization of diene 100 in the presence of p-cresol

Time (mins)	% 100 (ZS)	% 187 (ZI)
20	94.4	5.6
40	88.8	11.1
60	85.8	14.2
90	82.5	17.5
120	75.0	25.0
150	71.8	28.1
180	67.2	32.8
240	61.1	38.8
305	55.0	45.0
455	44.0	56.0
995	31.8	68.2
1475	28.7	71.3
1895	28.7	71.3

Table 7.2: Isomerization of diene 187 in the presence of p-cresol

Time (mins)	% 187 (ZI)	% 100 (ZS)
30	98.0	2.0
60	95.7	4.3
90	93.4	6.6
120	90.9	9.1
150	88.5	11.5
180	86.9	13.1
210	86.2	13.8
240	85.5	14.5
300	81.3	18.7
380	78.3	21.7
920	71.4	28.6
1340	71.4	28.6

Table 7.3 Reaction of diene 188 in the presence of p-cresol

Time (mins)	% 188 (EI)	% 189 (ES)	% 100 (ZS)	% 187 (ZI)	% 186 (CA)	% p-cresol remaining
20	90.9	7.7	-	-	1.4	94.6
40	84.3	11.0	-	-	4.6	66.6
60	82.6	10.3	-	-	7.0	44.2
90	77.5	15.5	-	-	7.3	38.0
120	76.9	12.3	-	-	10.8	23.2
150	72.4	16.4	-	-	11.2	4.8
180	71.2	15.7	-	-	13.7	0
240	60.0	6.3	2.9	4.6	26.1	

Table 7.4 Isomerization of diene 101 in presence of p-cresol

Time (mins)	% 101 (ZS)	% 190 (ZI)
20	92.8	7.1
40	88.4	11.6
60	83.3	16.6
90	78.8	21.2
120	72.7	27.3
150	62.5	37.5
180	59.2	40.8
240	56.7	43.3
305	47.6	52.4
455	36.2	63.8
995	32.8	67.2
1475	25.7	74.2
1895	25.7	74.3

Table 7.5: Isomerization of diene 190 in the presence of p-cresol

Time (mins)	% 190 (ZI)	% 101 (ZS)
10		
30	97.1	2.9
60	96.8	3.2
90	93.6	6.4
120	90.0	10.0
150	89.3	10.7
180	86.9	13.1
210	85.0	15.0
240	84.0	16.0
300	81.0	19.0
380	79.0	21.0
920	76.9	23.1
1340	74.3	25.7

Table 7.6: Isomerization of diene 100

Time (min)	% 100 (ZS)	% 187 (ZI)	% 188 (EI)	% 189 (ES)	% 186 (CA)
20	93.5	3.6	2.8	-	-
40	85.7	7.8	5.8	0.6	-
60	80.8	10.8	7.2	1.2	-
90	69.5	16.8	10.8	2.9	-
120	60.4	20.1	14.7	4.7	-
150	48.5	23.2	18.8	4.3	2.9
180	38.3	31.4	20.3	5.8	4.1
240	36.3	31.5	21.7	5.0	5.4
305	25.9	32.1	25.9	8.8	6.2
455	18.6	33.8	28.8	7.0	11.8
995	8.2	30.6	23.5	6.1	31.6

Table 7.7 Isomerization of diene 188

Time (mins)	% 188 (EI)	% 100 (ZS)	% 189 (ES)	% 187 (ZI)	% 186 (CA)
20	88.0	1.3	7.0	1.3	-
40	81.8	2.7	10.9	2.7	1.8
60	73.5	3.9	12.9	3.9	5.8
90	73.3	3.9	11.7	3.9	7.1
120	67.0	6.7	10.0	6.7	9.6
180	59.3	7.6	14.4	9.3	16.9
240	51.0	7.4	9.0	13.3	19.1
305	44.9	8.0	10.5	16.7	20.5
455	37.6	9.6	11.2	12.8	28.8

Table 7.8 Isomerization of diene 101

Time (mins)	% 101 (ZS)	% 190 (ZI)	% 191 (EI)	% 192 (ES)	% 193 (CA)
20	84.6	12.0	3.4	-	-
40	80.2	14.6	5.1	-	-
60	72.2	18.8	9.0	-	-
90	69.4	20.4	10.2	-	-
120	53.1	26.5	17.7	-	-
150	46.0	30.0	23.0	-	-
180	38.5	36.5	23.0	1.9	-
240	28.4	36.1	24.5	4.5	6.4
305	19.4	40.0	23.8	6.6	9.3
455	14.4	35.5	26.0	7.6	16.3
995	10.8	28.4	17.6	5.4	37.8

Table 7.9 Isomerization of diene 191

Time (mins)	% 191 (EI)	% 190 (ZI)	% 192 (ES)	% 101 (ZS)	% 193 (CA)
20	87.0	-	11.3	1.6	-
40	74.3	4.9	13.3	2.5	4.2
60	69.5	5.1	16.9	3.4	5.1
90	68.9	6.7	11.9	5.4	8.0
120	63.0	8.0	11.8	5.0	8.1
150	58.3	8.3	11.8	6.4	15.0
180	55.9	11.8	9.3	5.9	17.2
240	48.9	12.7	8.5	6.4	23.4
305	40.2	14.1	6.6	5.8	33.2
455	28.1	17.6	10.7	9.8	33.7

Table 7.10: Isomerization of diene 204 at 25°C

Time (mins)	% 204 (ZS)	% 212 (ZI)
3	86.0	13.9
4	81.5	18.5
5	78.3	21.7
6	72.5	27.5
7	69.4	30.6
8	64.4	35.5
9	62.3	37.7
10	60.1	39.9
11	59.6	40.4
12	57.8	42.2
13	56.6	43.4
14	56.1	43.9
21	54.5	45.5

7.7 Small Scale Isomerization Reactions followed on the R-32 (90MHz) NMR Spectrometer:

The solutions of the dienes (~0.1mmol) in the mentioned solvent were heated in a water bath thermostated at the desired temperature and the reactions were monitored by ^{1}H-NMR spectroscopy on the R32 (90MHz) NMR spectrometer , at regular intervals. The composition of the reaction mixtures when amounts of dienes were at their maximum values or when, in the case of a very fast reaction, complete aromatization had occurred are given in tabular form.

(a) Reactions of (Z)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (100) (ZS):

The results from the isomerization of the diene 100 are summarized in table 3.7 and 3.8 in chapter III and are not repeated here.

(b) Reactions of (Z)-5-chloro-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate 187 (ZI):

#	Solvent	Additive (mol prp)	Temp °C	Time	%100 (ZS)	%187 (ZI)	%188 (EI)	%189 (ES)	%186 (CA)	%122 (3N)
1	C_6D_6	-	75	2h	22	46	24	a	8	-
2	$CDCl_3$	-	25	6d	a	58	13	a	20	-
3	CD_3OD	-	65	5h	-	-	-	-	4	96
4	pyridine	-	25	10m	-	-	-	-	-	100
5	$CDCl_3$	p-cresol (0.50)	70	7h	33	67	-	-	a	-
6	$CDCl_3$	p-cresol (0.25)	60	18h	29	71	-	-	a	-
7	$CDCl_3$	mesitylene (1)	70	3.5h	20	20	51	a	8	-

The symbol a has been used when peaks due to trace amounts of a compound were detected in the ^{1}H-NMR spectrum but integration was not possible.

(c) Reactions of (E)-5-chloro-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate (188) (EI):

Solvent	Additive (mol prp)	Temp °C	Time	%100 (ZS)	%187 (ZI)	%188 (EI)	%189 (ES)	%122 (3N)	%186 (CA)
C_6D_6	-	75	2h	22	22	31	a	-	25
$CDCl_3$	-	25	7d	7	10	13	a	-	70
CD_3OD	-	65	2h	-	-	23	4	67	6
pyridine	-	25	5m	-	-	-	-	100	-
$CDCl_3$	p-cresol (1.0)	62	11.5h	-	-	42	8	-	50
$CDCl_3$	p-cresol (0.5)	52	3.5h	-	-	81	19	-	-
$CDCl_3$	p-cresol (0.5)	62	11.5h	-	-	35	8	-	57
$CDCl_3$	p-cresol (.25)	8.5	2.5h	-	-	73	16	-	11
$CDCl_3$	mesitylene (1.0)	70	3.5h	3	4	55	8	-	30

(d) Reactions of (Z)-3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate 101 (ZS):

Solvent	Additive (mol prop)	Temp °C	Time	%101 (ZS)	%190 (ZI)	%191 (EI)	%192 (ES)	%124 (3N)	%193 (CA)
C_6D_6	-	75	1h	19	34	37	a	-	10
$CDCl_3$	-	75	1h	21	34	34	a	-	10
$CDCl_3$	-	60	1h	72	19	9	a	-	-
$CDCl_3$	-	50	1h	75	17	8	a	-	-
$CDCl_3$	p-cresol (0.25)	54	24h	26	64	-	-	-	a
$CDCl_3$	p-cresol (0.25)	60	15h	32	68	-	-	-	a

(e) Reactions of (Z)-5-bromo-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate 190 (ZI):

Solvent	Additive (mol prop)	Temp °C	Time	%101 (ZS)	%190 (ZI)	%191 (EI)	%192 (ES)	%124 (3N)	%193 (CA)
$CDCl_3$	-	50	1.8h	5	95	a	a	-	-
$CDCl_3$	-	70	2h	9	91	a	a	-	-
$CDCl_3$	p-cresol (0.25)	60	15h	23	77	-	-	-	a
$CDCl_3$	pyridine-d_5 (0.2)	25	5m	-	-	-	-	100	-

(f) Reactions of (E)-5-bromo-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate 191 (EI):

Solvent	Additive (mol prop)	Temp °C	Time	%101 (ZS)	%190 (ZI)	%191 (EI)	%192 (ES)	%124 (3N)	%193 (CA)
$CDCl_3$	-	50	5h	5	5	68	12	-	10
$CDCl_3$	-	60	5h	6	14	40	7	-	33
$CDCl_3$	p-cresol (0.25)	60	2h	-	-	82	11	-	7
$CDCl_3$	pyridine-d_5 (.2)	25	5m	-	-	-	-	100	-

(g) Reaction of (E)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (189):

The ^{1}H-NMR spectrum of a solution of diene 189 in $CDCl_3$, kept at ambient temperature for 24h, indicated the composition as 5% of 100, 60% of 188, 4% of 187, 19% of 186 and 12% of unreacted diene 189.

(h) Reactions of (E)-3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (192):

The ^{1}H-NMR spectrum of a solution of diene 192 in $CDCl_3$ after 2 days at ambient temperature indicated the composition as 8% of 101, 62% of 191, traces of diene 190 and 30% unreacted diene 192.

When a $CDCl_3$ solution of diene 192 was kept at 60°C for 1h, it yielded a mixture containing 10% diene 101, 75% diene 191, 14% of unreacted diene 192 and traces of diene 190.

(i) Reaction of (Z)-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (102):

A solution of diene 102 (33mg, 0.15mmol) in $CDCl_3$ (0.5cm^3) was kept at 60°C for 15h. The ^{1}H-NMR spectrum of the mixture indicated the formation of 9% acetate 197, 4% anisole 116, 3% anisole (112), 30% cresol 168, 15% diene 195, 9% diene 194, 7% diene 196.together with unreacted diene 102.

When the experiment was repeated and p-cresol (0.04mmol) was added to the original solution, after 15h a mixture of 18% dienes 196, 194, 195

and 102, 3% anisole 116, 28% ketal 226, 33% nitrocresol 168 and 18% of a mixture of anisole (112) and acetate 196 was obtained. Approximately 25% of the p-cresol was converted to the nitrocresol 168. The final composition of the reaction mixture was determined from an integrated spectrum obtained on the WM-250 (250MHz) spectrometer.

(j) Reactions of (E)-5-methoxy-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate (195):

In $CDCl_3$ at 60°C diene 195 yielded acetate 197 as the major product along with anisole (112) over a period of 20h. During the reaction dienes 194, 196 and 102 were formed in trace amounts.

A similar result was obtained when the reaction was repeated in the presence of p-cresol (0.25mol proportion).

(k) Reactions of (Z)-3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl chloride 200:

In $CDCl_3$ at 60°C diene 200 yielded 43% of diene 206, 8% of toluene 207 togther with unreacted diene 200, after a period of 2h.

When the reaction was repeated and p-cresol (0.32 mol proportion) was added to the original solution after 2h there was obtained a mixture of ~10% toluene 207 and ~90% unreacted diene 200. Approximately 25% of the added p-cresol was converted to nitrocresol 168.

(i) Reaction of (Z)-4-chloro-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (130) at ambient temperature in chloroform:

A ^{1}H-NMR sample of diene 130 (18mg, 0.07mmol) in $CDCl_3$ (400µl) was kept at ambient temperature and the aromatization was monitored by ^{1}H-NMR. There was no noticeable change after 18h, but

after 7days the diene 130 had disappeared and cresol 137 and ketal 135 were present in the mixture. There were also peaks present due to methanol and acetic acid. Over the next 70 days the ketal 135 decomposed totally and cresol 137 was the only product.

(m) Reaction of diene (130) at 60°C in chloroform-d:

When the reaction was repeated at 60°C, after 3h a mixture containing 15% of anisole 136, 77% of cresol 137 and 8% ketal 135 was obtained. After 12h the composition was 80% cresol 137 and 20% anisole 136.

(n) Reaction of (Z)-3-methoxy-6-methyl-2,6-dinitrocyclohexa-2,4-dienyl acetate (151) at ambient temperature:

Diene 151 (22mg, 0.08mmol) was dissolved in $CDCl_3$ ($0.5cm^3$) and the decomposition of the diene was followed by NMR. No change was observed before 18h, after which there was slow accumulation of diene 154 along with aromatic compounds. Integration of the NMR spectra after 32 days indicated 18.5% diene 154, 5.5% ketal 156, 35% mixture of 155, 116 and 231 along with 41% unreacted diene 151. After 80 days $CDCl_3$ was removed by bubbling N_2 through the sample and the ^{1}H-NMR spectrum of the residue (250MHz, acetone-d_6) indicated 39% cresol 231, 29% anisole 155, 12% anisole 116 and 6% unchanged diene 151.

(o) Reaction of Diene (151) in chloroform-d at 60°C:

Diene 151 (15mg, 0.06mmol) was dissolved in $CDCl_3$ in an NMR tube and kept in a thermostatted water bath (60°C). The decomposition of the diene was followed by NMR. After 24h an equilibrium mixture of 26% diene 154, 18% anisole 155, 7.5% anisole 116 and 48.5% unchanged diene 151 was obtained.

(p) Reaction of (Z)-3-methoxy-6-methyl-4,6-dinitrocyclohexa-2,4-dienyl acetate (154) at ambient temperature:

A solution of diene 154 (15mg, 0.06mmol) in $CDCl_3$ ($0.5cm^3$) was kept at ambient temperature and the decomposition followed by ^{1}H-NMR. After 80 days there was still some diene 154 remaining along with a mixture of several compounds. The $CDCl_3$ was removed by bubbling N_2 through the solution and the ^{1}H-NMR (250MHz, acetone-d_6) spectrum of the residue indicated 22% cresol 231, 28% anisole 116, 35% anisole 155, 2% ketal 156 and 14.5% of unchanged diene 154.

(q) Reaction of Diene 154 in chloroform-d at 60°C:

A ^{1}H-NMR sample of diene 154 (30mg, 0.11mmol) in $CDCl_3$ ($0.5cm^3$) was heated in a water bath thermostatted at 60°C and the decomposition was monitored by ^{1}H-NMR. After 17h at 60°C, the mixture contained 14.5% anisole 155, 21.5% cresol 231 13.5% ketal 156 and 50.5% unchanged diene 154. The reaction was continued to 58h, but no integration was possible, however the only noticeable change was the decrease in dienes 154 and ketal 156 with the formation of some anisole 116.

7.8 Pyrolysis of Dienes at 150°C:

A summary of the results obtained from the reactions of the dienes are given in table 3.11 As an example the description of the reaction of diene 134 is given below.

Diene 134 (30mg) was taken in an NMR tube and heated in an oil bath thermostatted at 150°C, for 5min, during which there was evolution of brown fumes. The residual dark brown oil was dissolved in acetone-d_6. The ^{1}H-NMR spectrum (250MHz) of this solution indicated the presence of 41.5% cresol 137, 22.5% anisole 136, 20.5% anisole 115 and 15.5% cresyl acetate.

7.9 Acid Catalyzed Reactions of Dienes:

7.9.1 Reactions of (Z)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (100):

(a) Trifluoroacetic acid:

Diene 100 (30mg, 1.3 mmol) was dissolved in TFA (0.3cm^3) in an NMR tube at -30°C and the disappearance of the diene was monitored by ^{1}H-NMR. After 10 min at -30°C. 82% of the diene had reacted. The solution was slowly warmed to ambient temperature and allowed to stand for 2h, after which time the ^{1}H-NMR spectrum of the reaction mixture indicated that the diene had completely reacted. The solution was poured into ether (20cm^3) cooled in an ice bath and 10% aqueous sodium bicarbonate (5cm^3) was slowly added. The mixture was stirred for 30mins, the ether layer was separated and the aqueous layer (diluted to 10cm^3) was extracted with ether (10cm^3). The combined ether layers were dried over anhydrous magnesium sulfate and concentrated on the rotavapor (20°C). The ^{1}H-NMR spectrum and GC MS of the residue (19mg) indicated the composition as 80% of toluene 121, (m/e 171, 173) and 20% of acetate 186, (m/e 184,186).

When the reaction was repeated in a mixture of TFA (0.15cm^3) and trifluoroacetic anhydride (0.15cm^3) diene 100 gave a mixture of 38% toluene 121, (m/e 171, 173) and 62% acetate 186, (m/e = 184, 186).

b) Trifluoromethanesulfonic acid:

Diene 100, (30mg) was added to CF_3SO_3H (0.3cm^3) at 0°C to yield a dark red solution. The ^{1}H-NMR spectrum of this solution after 5 min indicated that the diene had aromatized completely to toluene 121. When the reaction was repeated in methanesulfonic acid a similar

reaction occurred and toluene 121 was the only product.

c) Boron trifluoride:

Diene 100, (30mg) was dissolved in boron trifluoride etherate ($0.3cm^3$) at -20°C. The ^{1}H-NMR spectrum, recorded immediately, indicated that all of the diene had reacted. After work up with sodium bicarbonate, the ^{1}H-NMR spectrum of the residue indicated toluene 121 as the major product. GC-MS of the product mixture however indicated the presence of trace amounts of acetate 186, (m/e: 184, 186), cresol 213, (m/e: 142,144) and cresol 168, (m/e: 153) along with toluene 121, (m/e:171,173). When anhydrous BF_3 gas was bubbled through a solution of diene 100 (30mg) in CD_2Cl_2 at -78°C, the ^{1}H-NMR spectrum of the reaction mixture indicated complete aromatization to toluene 121, which was confirmed by GC-MS of the product mixture after work up.

d) Boron trifluoride etherate in the presence of mesitylene:

A solution of diene 100, (75mg, 3.6 mmol) and mesitylene (200mg, 1.7mmol) in CD_2Cl_2 ($0.25cm^3$) was cooled to -78°C and to it was added boron trifluoride etherate ($0.25cm^3$). The mixture was slowly warmed to ambient temperature and the mixture was then worked up with sodium bicarbonate. The ^{1}H-NMR spectrum of the product mixture indicated the presence of excess mesitylene; however after prolonged evaportaion on the high vacuum pump, aromatic peak similar to those of mesitylene was still present. GC-MS of the product mixture showed toluene 121, (m/e:173,171) as the major compound along with trace amounts of acetate 186, (m/e:186,184), cresol 168, (m/e:153) and another compound with (m/e:244,246). This peak could be explained by the formation of 5'-chloro-2,2',4,6-tetramethylbiphenyl.

f) Trifluoromethanesulfonic acid in chloroform-d

Trifluoromethanesulfonic acid ($0.02cm^3$) was added to a

solution of diene 100, (45mg) in $CDCl_3$ ($0.28cm^3$) at 0°C, and the reaction was monitored by ^1H-NMR. After 15min at 0°C, only 10% of the diene remained. The reaction was warmed to ambient temperature over a period of 1h and then worked up with $NaHCO_3$. The composition of the product mixture, as indicated by ^1H-NMR and GC-MS was >95% toluene 121, (m/e:171,173). The minor product was 2-nitro-p-cresol 168, (m/e:153).

g) Reactions with trifluoroacetic acid in methanol:

To a solution of diene 100, (30mg) in CD_3OD ($0.06cm^3$) at -20°C was added TFA ($0.24cm^3$) and the reaction was monitored by NMR. There was no noticeable change after 20min at -20°C, so the temperature was increased to 0°C. No reaction occurred over 10min and the mixture was warmed to ambient temperature (22°C). After 10min , 42% of the diene had reacted. After 60h the reaction was worked up with sodium bicarbonate. The ^1H-NMR spectrum and the GC-MS of the mixture indicated the presence of 30% toluene 121, (m/e:171,173), 47% acetate 186, (m/e:184,186) and 20% cresol 213, (m/e:142,144).

In a mixture of CD_3OD ($0.15cm^3$) and TFA ($0.15cm^3$) 54% of diene 100 had reacted after 72h at ambient temperature. The reaction was complete after 17 days. After work up with sodium bicarbonate, the product mixture, as indicated by ^1H-NMR and GC-MS, contained 72% cresol 213, (m/e:142,144), 19% toluene 122, (m/e:171,173) and 9% acetate 186, (m/e:184,186).

In a mixture of CD_3OD ($0.27cm^3$) and TFA ($0.03cm^3$), 68% of diene had reacted after 14 days and all of it had disappeared after 32 days. After bicarbonate work up, the ^1H- NMR spectrum and the GC-MS of the product mixture indicated 41% toluene 122, (m/e:171,173) and 59% cresol 213, (m/e:142,144).

h) Reactions with trifluoroacetic acid in chloroform-d

Diene 100, (30mg) was added to a mixture of $CDCl_3$ (0.10cm^3) and TFA (0.3cm^3) at 0°C and the reaction was monitored by ^{1}H-NMR. The reaction ($\tau_{1/2}$=42min) was worked up after 18h at 0°C. The ^{1}H-NMR spectrum and the GC-MS of the mixture indicated the presence of 83% toluene 121, (m/e:171,173) and 17% acetate 186, (m/e:184,186).

In a mixture of $CDCl_3$ (0.20cm^3) and TFA (0.2cm^3) at 0°C, diene (100, $\tau_{1/2}\approx$2.5h) gave a mixture of 74% toluene 141, (m/e:171,173) and 25% acetate 186, (m/e:184,186).

No noticeable reaction of diene 100 was observed in a mixture of $CDCl_3$ (0.3cm^3) and TFA (0.1cm^3) at 0°C (time 30 min). After 1h at ambient temperature 44% of the diene had reacted. The reaction was complete after 9h . After work up, the ^{1}H-NMR spectrum and GC-MS indicated the presence of 50% toluene 121, (m/e:171,173) and 50% acetate 186, (m/e:184,186).

With a mixture of $CDCl_3$ (0.39cm^3) and TFA (0.01cm^3) the reaction ($\tau_{1/2}$=12h) was complete after 24h at ambient temperature. After work up, the ^{1}H-NMR spectrum and the GC-MS of the product mixture indicated the presence of 32% toluene 121, (m/e:171,173) and 68% acetate 186, (m/e:184,186).

i) Reaction with sulfuric acid in acetic anhydride:

Diene 100, (30mg) was added to a mixture of acetic anhydride (0.27cm^3) and sulfuric acid (0.03cm^3) at -20°C and the reaction was monitored by ^{1}H-NMR. The reaction ($\tau_{1/2}$=20min) was worked up with sodium bicarbonate after 24h. The ^{1}H-NMR spectrum and the GC-MS of the mixture indicated the presence of 82% toluene 121, (m/e:171,173) and 18% acetate 186, (m/e:184,186).

When the reaction was repeated using a 0.1% (v/v) mixture ($0.3cm^3$) of sulfuric acid in acetic anhydride the reaction was very slow even at 22°C. From the NMR spectra of the reaction mixture, formation of Z- and E-5-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl acetates was evident. After 90 days all diene products had disappeared. After sodium bicarbonate work up the ^{1}H-NMR spectrum and the GC-MS indicated the presence of 33% toluene 121, 5% toluene 111, 28% toluene 122 and 33% of a mixture of cresol 213 and acetate 186.

j) Reaction with sulfuric acid in acetone:

Diene 100, (30mg) was added to a mixture of 10% (v/v) sulfuric acid in acetone-d_6 ($0.3cm^3$) and the reaction was monitored by ^{1}H-NMR at 0°C. After 20min at 0°C the reaction ($\tau_{1/2}$≈10min) was warmed to room temperature and it was worked up after 12h. The ^{1}H-NMR spectrum and the GC-MS of the mixture indicated the presence of 80% cresol 213, (m/e:142,144), 7% toluene 122, (m/e:171,173) and 7% toluene 121, (m/e:171,173).

k) Reaction with sulfuric acid in methanol:

Diene 100, (1.5g, 6.5mmol) was added to a mixture of 25% (w/w) sulfuric acid and methanol (20g) at -78°C. The mixture was warmed to 0°C and stirred for 8h, then cooled and stored at -20°C for 12h. After concentrating the solution at -40°C on a rotavapor the mixture was poured into ether ($250cm^3$) and neutralized with ammonium hydroxide ($50cm^3$, 0.7mol). The organic layer was decanted out and the aqueous layer was extracted with ether ($2x50cm^3$). The combined ether solutions were washed with water ($2x100cm^3$), dried over anhydrous magnesium sulfate and evaporated to dryness at -50°C to yield an oil (1.2g). The NMR of the mixture indicated the presence of 40%

(Z)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienol (204) and 60% cresol (214). The mixture was separated by chromatography on alumina using ether-petroleum ether mixtures as eluent. The mixture (1g) was loaded onto a column of neutral alumina (110g) cooled to -78°C. Evaporation of the first fraction ($500cm^3$, 40% ether) at -40°C yielded a mixture of 70% dienol 212, 5% toluene 122 and 25% cresol 213. The second fraction ($500cm^3$, 60% ether) yielded 30% dienol 212, and cresol 213. The later fractions ($500cm^3$ at 80% and 100% ether) contained pure cresol.

The first fraction (170mg) from this column was separated again on an alumina (85g) column at -78°C using mixtures of ether and petroleum ether (each $125cm^3$ volume of eluent was collected separately) as eluent [no. of fractions,(% ether) = 2(0%), 2(5%), 2(10%), 2(20)%, 2 (30%), 2(40%), 3(100%)]. The toluene 122 was eluted in the sixth fraction. In fractions 10-11, pure dienol 204, (90mg) was obtained, followed by cresol 214 in the later fractions. The dienol 212 was characterized by NMR spectroscopy at low temperature without further purification. ^{1}H-NMR (250MHz, $CDCl_3$, -40°C): δ 1.71 (3H, s, CH_3), 2.5 (1H, brs, OH), 4.45 (1H, d, J=6.00Hz, H), 6.01 (1H, d, J=10.10Hz, 4-H), 6.07 (1H, d, J=6.00Hz, 2-H), 6.35 (1H, d, J=10.10Hz, 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$, -50°C): δ_C 22.0 (CH_3), 69.6 (C-1), 88.3 (C-6), 121.5 (C-2), 125.8 (C-4), 128.1 (C-5), 129.9 (C-3);

In another experiment, diene 100, (116mg, 0.5mmol) was stirred at ambient temperature for 6h in a mixture of 25% (w/w) sulfuric acid and methanol (1.5g). After work up with sodium bicarbonate, pure cresol 214, (65mg, 91% yield) was obtained. mp 73°C (lit[129] 73-74°C) ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.14 (3H, s, CH_3), 4.71 (1H, br s, OH), 6.72 (1H, d, J=1.53Hz, 6-H), 6.76 (1H, dd, J=1.53 and 7.90Hz, 4-H), 6.96 (1H,

d, J=7.90Hz, 3-H)ppm; ^{13}C-NMR (62.9 MHZ, $CDCl_3$): δ_C 15.2 (CH_3), 115.4 (C-6), 120.9 (C-4), 122.4 (C-2), 131.7 (C-3), 132.0 (C-5), 154.4 (C-1) ppm.

1) Reaction with hydrogen chloride:

Anhydrous HCl gas was bubbled through a solution of diene 100, (1.5g, 6.5mmol) in ether (25cm^3) at -78°C for 15min. The mixture was warmed to 0°C over a period of 30min, stirred for 15min at 0°C, then diluted with ether (100cm^3) at -78°C and neutralized with ammonium hydroxide (50cm^3, 0.7mol). After stirring the mixture for 1h, the organic layer was separated and the residue dissolved in water (100cm^3) was extracted with ether (2x50cm^3), dried over anhydrous magnesium sulfate and concentrated on the rotorvapor at 15°C to yield a pale yellow residue. The ^{1}H-NMR spectrum of this residue indicated the presence of ~90% (Z)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl chloride (201) along with some aromatic compounds. Pure diene 201, (0.69g) was obtained from the crude mixture by fractional crystallization from ether-petroleum ether mixtures at -20°C as colourless crystals mp76°C; UV (CH_3OH) λ_{max}=269nm, (ε=430 m^{2}mol^{-1}); IR: (KBr). 3040, 1640 (C=C), 1555, 1375 (NO_2); ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.81 (3H, s, CH_3), 4.96 (1H, dd, J=6.70 and 1.68Hz, 1-H), 6.10 (1H, dd, J=10.15 and 1.81Hz, 4-H), 6.13 (1H, ddd, J=6.70, 1.81 and 0.57Hz, 2-H), 6.64 (1H, ddd, J=10.15, 1.68 and 0.57Hz, 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 23.3 (CH_3), 58.4 (C-1), 88.3 (C-6), 120.3 (C-2), 126.2 (C-4), 128.5 (C-5), 132.5 (C-3); analysis: C 40.28%, H 3.79%, N 6.65%, Cl 33.83 % (calculated for $C_7H_7Cl_2NO_2$: C 40.41%, H 3.39%, N 6.73%, Cl 34.08%). When the reaction was repeated with a 6N solution of HCl solution in ether at -40°C, unchanged diene was recovered. Diene 100, (50mg) on stirring with a solution of HCl (0.05cm^3) and acetic anhydride

($0.25\ cm^3$) at room temperature for 4h gave 48% of diene 201 together with acetate 186 and toluene 122.

m) Reaction with anhydrous hydrogen bromide:

Anhydrous HBr gas was bubbled through a solution of diene 100, (1g, 4.3mmol) in ether ($10cm^3$) at -78°C for 10min and the solution was then stirred for 1h as the temperature was increased to -40°C. The ^{1}H-NMR spectrum of the residue after work up (500mg) indicated 76.5% (Z)-3-chloro-4-methyl-6-nitrocyclohexa-2,4-dienyl bromide (224) was present together with 2-bromo-4-chlorotoluene. Crystallization from ether-pentane mixture at -20°C gave pure diene (224) mp: 71°C; UV (CH_3OH): λ_{max}=280nm ($e=527 m^2 mol^{-1}$): IR (KBr) 1555 (NO_2); ^{1}H-NMR (250MHz, $CDCl_3$) δ: 1.78 (3H, s, CH_3), 5.14 (1H, dd, J=6.64 and 1.84Hz, 1-H), 6.10 (1H, dd, J=10.33 and 1.84Hz, 4-H), 6.17 (1H, dd, J=6.64 and 1.84Hz, 2-H), 6.66 (1H, dd, J=10.33 and 1.84Hz, 5-H); ^{13}C-NMR (62.9MHz, $CDCl_3$) δ_C 23.9 (CH_3), 50.2 (C-1), 89.2 (C-6), 121.5 (C-2), 126.1 (C-4), 129.4 (C-5), 131.8 (C-3); analysis C 33.46%, H 2.61%, N 5.46% (Calculated for $C_7H_7NO_2ClBr$: C 33.29%, H 2.79%, N 5.54%);

7.12.2 Reactions of (Z)-3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (101):

The procedure employed for the acid catalyzed reactions of diene 101 were similar to that of diene 100 and the results have been summarized in section 4.2. Only the experiments leading to the characterization of compounds not characterized elsewhere in this dissertation are described here.

a) Reaction with trifluoromethanesulfonic acid:

Diene (101, 27.5mg, 0.1mmol) was added to a cold solution of CF_3SO_3H ($0.3cm^3$) at 0°C, the colour of the solution changed

instantaneously to dark brown. The ^{1}H-NMR spectrum indicated complete disappearance of diene 101 and toluene 123 as the only product. After work up with sodium bicarbonate toluene (123) was isolated as the only product. It had mp=45-47°C (lit.[104b] 47°C); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.55 (3H, s, CH_3), 7.16 (1H, d, J=8.6Hz, 6-H), 7.55 (1H, dd, J=8.6 and 2.1Hz, 5-H), 8.05 (1H, dd, J=2.1Hz, 3-H); ^{13}C-NMR (62.9MHz, $CDCl_3$) δ_C: 20.0 (CH_3), 119.6 (C-4), 127.4 (C-3), 132.5 (C-1), 134.0 (C-6), 135.9 (C-5), 149.6 (C-2).

b) Reactions with trifluoroacetic acid in chloroform:

Diene 101, (27.5mg) was dissolved in a mixture of TFA ($0.3cm^3$) and $CDCl_3$ ($0.1cm^3$) at 0°C and the reaction was monitored by ^{1}H-NMR. There was slow formation of aromatic compounds, and after 5h the diene had completely aromatized to a mixture of toluene 123 and acetate 192. After work up, the ^{1}H-NMR spectrum of the product mixture indicated the presence of 37% acetate 193 and 63% toluene 123.

The reaction was repeated with $CDCl_3$ ($0.2cm^3$) and TFA ($0.2cm^3$). However the aromatization was slow at 0°C, so the reaction mixture was warmed up to ambient temperature, when the diene aromatized completely within 1h. After work up the ^{1}H-NMR spectrum of the product indicated 59% acetate 193 and 41% toluene 123.

In a mixture of TFA ($0.1cm^3$) and $CDCl_3$ ($0.3cm^3$) diene 101 had a halflife of 20min at ambient temperature. The mixture was allowed to stand overnight at ambient temperature, then worked up. The ^{1}H-NMR spectrum and GC-MS of the mixture indicated the presence of 70% acetate 193, (m/e =230, 228), toluene 123, (m/e =217,215) and 8% of another compound (m/e =275,273) which had NMR peaks at δ: 8.26 (1H, s), 7.77

(1H, s), 2.59 (3H, s), 2.11 (3H, s). This compound was assigned as 5-bromo-4-nitro-o-cresyl acetate .

Diene 101 decomposed at ambient temperature over a period of 15h in a mixture of $CDCl_3$ ($0.38cm^3$) and TFA ($0.02cm^3$) to yield 73% acetate 193, 14% toluene 123 and 13% nitroacetate 254.

c) Reaction with anhydrous hydrogen chloride:

HCl gas was bubbled through a solution of diene (101, 275mg, 1mmol) in ether ($5cm^3$) at -78°C for 15min and stirred for 45min during which the bath was allowed to warm up to -40°C. The ^{1}H-NMR spectrum of the mixture at this stage indicated the presence of a new diene 200 as the only product. After work up with aqueous ammonia at -78°C pure (Z)-3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl chloride (200) (206mg, 82% isolated yield) was isolated as the only product. This was purified by crystallization from ether-petroleum ether mixture at -20°C to yield pale yellow crystals. It had mp: 87°C; UV (CH_2Cl_2): λ_{max} 273nm (ε=351m^2 mol^{-1}); IR: 1540 (NO_2), 740 (C-Cl); ^{1}H-NMR (250MHz, $CDCl_3$) δ: 1.81 (3H, s, CH_3), 4.89 (1H, dd, J=6.47 and 1.72Hz, 1-H), 6.20 (1H, dd, J=10.30 and 1.81 Hz, 4-H), 6.36 (1H, dd, J=6.47 and 1.81Hz, 2-H), 6.54 (1H, dd, J=10.30 and 1.72Hz, 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 24.2 (CH_3), 58.6 (C-1), 89.1 (C-6), 121.2 (C-3), 124.2 (C-2), 128.1 (C-4), 129.1 (C-5); Analysis: C 33.39%, H 2.67%, N 5.51% (Calculated for $C_7H_7NO_2ClBr$ C 33.29%; H 2.79%; N 5.55%).

d) Reaction with hydrogen bromide:

Anhydrous HBr gas was bubbled through a solution of diene 101, (275mg, 1.0mmol) in ether ($5cm^3$) at -78°C for 15min. The mixture

was stirred for 45min, during which time the temperature was allowed to rise to -40°C. After low temperature work up with aqueous ammonium hydroxide, followed by crystallization of the residue, pure (Z)-6-methyl-6-nitrocyclohexa-2,4-dienyl-1,3-dibromide 255, (88mg) was obtained. It had mp 68.5°C; IR (KBr) 1540 (NO_2), 590 (C-Br); UV (CH_2Cl_2): λ_{max}=286nm (ε=477 $m^2 mol^{-1}$); ^{1}H-NMR (250MHz, $CDCl_3$) δ: 1.82 (3H, s, CH_3) 5.11 (1H, dd; J=6.54 and 1.92Hz, 1-H), 6.25 (1H, dd, J=10.25 and 1.60Hz, 4-H), 6.44 (1H, dd, J=6.54 and 1.60, 2-H), 6.60 (1H, dd, J=10.25 and 1.92Hz, 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$) δ_C: 24.0 (CH_3) 50.4 (C-1), 88.9 (C-6), 120.7 (C-3), 125.4 (C-2), 128.0 (C-4), 129.1 (C-5)ppm; Analysis: C 28.29%, H 2.20%, N 4.70% (Calculated for $C_7H_7NO_2Br_2$. C 28.31%, H 2.31%, N 4.71%).

e) Reaction with sulfuric acid in methanol:

Diene 101, (690mg, 2.5 mmol) was added to a mixture of methanol (5.4g) and sulfuric acid (1.08g) at -20°C and stirred for 30min. The mixture was then stored in a freezer at -20°C for 7 days. Methanol was then removed on the rotorvapor at -40°C, the residue was diluted with ether (130cm^3) and neutralized with ammonium hydroxide (10cm^3, 1.4 mol) diluted with ether (50cm^3). After separating the organic layer the residue was dissolved in water and extracted with ether (2x25cm^3). The combined ether solution was washed with water (4x50cm^3), dried over anhydrous magnesium sulfate and the ether was removed at -40°C. The ^{1}H-NMR spectrum of the residue indicated 77% (Z)-3-bromo-6-methyl-6-nitrocyclohexa-2,5-dienol 205 and 22% cresol 215. Prior to separation, the ^{1}H-NMR spectrum of the sample kept in the freezer overnight at -78°C, was rerun and indicated the presence of 61% dienol 205, 28% cresol 215 and 4% of a new dienol identified later on as (Z)-5-bromo-2-methyl-6-nitrocyclohexa-2,4-dienol (214). The

mixture was separated by chromatography over basic alumina (45g, Brockmann Activity 758717, deactivated by shaking for 30min with 3% by weight of 10% (v/v) acetic acid-water mixture) at -78°C using mixtures ($3x200cm^3$ of 20%, $2x125cm^3$ of 40%, $1x25-cm^3$ 75% and $1x250cm^3$ 100%) of ether and petroleum ether as eluent. Evaporation of fraction 2 gave only toluene 124. Pure dienol 205 was obtained from the fourth, fifth and sixth fractions. The last fraction contained a mixture of 54% cresol 215, 28% of dienol 214 and 18% dienol 205. Dienol 205 was characterized by NMR without further purification. ^{1}H-NMR (250MHz, $CDCl_3$, -40°C): δ 1.71 (3H, s, CH_3), 2.85 (1H, brs, OH), 4.37 (1H, m, H), 6.11 (1H, dd, J=10.20 and 1.60Hz, 4-H), 6.25 (1H, d, J=10.20Hz, 5-H), 6.31 (1H, dd, J=5.43 and 1.60Hz, 2-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$, -40°C): δ_C 22.1 (CH_3) 70.5 (C-1), 87.9 (C-6), 118.4 (C-3), 127.9, 127.8 and 126.2 (C-2, C-4 and C-5)ppm.

In another experiment diene 101, (27.5mg) was dissolved in a mixture of CD_3OD-H_2SO_4 (0.3ml of 25% w/w) at 0°C and the reaction was monitored by ^{1}H-NMR. After 45min at 0°C there was 76% unchanged diene 101 along with 24% dienol 205. On increasing the temperature to ambient temperature rapid aromatization took place. After 45min the spectrum indicated 50% cresol 215, 31% dienol 205 and 19% unchanged diene 101. After 3h the dienes had completely aromatized and the only product obtained after bicarbonate work up was cresol 215 mp:80°C (lit[150] 80°C); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.19 (3H, s, CH_3), 4.75 (1H, br s, OH), 6.94 (1H, d, J=0.8Hz, 6-H), 6.97 (2H, m, 3- and 4-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C15.2 (CH_3), 118.1 (C-6), 119.5 (C-2), 122.9 (C-5), 123.7 (C-4), 132.0 (C-3), 154.5 (C-1)ppm.

7.9.3 Reactions of (Z)-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (102).

The procedure employed for the acid catalyzed reactions are similar to those described for diene 100. The results are summarized in

scheme 4.18.

7.9.4. Reactions of 4-methyl-4-nitrocyclohexa-2,5-dienedimethyl ketal (226).

a) Borontrifluoride gas:

Anhydrous BF_3 gas was bubbled through a solution of diene 226 (30mg, 1.4 mmol) in CH_2Cl_2 ($0.5cm^3$) with continuous stirring at -78°C for 5min. The resulting solution was warmed to ambient temperature over a period of 30min, then diluted with CH_2Cl_2 ($15cm^3$) and washed with water ($2x10cm^3$). The ^{1}H-NMR spectrum of the residue after removal of solvent indicated the presence of 40% cresol 168 and 60% anisole 116.

b) Methanol and chloroform:

The diene 226, in a mixture of CD_3OD ($0.03cm^3$) and $CDCl_3$ ($0.30cm^3$) aromatized over a period of 9 days to yield cresol 168 as the major product.

7.9.5 Reactions of (Z)-4-chloro-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (130):

(a) Reaction with trifluoromethanesulfonic acid:

Diene 130 (30mg, 0.11mmol) was added to CF_3SO_3H ($0.5cm^3$) at -78°C and the mixture was stirred for 1h, during which time the temperature was allowed to rise to ambient temperature. The mixture was diluted with CH_2Cl_2 ($25cm^3$), and washed successively with water ($10cm^3$), 10% aqueous bicarbonate ($10cm^3$) and water ($10cm^3$), then dried over anhydrous $MgSO_4$. The ^{1}H-NMR spectrum of the residue obtained after removal of the solvent indicated the presence of 42% 2-chloro-4-methyl-5-nitroanisole (257), 19% anisole 115 and 39% cresol 137.

(b) Reaction with boron trifluoride gas in methylene chloride-d_2:

BF_3 gas was bubbled through a ^{1}H-NMR solution of diene 130 (30mg) in CD_2Cl_2 (0.4cm^3) at -78°C. The ^{1}H-NMR spectrum of the resultant solution at -60°C after 10min indicated complete disappearance of the diene 130.

Solvent was evaporated from the reaction mixture by bubbling nitrogen gas and the residue was kept on the vacuum line for 2h to remove any remaining acid. The ^{1}H-NMR spectrum of the residue indicated 85% of anisole 257 and 15% of cresol 137.

The residue was dissolved in ether (25cm^3) and the solution was washed with 10% aqueous sodium bicarbonate solution (2x10cm^3). Removal of ether after drying over $MgSO_4$ gave pure 257 as a yellow solid: mp 92°C (lit[142] 92°C); UV (CH_2Cl_2): λ_{max} 335nm (ε=453 m^{2}mol^{-1}), 279nm (ε=625 m^{2}mol^{-1}); IR (KBr): 1520 and 1320 (NO_2), 1290 (Ar-OCH_3), 780 (C-Cl); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.54 (3H, s, CH_3), 3.96 (3H, s, OCH_3), 7.35 (1H, s, 6-H), 7.60 (1H, s, 3-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 19.8 (CH_3), 56.7 (OCH_3), 108.3 (C-6), 126.9 (C-4), 128.2 (C-2), 133.8 (C-3), 147.5 (C-5), 153.6 (C-1)ppm; MS (70ev) m/e (relative intensity): 203(11), 201(31), 186(19), 184(59), 156(28), 154(11), 112(23), 105(31), 91(25), 89(35), 79(25), 77(100); exact mass: found 201.026 (Calculated for $C_8H_8NO_3{}^{35}Cl$: 201.019).

(c) Reaction with borontrifluoride etherate:

Diene 130 (30mg) was added to a solution of BF_3-Et_2O at -20°C in a reactivial and the mixture was stirred at -20°C for 1h. The reaction mixture was warmed to ambient temperature and further stirred for 1h. The ^{1}H-NMR of the residue indicated 46% anisole 257, 23% anisole 136 and 31% cresol 137.

(d) Reaction with sulfuric acid in methanol-d_4:

Diene 130 (30mg) was added to a 25% (w/w) H_2SO_4 solution in CD_3OD ($0.4cm^3$) solution in methanol-d_4 contained in a ^{1}H-NMR tube at -20°C and the reaction was monitored by ^{1}H-NMR. After 10min at -20°C the ^{1}H-NMR spectrum indicated 39% ketal 135, 31% dienone 134 and 30% unreacted diene 130 was present. The diene 130 and ketal 135 disappeared after 6h at -20°C yielding a mixture of 95% dienone 134 and 5% cresol 137. After 4 days at -20°C the ^{1}H-NMR spectrum indicated 60% dienone 134 and 40% cresol 137. At this stage the solution was kept at room temperature for 1 day, then worked up. The ^{1}H-NMR spectrum of the residue indicated that 97% cresol 137 and 3% cresol 119 were present.

(e) Reaction with trifluoroacetic acid:

Diene 130 (30mg) was added to TFA ($0.4cm^3$) contained in a nmr tube at 0°C. The ^{1}H-NMR spectrum, recorded after 6min, indicated the complete disappearance of the diene 130. Removal of the acid on the vacuum pump yielded a yellow residue. Integration of the ^{1}H-NMR spectrum indicated that 50% anisole 136, 8.5% cresol 137 and 41.5% anisole 257 was present.

(f) Reactions with trifluoroacetic acid in chloroform-d:

Diene 130 rearomatized instantaneously at 0°C in varying mixtures of $CDCl_3$-TFA to yield the following products:

TFA	$CDCl_3$ (v:v)	136	137	257
3	1	44%	17%	39%
1	1	51%	15%	34%
1	3	43%	24%	33%

g)Reactions with trifluoroacetic acid in methanol-d_4:

The reaction of diene 130 in mixtures of CD_3OD and TFA at 0°C was monitored by ^{1}H-NMR and the composition of the reaction mixtures at intervals are given below:

TFA	CD_3OD(v:v)	Time	130	134	135	137
3	1	8min	-	100%	-	-
3	1	33min	-	50%	-	50%
3	1	4h	-	-	-	100%
1	1	8min	5%	89%	3%	3%
1	1	50min	-	40%	-	60%
1	1	4h	-	-	-	100%
1	3	45min	30%	47%	6%	17%
1	3	4h	-	39%	-	61%
1	3	1h(ambient)	-	-	-	100%

(h) Reactions with hydrogen chloride gas in ether:

Anhydrous HCl gas was bubbled through a solution of diene 130 (250mg, 0.95mmol) in ether ($5cm^3$) contained in a $10cm^3$ two necked round bottom flask at -78°C for 5min. The mixture was slowly warmed to 0°C over a period of 1h and evaporated to dryness on the vacuum line at 0°C.

The ^{1}H-NMR spectrum of the yellow oil indicated the composition was 43% cresol 137, 6% cresol 119 and 51% (1:1) mixture of two diastereomeric hydrogen chloride adducts, 2,5-dichloro-4-methyl-4-nitrocyclohexa-2-enone, (258) and (259).

The mixture was separated by HPLC on a silica column (Si-10, 0.8x50cm) using a linear gradient elution programme with mixtures of hexane-CH_2Cl_2 as solvent. The composition of the eluent was changed from 50% hexane-CH_2Cl_2 mixture to 100% CH_2Cl_2 over a period of 15min and kept unchanged for 20min at a constant flow rate of 2cm^{3} min^{-1}.

Cresol 137 and a mixture of cresols 137 and 119 was collected in the first two fractions (16.5min and 21.3min) respectively. Fraction 3 (26.3min) contained a mixture of 85% 258 and 15% cresol 137. Fraction 4 (30min) contained 95% diastereomer 259 and 5% cresol 137.

Pure diastereomer 258 was obtained after two successive HPLC separations of fraction 3, using similar gradient elution techniques as a colorless oil which was characterized by NMR. ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.97 (3H, s, CH_3), 2.98 (1H, dd, J=8.85 and 17.60Hz, 6'-H), 3.20 (1H, dd, J=4.5 and 17.6Hz, 6-H), 5.11 (1H, ddd, J=0.68, 4.50 and 8.80Hz, 5-H), 7.02 (1H, d, J=0.68Hz, 3-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 21.6 (CH_3), 43.8 (C-6), 57.0 (C-5), 90.4 (C-4), 130.1 (C-2), 135.6 (C-3), 184.7 (C-1).

Diastereomer 259 crystallized from ether-petroleum ether mixture at -20°C as white crystals. It had mp 99°C; UV (CH_2Cl_2): λ_{max} 241.5nm (ε=1235 m^{2} mol^{-1}); IR (KBr) 3030 (H-C=C), 1705 (α,β-unsaturated C=O), 1560 and 1310 (NO_2), 735 (C-Cl); ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.96 (3H, s, CH_3), 3.15 (1H, dd, J=4.37 and 17.60Hz, 6-H), 3.34 (1H, dd, J=6.67 and 17.60Hz, 6'-H), 4.79 (1H, ddd, J=4.37, 6.67 and 1.22Hz, 5-H),

7.32 (1H, d, J=1.22Hz, 3-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 24.8 (CH_3), 43.01 (C-6), 57.9 (C-5), 89.2 (C-4), 135.6 (C-2), 137.9 (C-3), 184.9 (C-1)ppm; analysis: C 37.52%, H 2.65 %, N 6.13% (Calculated for $C_7H_7NO_3Cl_2$: C 37.52%, H 3.12%, N 6.25%).

Cresol 137 obtained in the first fraction as a yellow solid was crystallized from ether-petroleum ether mixtures. It had mp 65°C; IR (KBr): 3200 (OH), 1538 (NO_2); UV (CH_2Cl_2): λ_{max} 372.6nm (ε=415 $m^2 mol^{-1}$); ^{1}H-NMR (250MHz, $CDCl_3$): δ: 2.34 (3H, s, CH_3), 7.53 (1H, d, J=1.1Hz, 3-H), 7.85 (1H, d, J=1.1Hz, 5-H), 10.85 (1H, s, OH)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$) δ_C: 20.2 (CH_3), 123.3 (C-3), 124.2 (C-2), 129.9 (C-4), 134.3 (C-6), 138.6 (C-5), 149.6 (C-1)ppm; MS (70ev) m/e (relative intensity) 189(Cl^{37},26), 187(Cl^{35},82), 142(11), 113(16), 78(17), 77(100); analysis C 44.85%, H 2.97%, N 7.23% (Calculated for $C_7H_6NO_3{}^{35}Cl$: C 44.82%, H 3.22%, N 7.46%).

The above experiment was repeated by bubbling HCl gas through an ethereal solution of diene (250mg, 0.95mmol) at -78°C for 5min. The reaction mixture was worked up with NH_4OH at -78°C after 5min stirring. Removal of the solvent at -40°C yielded a yellow oil. The ^{1}H-NMR spectrum of the oil at -40°C indicated that 30% dienone 134 and 70% (1:1) mixture of 258 and 259 were present.

7.9.6 Reactions of (Z)-3-methoxy-6-methyl-2,6-dinitrocyclohexa-2,4-dienyl acetate (151):

(a) Reaction in trifluoromethanesulfonic acid:

Diene 151 (30mg, 0.11mmol) was added to CF_3SO_3H (0.5cm^3) in a reactivial at -78°C and the mixture was stirred for 1h during which time the temperature was increased to 22°C. After dilution with CH_2Cl_2

($25cm^3$) the mixture was washed with water ($10cm^3$), 10% aqueous bicarbonate ($10cm^3$) and water ($10cm^3$), then evaporated to dryness, after drying over anhydrous $MgSO_4$. The ^{1}H-NMR spectrum of the residue in acetone-d_6 indicated the presence of 19% anisole 155, 35.5% cresol 231; 35% anisole 116 and 9.5% cresol 168.

(b) Reaction with borontrifluoride gas in methylene chloride:

Anhydrous BF_3 gas was bubbled through a solution of diene 151 (30mg, 0.11mmol) in CD_2Cl_2 ($0.4cm^3$) contained in a NMR tube at -78°C for 5min and the ^{1}H-NMR spectrum of the reaction mixture indicated complete aromatization after 5min. The ^{1}H-NMR spectrum of the residue obtained after removal of the solvent and acid at ambient temperature indicated a mixture of 40% anisole 155 and 60% anisole 116.

(c) Reaction with neat boron trifluoride etherate:

To a solution of $BF_3.Et_2O$ ($0.4cm^3$) at -20°C contained in a reactivial was added diene 151 (30mg, 0.11mmol) and the mixture was stirred for 1h at -20°C and 1h at ambient temperature. After work up the ^{1}H-NMR spectrum of the residue indicated that 39% cresol 231, 4.5% anisole 155, 25.5% anisole 116 and 30% cresol 168 were present.

(d) Reaction with anhydrous hydrogen chloride gas at -78°C:

Anhydrous HCl gas was bubbled for 5min through a solution of diene 151 (200mg, 0.72mmol) in anhydrous ether ($5cm^3$) contained in a $10cm^3$ 2 necked round bottom flask at -78°C. The mixture was stirred for 30min, then transferred into ether ($50cm^3$) at -78°C. After low temperature work up with NH_4OH solution ($15cm^3$, 0.2mol), the ^{1}H-NMR spectrum of the residue indicated a mixture of cresols 231 and 168 along

with 4-methyl-2,4-dinitrocyclohexa-2,5-dienone (305). Warming the solution to ambient temperature yielded only cresols 231 and 168.

(e) Reaction with sulfuric acid in methanol-d_4:

Diene 151 (30mg) was added to a mixture of H_2SO_4 (25% w/w) in CH_3OH ($0.4cm^3$) at ~20°C in a ^{1}H-NMR tube and the reaction was monitored by ^{1}H-NMR. Over a period of 4 days there was formation of ketal 156 and dienone 305, but undissolved diene however remained, so the mixture was warmed to ambient temperature. After 1 day at ambient temperature, the starting diene had aromatized and the ^{1}H-NMR spectrum of the residue indicated a mixture of 73% cresol 231 and 27% cresol 168.

(f) Reaction in trifluoroacetic acid:

Diene 151 (30mg, 0.11mmol) was added to TFA ($0.4cm^3$) in a ^{1}H-NMR tube at 0°C and the reaction was monitored by NMR. After 5min diene 151 was absent and the mixture contained dienone 305 along with aromatic compounds. The dienone 305 decomposed after 15min. Removal of the solvent after 2h on the vacuum line gave 25% anisole 116, 27% anisole 155 and 48% cresol 231.

(g) Reaction with trifluoroacetic acid in chloroform-d:

Reactions of diene 151 in mixtures of TFA and $CDCl_3$ gave the following product mixtures:

TFA	$CDCl_3$(v:v)	Time	Temp	116	155	231
3	1	7min	0°C	21%	28%	51%
1	1	20min	0°C	23%	21%	56%
1	3	80min	22°C	21%	17%	62%

(h) Reactions with trifluoroacetic acid in methanol-d_4:

The composition of the reaction mixtures of diene 151 in TFA-CD_3OD is given as follows:

TFA	CD_3OD(v/v)	Time	Temp	151	156	168	231
3	1	140min	0°C	-	-	10%	90%
1	1	127min	0°C	67%	33%	-	-
1	1	15h	22°C	-	-	25%	75%
1	3	120min	0°C	90%	10%	-	-
1	3	15h	22°C	40%	30%	5%	25%
1	3	7d	22°C	-	-	28%	72%

(i) Reactions with trifluoroacetic acid in acetic anhydride:

To a mixture of TFA ($0.2cm^3$) and acetic anhydride ($0.2cm^3$) at -20°C was added diene 151 (30mg) and the reaction was followed by ^{1}H-NMR. After 10min at -20°C there was a mixture of dienes 151 and 150. On warming the mixture to 0°C, no noticeable aromatization occurred. The temperature was further increased to ambient temperature and after 45min a mixture of 20% cresol 231, 20% anisole 155 and 60% anisole 116 was formed.

The reaction was repeated using acetic anhydride-d_6 ($0.3cm^3$) and TFA ($0.1cm^3$) at -40°C. The ^{1}H-NMR spectrum of the mixture was poorly resolved and the reaction was discontinued after no noticeable change in the NMR spectra at -20°C could be detected.

The reaction was repeated on a larger scale using diene 151 (270mg, 1mmol), TFA ($0.3cm^3$) and acetic anhydride ($0.9cm^3$) at -40°C. The reaction was worked up with NH_4OH at -78°C after 30min of stirring

at -40°C. The NMR of the product mixture indicated 17% anisole 116, 20.5% ketal 156 and 62.5% diene 151 was present. The nitrocresols formed were extracted in the ammonia layer.

(j) Reaction with trifluoromethane sulfonic acid in the presence of p-chlorophenol:

Trifluoromethane sulfonic acid ($0.2cm^3$) was added to a mixture of diene 151 (27mg, 0.1mmol) and p-chlorophenol (247) (13mg, 0.1mmol) in CH_2Cl_2 ($0.2cm^3$) at -78°C. The mixture was stirred for 15min at -78°C then warmed to room temperature and stirred for another 30min. The mixture was diluted with CH_2Cl_2 ($25cm^3$), washed with water ($10cm^3$), 10% aqueous sodium bicarbonate solution ($10cm^3$) and water ($10cm^3$). The ^{1}H-NMR spectrum of the residue obtained on removal of solvent after drying indicated the presence of 4-chloro-2-nitrocresol (246), anisole 116, cresol 168 along with unreacted p-chlorophenol. Integration of the ^{1}H-NMR spectrum the GC analysis of the mixture indicated that the molar proportion of the compounds was 116:168:246:247::7:1:5.6:2.4.

7.9.7: Reactions of (Z)-3-methoxy-6-methyl-4,6-dinitrocyclohexa-2,4-dienyl acetate (154):

The procedure employed for the reactions of diene 154 was similar to those described for diene 151 and the results are described in scheme 4.19.

7.9.8 Reaction of 4-methyl-2,6-dinitroanisole with trifluoromethane-sulfonic acid:

Anisole 155 (30mg, 1.3 mmol) was added to CF_3SO_3H($0.5cm^3$) cooled to -78°C. The mixture was stirred for 1h during which time the

mixture was allowed to warm up to ambient temperature. The mixture was diluted with CH_2Cl_2 ($25cm^3$) and washed with water ($10cm^3$), 10% aqueous bicarbonate solution ($10cm^3$) and water ($10cm^3$). The ^{1}H-NMR spectrum of the residue after removal of solvent after drying over anhydrous $MgSO_4$ indicated the presence of 42% cresol 231 and 58% unreacted anisole 155.

7.9.9 Reactions of 5-X-2-methyl-6-nitrocyclohexa-2,4-dienyl acetates [187, 188, 196 and 191].

The results obtained from the reactions of all four dienes have been discussed in section 4.2.2. The description of the reactions of diene 187 is included below to exemplify the general experimental procedure employed for these reactions.

Reactions of (Z)-5-chloro-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate 187:

(a) Reaction with trifluoroacetic acid:

Diene 187 (23mg, 1mmol) was dissolved in TFA ($0.3cm^3$) at 0°C and the decomposition of the diene was monitored by ^{1}H-NMR. No noticeable reaction was observed at 0°C for 10min. On warming the reaction mixture in the probe to ambient temperature the diene decomposed ($\tau_{1/2}$≈8min) to a mixture of acetate 186 and toluene 122. The reaction was worked up with sodium bicarbonate after 24h at ambient temperature. The ^{1}H-NMR spectrum of the mixture indicated the presence of 54% acetate 186 and 46% toluene 122.

(b) Reaction with trifluoromethanesulfonic acid:

On dissolving diene 187 (23mg) in CF_3SO_3H($0.3cm^3$) at 0°C, there was instantaneous colour change and the ^{1}H-NMR spectrum of the reaction mixture at 0°C indicated complete aromatization to toluene 122. After bicarbonate work up the ^{1}H-NMR spectrum of the product

mixture indicated the presence of toluene 122 as the only product.

(c) Reaction with trifluoroacetic acid in methanol:

Diene 187 (23mg) was added to a mixture of TFA ($0.075cm^3$) and CD_3OD ($0.225cm^3$) at 0°C and the decomposition was monitored by NMR. After 10min at 0°C there was no noticeable change. The mixture was warmed to ambient temperature. After 3h, there was 10% toluene 122 and 90% unchanged diene. The diene completely aromatized after 48h. The ^1H-NMR spectrum of the mixture obtained after work up indicated the presence of toluene 122 as the only product.

(d) Reaction with trifluoroacetic acid in $CDCl_3$:

Diene 187 (24mg) decomposed in a mixture of TFA ($0.075cm^3$) and $CDCl_3$ ($0.225cm^3$) at ambient temperature ($\tau_{1/2}$≈3h) over a period of 10 days to acetate 186 as the only product as determined by ^1H-NMR.

(e) Reaction with pyridine-d_5:

Diene 102 (19.5mg), decomposed instantaneously in the presence of pyridine-d_5 ($0.3cm^3$) at 0°C. Removal of pyridine from a diluted ether ($10cm^3$) solution by washing with 1:1 HCl and evaporation of ether gave toluene 122 as the only product.

7.9.10 Reactions of 3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl chloride (201):

(a) Reaction with trifluoromethane sulfonic acid:

Diene 201 (30mg, 0.14mmol) was dissolved in CF_3SO_3H($0.3cm^3$) at 0°C and the ^1H-NMR spectrum of the reaction mixture recorded instantaneously indicated complete aromatization. After work up with sodium bicarbonate, the ^1H-NMR spectrum and the GC-MS of the product mixture indicated the presence of 64% toluene 121 (m/e 171,173) and 36%

2,4-dichlorotoluene (209) (m/e: 160,162).

(b) Reaction with trifluoroacetic acid:

Diene 201 (30mg) was dissolved in TFA (0.3cm^3) at 0°C and the reaction was monitored by ^{1}H-NMR. After 30min at 0°C the ^{1}H-NMR spectrum of the reaction mixture indicated the presence of 35% toluene 121, 19% toluene 209 and 46% unreacted diene 201. The mixture was allowed to warm to ambient temperature. After completion the ^{1}H-NMR spectrum of the mixture indicated that a mixture of 63% toluene 121 and 37% toluene 209 was formed.

7.9.11 Reactions of (Z)-3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl chloride 209:

(a) Reaction with trifluoromethane sulfonic acid:

Diene 200 (15mg,0.06mmol) aromatized instantaneously in a solution of CF_3SO_3H (0.3cm^3) at 0°C. The ^{1}H-NMR spectrum and the GC-MS of the product mixture obtained after bicarbonate work up indicated the presence of 37.5% 2-chloro-4-bromotoluene (207) (m/e 204,206,208) and 62.5% toluene 123 (m/e 215,217).

(b) Reaction with trifluoroacetic acid in chloroform-d:

Diene 200 (15mg) was dissolved in a mixture of $CDCl_3$ (0.225cm^3) and TFA (0.75cm^3) at 0°C and the reaction was monitored by NMR. There was no noticeable change after 20min at 0°C so the reaction mixture was warmed to ambient temperature. After 12h the diene aromatized completely. The ^{1}H-NMR spectrum and the GC-MS of the product mixture indicated the presence of 35% toluene 207 (m/e 208,206,204) and 65% toluene 123 (m/e 215,217).

7.10 Reactions of Dienes with Nucleophiles;

7.10.1 Reactions of (Z)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (100)

(a) Reaction with aqueous methanol:

Diene 100, (30mg) was stirred overnight in a mixture of CH_3OH ($2cm^3$) and water ($2cm^3$) at ambient temperature. The mixture was concentrated on the roto-vapor, then saturated with NaCl and extracted with ether ($2x10cm^3$). The ^{1}H-NMR spectrum of the residue after evaporation of ether indicated the presence of 30% unreacted diene 100, 61% cresyl acetate 186 and 9% toluene 122.

(b) Reaction with aqueous methanolic sodium acetate:

Diene 100, (0.7g, 3.0mmol) was stirred in a mixture of CH_3OH ($4cm^3$) and water ($1cm^3$) containing sodium acetate (0.5g, 6.1mmol) at ambient temperature for 54h. The reaction mixture after work up yielded a residue of 0.55g. The ^{1}H-NMR spectrum and the GCMS indicated the presence of 88% acetate 186, (m/e 184, 186) and 12% toluene 122, (m/e 171, 173). This mixture was separated by column chromatography on silica gel (65g). Elution with 2% ether - petroleum ether gave pure toluene 122. The initial fraction with 5% ether - petroleum ether gave mixtures of toluene 122 and acetate 186. Pure acetate 186 was obtained as a colourless oil in the later 5% ether fractions. The acetate 186 crystallized at -20°C and had mp: 25-28°C (lit[129] 27-28°C); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.14 (3H, s, $OCOCH_3$), 2.32 (3H, s, 2-CH_3), 7.04 (1H, s, 6-H), 7.14 (2H, s, 4-H and 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 15.7 (CH_3), 20.6 ($OCOCH_3$), 122.4 (C-6), 126.1 (C-4), 128.7 (C-2), 131.7 (C-3), 133.8 (C-5), 149.6 (C-1), 168.6

($O\underline{C}OCH_3$)ppm; MS (eV) m/e (relative intensity): 186(9), 184(19), 144(33), 143(13), 142(100), 141(11), 107(87), 77(44).

(c) Reaction with potassium cyanide in presence of 18-crown-6:

Diene 100, (30mg) was added to a solution of potassium cyanide (12mg, 0.18mmol) and 18-crown-6 (45mg, 0.18mmol) in CD_3CN ($0.3cm^3$) at 0°C and the reaction was monitored by NMR. The slow formation of cresol 213 was observed. The mixture was warmed to ambient temperature and the ^{1}H-NMR spectrum of the residue after work up indicated the presence of cresol 213 as the major product.

(d) Reaction with sodium thiophenoxide:

Sodium thiophenoxide was prepared by refluxing thiophenol (6g, 0.0545mol) with sodium pieces (2.1g, .0 9mol) in toluene ($50cm^3$) for 30min. Removal of toluene on the rotovapor yielded sodium thiophenoxide (8g, 0.048mol) as a white powder.

Diene 100, (30mg) was stirred for 15h with sodium thiophenoxide (30mg, 0.24mmol) in acetonitrile ($0.3cm^3$) at ambient temperature. The ^{1}H-NMR spectrum and GC-MS of the residue after work up indicated the presence of acetate 186, (m/e 184, 186) and diphenyl disulfide (m/e 217, 218) as the only products.

7.10.2 Reactions of Z-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl chloride (201)

(a) With aqueous methanol:

Diene 201, (27mg, 0.1mmol) was added to a mixture of methanol ($1cm^3$) and water ($0.5cm^3$) at ambient temperature and the mixture was stirred for 12h. The ^{1}H-NMR spectrum and the GCMS of the residue indicated the presence of 12% toluene 111, (m/e 126,128), 38% 5-chloro-o-cresyl methyl ether 256, (m/e 156,158 RT 19.1min), 26% nitrocresol 168, (m/e 153), 20% cresol 213, (m/e 142,144) and 4% toluene

122, (m/e 171,173)

(b) Reaction with potassium cyanide:

Diene 201, (30mg, 0.15mmol) was added to a mixture of potassium cyanide (15mg, 0.22mmol) and 18-crown-6 (55mg, 0.22mmol) in CH_3CN ($2cm^3$) at ambient temperature and the mixture was stirred for 4h. The ^1H-NMR spectrum of the mixture indicated toluene 209 and cresol 213 as the major products. The GC-MS indicated the presence of toluene 209, (m/e 160,162), cresol 213, (m/e 142,144), along with traces of cresol 168, (m/e 153), toluene 111, (m/e 126,128), toluene 122, (m/e 171, 173) and another compound (m/e 151,153) which was assigned to 5-chloro-2-methyl-benzonitrile (278).

(c) Reaction with sodium thiophenoxide:

A mixture of diene (201, 30mg) and sodium thiophenoxide (29mg, 0.22mmol) in acetonitrile was stirred for 15h at ambient temperature. The ^1H-NMR spectrum and GC-MS of the colorless oil after work up indicated the presence of toluene 209, (m/e 160,162) and diphenyldisulfide (m/e 218,219).

(d) Reaction with potassium acetate in acetic acid:

Diene 201, (25mg, 0.12mmol) was added to an ice cold solution of potassium acetate (19.7mg, 0.24mmol) in acetic acid ($0.3cm^3$) and the mixture was stirred at 0°C for 3h. After work up with aqueous ammonium hydroxide at -78°C, only unreacted diene 201 was recovered.

(e) Reaction with silver acetate:

Diene (201, 30mg) was added to a mixture of silver acetate (26.6mg, 0.22mmol) and acetic anhydride ($0.3cm^3$) at ambient temperature and stirred for 15h. Excess silver was precipitated by adding sodium chloride and filtration and the filtrate was worked up with ammonium hydroxide at -78°C. The ^1H-NMR spectrum of the residue indicated the

presence of 68% toluene 121, 9% cresol 168 and 5% toluene 209 and 18% diene 100.

(f) Reaction with silver cyanide:

Diene 201, (30mg) was stirred in a mixture of silver cyanide (37mg, 0.29mmol) and acetonitrile (0.5cm^3) at ambient temperature for 15h. After work up the ^{1}H-NMR spectrum of the residue indicated unreacted diene 201.

(g) Reaction with silver nitrate in methanol:

A solution of silver nirate (1.02g, 6.1mmol) in CH_3OH (50cm^3) was added dropwise over a period of 30min to a solution of diene (201, 0.7g, 3.4mmol) at 0°C. The resultant solution was stirred for 1.5h, then saturated with sodium chloride and filtered at -78°C. The filtrate was concentrated on the rotovapor at -30°C. The ^{1}H-NMR spectrum of the residue indicated the presence of 36% (Z)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl methyl ether (202) and 63% dienone 56.

The mixture was separated by chromatography on an alumina column (87g, neutral 3% aqueous) at -78°C using mixtures of pentane as eluent, (2x200cm^3 10%, 2x200cm^3 25%, 4x100cm^3 40%, 4x100cm^3 50%). Evaporation of fraction 4 at -40°C yielded 50% anisole 256 and 50% toluene 122. Fraction 5 contained 40% toluene 122 and 60% diene 204. Pure diene 204 was eluted in fractions 6, 7 and 8. Later fractions containing mainly cresol 168 were discarded. Diene 204 was characterized in solution by NMR with further purification. ^{1}H-NMR (250MHz, $CDCl_3$, -40°C) δ: 1.73 (3H, s, CH_3), 3.34 (3H, s, OCH_3), 4.07 (1H, dd, J= 5.67 and 1.55Hz, 1-H), 5.99 (1H, dd, J=10.20 and 1.87Hz, 4-H), 6.16 (1H, dd, J=5.67 and 1.87Hz, 2-H), 6.48 (1H, dd, J=10.20 and 1.55Hz, 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$, -20°C) δ_C 23.2 (CH_3), 57.6 (OCH_3), 77.7 (C-1), 88.7 (C-6), 118.8 (C-2), 125.7 (C-4),

130.0 (C-5), 132.3 (C-3) ppm.

(h) Methylation of (Z)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienol (204):

Moist silver oxide was prepared by adding a solution of aqueous sodium hydroxide ($3cm^3$, 15mmol) to a solution of silver nitrate (1.6g, 0.4mmol) in water ($5cm^3$). The resultant solution was shaken vigorously and the brown precipiate obtained by filtration was washed with water ($3x10cm^3$) and filtered on the pump (15min).

A mixture containing 66% dienol 204, (100mg) was added to methyl iodide ($2cm^3$) at -78°C. Freshly prepared silver oxide (~500mg) was added to this solution and stirred for 200min, during which the temperature was allowed to rise to ambient. The mixture was filtered and the residue was washed with CH_2Cl_2 ($25cm^3$). The ^{1}H-NMR spectrum of the residual oil obtained on removal of solvent an ambient temperature indicated the presence of 35% diene 202, 25% toluene 122 and 40% cresol 213 and anisole 256.

7.10.3 Reactions of 3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl bromide (225)

(a) Reaction with potassium cyanide:

Diene 225, (25mg, 0.1mmol) was added to a mixture of KCN (33mg, 0.5mmol) and CH_3CN ($1.0cm^3$) at ambient temperature and stirred for 15h. The ^{1}H-NMR spectrum of the residue indicated 2-bromo-4-chlorotoluene as the only product.

(b) Reaction with sodium methoxide in methanol:

A solution of sodium methoxide (50mg, 1.2mmol) in methanol ($5cm^3$) was added to a solution of diene 225, (100mg, 0.4mmol) in methanol ($5cm^3$) at -78°C and the mixture was stirred for 20min, then warmed to 0°C over a period of 1h. After work up the only product

obtained was 2-bromo-4-chlorotoluene.

7.10.4 Reactions of (Z)-3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (101).

(a) Reaction with aqueous methanol in presence of sodium acetate:

Diene 101, (540mg, 2mmol) was added to a solution of sodium acetate (270mg, 2.4mmol) in methanol ($10cm^3$) and water($5cm^3$) and the mixture was stirred at ambient temperature for 24h. After work up, the ^{1}H-NMR spectrum of the pale yellow oil idnicated the presence of 37% acetate 193, 8% toluene 124 and 55% unreacted diene 101.

The residue was dissolved in a solution of sodium acetate in methanol and stirred for 6 days at ambient temperature. After work up a mixture of 80% acetate 192 and 20% toluene 124 was obtained.

The mixture (400mg) was separated by chromatography on silica gel (65g) using mixtures of ether and petroleum ether as eluent. Pure toluene (124) was eluted with 100% petroleum ether: ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.33 (3H, s, CH_3), 7.13 (1H, dd, J= 8.3 and 1.4 Hz, 6-H), 7.33 (1H, d, J=8.3Hz, 5-H), 7.59 (1H, d, J=1.4Hz, 2-H); ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 19.6 (CH_3) 122.9 (C-4), 124.8 (C-2), 130.5 (C-5), 132.9 (C-6), 137.3 (C-1), 146.7 (C-3).

Pure acetate 193 was obtained as a colourless oil in the later fractions with 100% petroleum ether and with 1% ether and 99% petroleum ether solution. IR (neat): 1770 and 1310 ($OCOCH_3$); UV (CH_2Cl_2): λ_{max} 276 (ε=672 $m^2 mol^{-1}$) 267nm (ε=835$m^2 mol^{-1}$); ^{1}H-NMR (250MHz, $CDCl_3$): 2.05 (3H, s, $OCOCH_3$), 2.24 (3H, s, CH_3), 7.02 (1H, d, J=8.4Hz, 3-H), 7.12 (1H, d, J=2.0Hz, 6-H), 7.20 (1H, dd, J=8.4 and 2.0Hz, 4-H); ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 15.8 (CH_3), 20.6 ($OCOCH_3$), 119.2 (C-5), 125.3 (C-6), 129.1 (C-4), 129.3 (C-2), 132.1 (C-3), 149.3 (C-1), 168.6 ($OCOCH_3$); MS (70eV), m/e (relative intensity): 230(22), 228(23), 188(94), 186(100), 107(76), 78(30), 77(28);

(b) Reaction with aqueous methanol:

A solution of diene 101, (54mg, 0.2mmol) in a CH_3OH ($3cm^3$) and water ($2cm^3$) mixture was stirred at ambient temperature for 24h. The ^{1}H-NMR spectrum of the oil obtained after work up indicated the presence of 57% acetate 193, 20% of toluene 124 and 23% of unreacted diene 101. The mixture was stirred in aqueous methanol for another 48h. The ^{1}H-NMR spectrum of the oil obtained after work up indicated 66% acetate 193, 24% toluene 124 and 10% unreacted diene 101.

7.10.5 Reaction of Z-3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl chloride (200)

(a) With methanolic silver nitrate:

A solution of diene (200, 151.8mg, 0.6mmol) in methanol ($10cm^3$) was added dropwise to a stirred solution of silver nitrate (306mg, 0.18mmol) in methanol ($3cm^3$), cooled in an ice bath, and the mixture was stirred at 0°C for 2h. The ^{1}H-NMR spectrum of the residual oil indicated the presence of 63% 3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl methyl ether (203) and 37% dienone 56.

The diene after separation on an alumina column at -78°C, was characterized in solution by NMR spectroscopy without further purification. ^{1}H-NMR (250MHz, $CDCl_3$, -40°C) δ: 1.70 (3H, s, CH_3), 3.32 (3H, s, OCH_3), 3.96 (1H,dd, J=5.15 and 1.70Hz, 1-H), 6.06 (1H, dd, J=10.25 and 1.50Hz, 4-H), 6.36 (1H,dd, J=10.25 and 1.70Hz, 5-H) 6.38 (1H,dd, J=5.15 and 1.50Hz, 2-H),ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$, -40°C) δ_C: 22.3 (CH_3), 56.6 (OCH_3), 77.6 (C-1), 79.9 (C-6), 120.2 (C-3), 122.2 (C-2), 126.7 (C-4), 128.9 (C-5) ppm.

7.10.6 Reaction of (Z)-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (102) with nucleophiles:

(a) with neat methanol:

Diene 102, (30mg) was dissolved in methanol-d_4 ($0.3cm^3$) at 0°C and the decomposition was monitoried by ^{1}H-NMR. After 30min at 0°C the ^{1}H-NMR spectrum showed 20% dienone 56 along with 80% unreacted diene 102. When the reaction mixture was warmed to ambient temperature the dienone decomposed to cresol 168, and some ketal 226 was detected. After 2 days at ambient temperature the reaction mixture contained mainly cresol 168.

(b) With aqueous methanol in presence of sodium acetate:

Diene 102, (30mg) was added to a clear solution of sodium acetate (22mg, 0.26mmol) in methanol ($2cm^3$) and water ($1cm^3$) at ambient temperature and the mixture was stirred for 15h. The ^{1}H-NMR spectrum of the residue after work up indicated 49% ketal 226, 45% cresol 168 and 6% anisole 112. This experiment was repeated without any water, and decreasing the stirring time to 2.5h. The products consisted of 40% cresol 168 and 60% ketal 226.

(c) With methanolic sodium methoxide:

Anhydrous sodium methoxide (6.7mg, 0.15mmol) was added to a solution of diene 102, (30mg) in methanol ($0.3cm^3$) cooled to -78°C, and the mixture was warmed to room temperature over a period of 1h. The ^{1}H-NMR spectrum of the residue after work up indicated the presence of 85% cresol (168) and 15% anisole (112).

(e) With aqueous methanol:

Diene 102, (30mg) was stirred in a mixture of methanol ($1cm^3$) and water ($0.5cm^3$) at ambient temperature for 5h. The ^{1}H-NMR spectrum

of the product mixture indicated the presence of mainly cresol 168 along with some p-cresol (219).

(f) With aqueous methanol in presence of tris(hydroxymethyl)aminomethane:

Diene 102, (30mg) was stirred for 15h at ambient temperature in a solution of TRIZMA (31.5mg, 0.26mmol) in methanol ($2cm^3$) and water ($1cm^3$). After work up, the NMR spectrum of the product mixture indicated the presence of 80% ketal 226 and 20% cresol 168.

(g) Reaction with methanol in presence of N,N-diisopropylethylamine;

Diene 102, (454mg, 1.98mmol) was dissolved in a methanolic solution ($5cm^3$) of N,N-DIPEA (516mg, 4mmol) and the mixture was stirred at ambient temperature for 3h. The mixture was diluted with CH_2Cl_2 ($50cm^3$) and washed with water ($3x15cm^3$). The ^{1}H-NMR spectrum of the product after work up indicated that it was pure ketal 226. This sample was used for characterization: UV (CH_2Cl_2): λ_{max} 277nm (ε=7.7 $m^2 mol^{-1}$); IR: (neat, NaCl pellets) 1545 and 1370 (NO_2) 1105 (OMe), ^{1}H-NMR (250MHz, $CDCl_3$) δ: 1.77 (3H, s, CH_3), 3.26 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 6.10 (2H, d, J=10.5Hz, 2-H and 6-H), 6.35 (2H, d, J=10.5Hz, 3-H and 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$) δ_C 26.9 (CH_3), 49.7 (OCH_3), 50.4 (OCH_3), 83.7 (C-4), 92.8 (C-1), 129.8. (C-2 and C-6), 130.4 (C-3 and C-5)ppm. Analysis C 53.73%, H 6.56%; N 7.20% (Calculated for $C_9H_{13}NO_4$: C 54.27%, H 6.57%, N 7.03%).

(h) Reaction with aqueous methanol in the presence of sodium perchlorate:

Diene 102, (30mg) was dissolved in a solution of $NaClO_4$ (22.4mg, .026mmol) in aqueous methanol and the mixture was stirred for 15h. After work up, the ^{1}H-NMR spectrum of the mixture indicated cresol 168 was the only product.

(i) Reaction with potassium iodide:

Diene 102, (30mg) was added to a solution of potassium iodide (115.5mg, 0.65mmol) and sodium acetate (22mg, 0.65mmol) in acetonitrile ($2cm^3$) and water ($1cm^3$) and the mixture was stirred overnight at ambient temperature. The ^{1}H-NMR spectrum of the product mixture indicated the presence of 90% cresol 168 and 10% 219.

(j) Reaction with potassium thiocyanate:

Diene 102, (30mg) was stirred overnight with a solution of potassium thiocyanate (67mg, 0.65mmol) in acetonitrile ($2cm^3$) and water ($1cm^3$). After work up the NMR spectrum of the product mixture indicated the presence of 81% cresol 168 and 19% cresol 219.

(k) Reaction with sodium nitrite:

Diene 102, (30mg) was stirred overnight in a solution of sodium nitrite (45mg, 0.65mmol) and sodium acetate (22mg, 0.26mmol) in acetonitrile ($2cm^3$) and water ($1cm^3$). After work up, the NMR spectrum of the product mixture indicated 72% anisole (120) and 28% cresol 168.

When the above reaction was repeated in the presence of N,N-DIPEA (33.5mg, 0.26mmol) in place of sodium acetate, the product mixture contained 80% anisole 120, 10% cresol 168 and 10% cresol 219.

(l) Reaction with potassium fluoride:

Diene 102, (30mg) was stirred overnight in a solution of potassium fluoride (37.7mg, 0.65mmol), NNDIPEA (33.5mg, 0.26mmol) and 18-crown-6 (171.6mg, 0.65mmol) in acetonitrile ($0.5cm^3$). After work up unreacted diene was obtained. When the reaction was repeated with water ($0.5cm^3$) present in the reaction mixture, no reaction occurred after 48h stirring at ambient temperature and unreacted diene (102) was recovered.

(m) Reaction with isopropanol:

Diene 102, (30mg) was stirred overnight in a mixture of NNDIPEA (33.5mg, 0.25mmol) and isopropanol (2cm^3). After work up unchanged diene was recovered. On repeating the experiment with water (0.5cm^3) present in the system, the product mixture contained 48% cresol (168), 29% cresol (219) and 24% of a mixture of (Z) and (E)-1-isopropoxy-1-methoxy-4-methyl-4-nitrocyclohexa-2,5-diene (289) ^{1}H-NMR ($CDCl_3$, 90MHz): δ 1.14 (6H, d, J=7Hz, O-CH-($\underline{CH_3}$)$_2$), 1.72 (3H, s, CH_3), 3.25 (1H, sp-tet, O-$\underline{CH}$), 3.22 (OCH_3) 6.05 (2H, d, J=10.50Hz, 2-H and 6-H), 6.27 (d, J=10.50Hz, 3-H and 5-H)ppm. No attempts were made to isolate or separate these adducts.

(n) Reaction with potassium cyanide:

Diene 102, (0.908g, 3.96mmol) was stirred overnight in a solution of potassium cyanide (.88g, 1 6mmol), NNDIPEA (1.032g, 8mmol) in acetonitrile (20cm^3) and water (10cm^3). The ^{1}H-NMR spectrum of the oil obtained after work up indicated the presence of 58% (E)-1-cyano-1-methoxy-4-methyl-4-nitrocyclohexa-2,5-diene (287), 30% of the Z-diastereomer (286) along with 12% of aromatic products. Fractional crystallization of this mixture from ether-petroleum ether mixture at -20°C yielded pure 287. which was characterized after purification. mp: 44°C; UV (CH_2Cl_2): λ_{max} 293nm (ε=10.5m^{2}mol^{-1}) IR: (KBr disc) 1545 and 1370 (NO_2), 1087 (OCH_3); ^{1}H-NMR (250MHz, $CDCl_3$) δ: 1.81 (3H, s, CH_3), 3.34 (3H, s, OCH_3), 6.15 (2H, d, J=10.2Hz, 2-H and 6-H), 6.5 (2-H, d, J=10.2Hz, 3-H and 5-H)ppm; ^{13}C-NMR (250MHz, $CDCl_3$) δ_C: 26.9 (CH_3), 52.6 (OCH_3), 66.5 (C-1), 82.6 (C-4), 116.6 (CN), 126.3 (C-2 and C-6), 131.6 (C-3 and C-5)ppm; Analysis: C 55.72%, H 5.19%, N 14.38%, (Calculated for $C_9H_{10}N_2O_3$C 55.66%, H 5.19%, N 14.42%). The mother liquor was then separated by semipreparative HPLC

on a CN-10 column using linear gradient elution with hexane and CH_2Cl_2. The solvent composition was changed from 50% CH_2Cl_2 - hexane to 100% CH_2Cl_2 over a period of 75min with a flow rate of 4 ml/min. After 17min diene 287 was eluted, followed by 286 28min, and cyanocresol 288 was eluted after 32min. The products were characterized without further purification. Diene 286 : UV (CH_2Cl_2): λ_{max} 280nm (ε=20m^{2}mol^{-1}), IR (neat): 1545 and 1375 (NO_2), 1080 (OCH_3); ^{1}H-NMR (250MHz, $CDCl_3$) δ: 1.80 (3H, s, CH_3), 3.41 (3H, s, OCH_3), 6.20 (2H, d, J=10.15Hz, 2-H and 6-H), 6.5 (2H, d, J=10.15Hz, 3-H and 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$), 26.7 (CH_3), 52.6 (OCH_3), 66.5 (C-1), 82.6 (C-4), 116.6 (CN), 126.3 (C-2 and C-6), 131.4 (C-3 and C-5)ppm; Analysis C 55.59%, H 5.21%, N 14.06%, (Calculated for $C_9H_{10}N_2O_3$: C 55.66%, H 5.19%, N 14.42%).

(o) Reaction with isobutylamine:

Diene 102, (227mg, 0.1mmol) was added to a soltuion of isobutylamine (365mg, 0.5mmol) in acetonitrile (10cm^3) and water (20cm^3) and the mixture was stirred overnight. The reaction mixture was diluted with methylene chloride (50cm^3) and washed with water (3x15cm^3). Removal of methylene chloride on the rotovapor yielded a red oil. The ^{1}H-NMR spectrum of the oil indicated that the composition was 40% N-isobutyl-p-toluidine (290), 60% N-isobutyl-2-nitro-p-toluidine (291) and minor amounts of other aromatic products.

The residue was dissolved in CH_2Cl_2 (50cm^3) and extracted with hydrochloric acid (3x15cm^3, 1N). The organic layer was washed with water (20cm^3), the dried over anhydrous magnesium sulfate and evaporated to dryness. The ^{1}H-NMR spectrum of this dark red residue indicated the composition as mainly nitrotoluidine 291 along with other aromatics. Attempts to separate this mixture by TLC failed although various

solvents (petroleum ether, ether-petroleum ether mixtures, benzene, methylene chloride) were used. Column chromatography on silica gel using petroleum ether as eluent gave mixtures enriched in nitrotoluidine 291 in the early fractions. Similar results were obtained with 5% ether-petroleum ether and 100% ether solutions as eluents. Gradient elution ($5x50cm^3$ of 100% petroleum ether, 2% ether-98% petroleum ether solutions) gave similar results. The nitrotoluidine was characterized in the mixture: ^{1}H-NMR (250MHz, $CDCl_3$), δ 1.04 (6H, d, J=6.6Hz, CH-($\underline{CH_3}$)$_2$), 1.99 (1H, m, $\underline{CH}(CH_3)_2$), 2.25 (3H, s, Ar-$\underline{CH_3}$), 3.10 (2H, dd, J=6.40 and 5.40Hz, $\underline{CH_2}$), 6.76 (1H, d, J=8.70Hz, 1-H), 7.24 (1H, dd, J=8.70 and 1.00Hz, 5-H), 7.97 (1H, d, J=1.00Hz, 3-H), 8.08 (1H, br s, N-$\underline{H}$)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 19.9 (Ar-CH_3), 20.4 (CH($\underline{CH_3}$)$_2$), 28.0 (CH), 50.8 (CH_2), 113.8 (C-6), 124.5 (C-4), 126.1 (C-3), 130.0 (C-2), 137.6 (C-5), 144.1 (C-1)ppm; GCMS (CI-methane) of this fraction indicated that the molecular weight of this compound is 208. The other fractions were enriched in another aromatic which had mass 163; ^{1}H-NMR (250MHz, CD_2Cl_2): δ 0.81 (6H, d, J=6.80Hz, CH-($\underline{CH_3}$)$_2$), 1.93 (1H, m, CH), 2.39 (3H, s, Ar-CH_3), 3.88 (2H, d, J=7.60Hz, $\underline{CH_2}$), 7.28 (2H, d, J=9.90Hz), 7.35 (2H, d, J=9.90Hz); The structure of this compound could not be assigned.

The original acid extracts were combined and neutralized with sodium hydroxide solution and extracted with CH_2Cl_2 ($3x20cm^3$). Removal of solvent after drying over anhydrous magnesium sulfate gave pure toluidine (290, 80mg). IR (neat): 3420 and 1620 (N-H), 2960 (C-H); UV (CH_2Cl_2): λ_{max} 303nm (ε=318 $m^2 mol^{-1}$), 250nm (ε=984 $m^2 mol^{-1}$); ^{1}H-NMR (250MHz, $CDCl_3$): δ 0.97 (6H, d, J=6.70Hz, CH-($\underline{CH_3}$)$_2$), 1.87 (1H, m, CH), 2.23 (3H, s, Ar-CH_3), 2.90 (2H, d, J=4.70Hz, NCH_2), 6.53 (2H, d,

J=8.50Hz, 2-H and 6-H), 6.97 (2H, d, J=8.50Hz, 3-H and 5-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 19.7 (CH_3), 20.3 (CH-($\underline{CH}$)$_3$)$_2$), 28.1 (CH), 52.3 (CH_2), 112.9 (C-2 and C-6), 126.2 (C-4), 129.7 (C-5 and C-3), 146.4 (C-1); MS (70eV), m/e (relative intensity): 162(12), 119(100), 90(18); analysis: calculated for $C_{11}H_{16}N$,: C 81.42%, H 9.94%, N 8.63%; (found: C 81.21%, H 9.99%, N 8.19%).

(p) Reaction with 2,4-dinitrophenylhydrazine:

A solution of 2,4-dinitrophenylhydrazine was prepared by dissolving the hydrazine (0.25g, 1.25mmol) in concentrated sulfuric acid ($1.25cm^3$). This solution was then added to a mixture of water ($1.75cm^3$) and 95% ethanol ($6cm^3$). A solution of diene 102, (114mg, 0.5mmol) in 95% ethanol ($1.25cm^3$) was added dropwise to the acidic 2,4-dinitrophenylhydrazine solution. Within a minute red crystals began to form. After recrystallization from hot ethanol pure 2,4-dinitrophenyl-4'-methylazobenzene 277, (153mg, 92% yield) was obtained as dark red needles: mp 134-6 °C (lit 135-136 °C); ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.47 (3H, s, CH_3), 7.36 (2H, d, J=8.40Hz, 2' and 6'-H), 7.81 (1H, d, J=8.80Hz, 6-H), 7.87 (2H, d, J=8.40Hz, 3' and 5'-H), 8.51 (1H, dd, J=8.80 and 2.40Hz, 5-H), 8.80 (1H, d, J=2.40Hz, 3-H)ppm.

7.10.7 Reactions of (Z)-4-chloro-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (130):

(a) Reaction with methanol in the presence of sodium acetate:

Diene (130, 350mg, 1.35mmol) was added to a previously stirred solution of sodium acetate (282mg, 2.8mmol) in methanol ($12cm^3$) and water ($6cm^3$). The mixture was stirred at ambient temperature for 2 days. Methanol was removed on the rotovapor at 20°C and the residue was dissolved in ether ($50cm^3$), washed with water ($2x20cm^3$), dried over anhydrous magnesium sulfate, and evaporated to dryness to yield a brown

oil. The ^{1}H-NMR spectrum of this oil indicated the presence of 17% 4-chloro-5-methoxy-o-cresyl acetate (292), 21% cresol 137, 5% anisole and 48% ketal (135) were present.

Cresol 137 was removed from the mixture by washing the ether solution (50cm^{3}) of the residue with 10% aqueous bicarbonate solution (2x20cm^{3}). Removal of ether at room temperature yielded a yellow oil (140mg) containing 5% anisole 136, 66% ketal 135 and 29% acetate 292.

The mixture was separated by HPLC on a nitrile column (CN-10, 0.8x50cm) using linear gradient elution. The composition of the eluent was changed from 100% hexane (2.5cm^{3}/min) to 100% methylene chloride (4cm^{3}/min) over a period of twenty minutes. The first fraction (21min) yielded pure acetate 292 followed by anisole 136 in the second fraction (23min). Pure ketal 135 was obtained in the third fraction (25min).

Acetate 292 was crystallized from ether-petroleum ether mixture as a yellow solid; mp: 44°C; UV (CH_2Cl_2): λ_{max} 280.9nm (ε=417m^{2}mol^{-1}), 287.5 (ε=346m^{2}mol^{-1}); IR (neat) 1765 ($OCOCH_3$), 1134 (OCH_3); ^{1}H-NMR (250MHz, $CDCl_3$) 2.08 (3H, s, $OCOCH_3$), 2.32 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 6.62 (1H, s, 6H), 7.22 (1H, s, 3H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$). 15.2 ($OCOCH_3$), 20.7 (CH_3), 56.4 (OCH_3), 106.8 (C-6), 119.6 (C-4), 122.9 (C-2), 131.8 (C-3), 148.3 (C-1), 163.7 (C-5), 168.0 ($OCOCH_3$); MS (70eV), m/e (relative intensity) 214(14), 174(33), 172(100), 137(26), 129(18), 77(23): analysis C 55.60%, H 5.28%; (calculated for $C_{10}H_{11}O_3Cl$ C 55.95%, H 5.16%)

Ketal 136, (yellow oil) was characterized as such: UV (CH_2Cl_2): λ_{max} 279.7 (ε=53m^{2}mol^{-1}); IR (neat) 1552 and 1350 (NO_2). 1065 and 1098 (OCH_3); ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.75 (3H, s, CH_3), 3.21 (3H, s, OCH_3), 3.2 (3H, s, OCH_3), 6.01 (1H, d, J=10.30Hz, 6H), 6.46 (1H, dd, J=2.50

and 10.30Hz), 6.58 (1H, d, J=2.50Hz, H-3)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$): δ_C 26.7 (CH_3), 51.0 (OCH_3), 51.6 (OCH_3), 65.8 (C-1), 86.4 (C-4), 130.1 (C-6 and C-3), 131.9 (C-5), 136.8 (C-2)ppm; Analysis: C 46.80%, H 5.05%, N 5.54% (calculated for $C_9H_{12}NO_4Cl$ C 46.66%, H 5.17%, N 5.99%).

(b) reaction with methanol in the presence of NNDIPEA:

Diene 130, (54mg, 0.2mmol) was added to a mixture of methanol ($2cm^3$), water ($1cm^3$) and N,N-diisopropylamine (51.6mg, 0.4mmol) and stirred for one day at ambient temperature. Methanol was removed on the rotovapor and the residue was dissolved in ether ($30cm^3$), washed with water ($2x10cm^3$) and evaporated to dryness after drying over anhydrous magnesium sulfate. The ^{1}H-NMR of the residual yellow oil after work up indicated 41% 4-chloro-5-methoxy-o-cresol (293), 41% ketal 135, 6.5% anisole 136 and 11.5% cresol 137 was present.

(c) Reaction with potassium cyanide in acetonitrile

Diene 130, (175mg, 0.67mmol) was added to a previously stirred solution of potassium cyanide (175mg, 2.7mmol) in acetonitrile ($6cm^3$), water ($3cm^3$) and NNDIPEA at ambient temperature and stirred for two days. After evaporation of acetonitrile at 20°C, the aqueous layer was dissolved in ether ($50cm^3$), washed with water ($2x20cm^3$), dried over anhydrous magnesium sulfate, and evaporated to dryness to yield a yellow oil. The ^{1}H-NMR spectrum of the oil indicated 26% anisole 136, 13% cresol 293 and 61% of a (2:1) mixture of both (E)- and (Z)-2-chloro-1-cyano-1-methoxy-4-methyl-4-nitrocyclohexa-2,5-diene (294 and 295 respectively).

The mixture was separated by HPLC on a nitrile column (CN-10, 0.8x50cm) using linear gradient elution. The composition of the solvent was increased from 25% hexane-methylene chloride to 100% methylene chlooride over a period of 25min.

The first fraction (8min) contained 90% anisole 136 and 10% anisole 115. Diene 294 (the major diastereomer) was present in the second fraction (9min). The third fraction contained mainly diene 295 and traces of an unknown compound with NMR signals at 5.92 (1H, s), 3.8 (3H, s), 2.05 (3H, d). Pure cresol 293 was eluted after 20min.

Attempts to obtain pure (295) by crystallization and HPLC under various conditions failed, so it was characterized as such by ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.83 (3H, s, CH_3), 3.28 (3H, s, OCH_3), 6.16 (1H, d, J=9.95Hz, 6-H), 6.55 (1H, dd, J=2.12 and 9.95Hz, 5-H), 6.66 (1H, d, J=2.12Hz, 3-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$) δ_C: 26.5 (CH_3), 52.08 (OCH_3), 70.7 (C-1), 84.5 (C-4), 114.4 (CN), 125.9 (C-6), 129.7 (C-3), 131.2 (C-5), 131.8 (C-2).

Pure diene 294 was obtained as white crystals from the second fraction: mp: 65°C; UV (CH_2Cl_2): λ_{max} 262nm (ε=41$m^2 mol^{-1}$); IR (KBr) 1548 and 1340 (NO_2), 1069 (OCH_3); ^{1}H-NMR (250MHz, $CDCl_3$)δ: 1.86 (3H, s, CH_3), 3.23 (3H, s, OCH_3), 6.14 (1H, d, J=9.90Hz, H-6), 6.52 (1H, dd, J=9.90 and 2.00Hz, H-5), 6.63 (1H, d, J=2.00Hz, H-3)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$) δ_C:26.6 (CH_3), 52.0 (OCH_3), 69.9 (C-1), 84.8 (C-4), 115.2 (CN), 126.5 (C6), 130.1 (C3) 131.9 (C-5) 132.2 (C-2)ppm; analysis C 47.59%, H 4.07%, N 11.86% (Calculated for $C_9H_9N_2O_3Cl$ 47.28%, H 3.96%, N 12.25%). Pure cresol (293) was obtained as a pale yellow liquid: UV (CH_2Cl_2): λ_{max} 272nm (ε=709$m^2 mol^{-1}$); IR (neat) 3400 (OH), 1300 (OMe);
^{1}H-NMR (250MHz, $CDCl_3$) δ, 2.15 (3H, s, CH_3), 3.84 (3H, s, OCH_3), 4.80 (1H, br s, OH), 6.44 (1H, s, H-2), 7.08 (1H, s, H-5); ^{13}C-NMR (62.9MHz, $CDCl_3$) 14.8 (CH_3), 56.5 (OCH_3), 100.8 (C-2), 113.8 (C-4), 116.6 (C-6), 131.7 (C-5), 153.2 (C-1), 154.2 (C-3); MS (EI, 70eV), 174(33),

172(100), 157(12), 137(38), 131(16), 129(48), 94(17), 93(15), 77(30); Exact mass: found: 172.031 (Calculated for $C_8H_9^{35}ClO_2$ 172.029).

7.10.8 Reactions of (Z)-3-methoxy-6-methyl-2,6- and 2,4-dinitrocyclohexa-2,4-dienyl acetates (151) and (154):

(a) Reaction with methanol in the presence of sodium acetate:

Diene 151, (272mg, 1mmol) was added to a mixture of sodium acetate (170mg, 5mmol), methanol (5cm^3) and water (2cm^3) and the mixture was stirred at ambient temperature for 48h. The residue obtained after drying and evaporation of ether contained mainly ketal 156 and traces of cresol 231.

Pure ketal 156 was obtained from this mixture as a pale brown oil (110mg, 46% yield) after removal of cresol 231 by washing with aqueous sodium bicarbonate (10%, 2x25cm^3): IR (neat):1552, 1538 and 1340 (NO_2), 1065 and 1098 (OCH_3); UV (CH_2Cl_2): λ_{max} 242nm (ε=41m^{2}mol^{-1}); ^{1}H-NMR (250MHz, $CDCl_3$) δ: 1.93 (3H, s, CH_3), 6.06 (1H, d, J=10.30Hz, 6-H), 6.46 (1H, dd, J=10.30 and 2.50Hz, 5-H), 7.32 (1H, d, J=2.50Hz, 3-H)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$) δ_C: 26.5 (CH_3), 51.3 (OCH_3), 52.2 (OCH_3), 84.5 (C-4), 94.5 (C-1), 131.7 (C-5), 149.0 (C-2) 129.7 & 130.1 (C-3 & C-6) ppm Reaction of diene 154, (27mg, 0.1mmol) with aqueous methanol (1cm^3) and water (0.5cm^3) and sodium acetate (17mg, 0.5mmol) yielded ketal 226 as the major product after 48h. Neither reaction proceeded in the absence of water.

(b) Reaction with methanol in the presence of NNDIPEA:

Diene 151, (54mg) was stirred for 24h with a mixture of methanol (2cm^3), water (1cm^3) and NNDIPEA (52mg). After work up the ether layer contained trace amounts of unidentified compounds. The aqueous layer after acidification yielded cresol 231.

7.11 Reactions of Dienes with Hydrides:

7.11.1 Reactions of (Z)-3-chloro-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (100):

(a) Reaction with AlH_3

Aluminium chloride (133.5mg, 1.0mmol) was slowly added to a well stirred solution of lithium aluminium hydride (114mg, 3mmol) in THF (1.5cm^3) under argon and the mixture was stirred at room temperature for 1h. A solution of diene 100, (231mg, 1mmol) in tetrahydrofuran (0.5cm^3) was slowly injected into the suspension of aluminium hydride, cooled to -20°C and stirred for 1h, during which time period the temperature was allowed to increase to 0°C. The reaction mixture was cooled to -78°C, water (0.5cm^3) was added and the mixture stirred for 5min. The mixture was transferred to a separating funnel with ether (25cm^3) and the water layer was separated . The ether layer was washed with water (2x10cm^3), dried over anhydrous magnesium sulfate and evaporated to dryness at -40°C. The NMR spectrum of the residual oil (142mg) indicated the presence of 24% 4-chlorotoluene (111), 11% cresol (213) and 65% 4-chloro-1-methyl-1-nitrocyclohexa-2,4-diene (296). Identical results were obtained when a clear solution of AlH_3, obtained by filtration under argon, was used for the reaction.

Diene (296) was characterized in the mixture without further purification. ^{1}H-NMR (250MHz, $CDCl_3$, -5°C): δ 1.66 (3H, s, CH_3), 2.57 (1H, dd, J=18.90 and 3.30Hz, 6-H), 3.40 (1H, dd, J=18.90 and 5.60Hz, 6'-H), 5.89 (1H, m, 5-H), 5.99 (1H, d, J=9.80Hz, 4-H), 6.12 (1H, dd, J=9.80 and 1.48Hz, 3-H). (Irradiating the centre of the multiplet at 5.89ppm, reduced the doublet of doublets at 2.57 and 3.40ppm to 18.90Hz doublets and the doublet of doublets at 6.12ppm to a 9.8Hz doublet.) ^{13}C-NMR (62.9MHz, $CDCl_3$, -50°C): δ_C 25.7 (CH_3), 34.2 (CH_2), 83.5 (C-1),

120.5 (C-5), 126.4 (C-3), 129.3 (C-2), 130.6 (C-4)ppm.

(b) Reaction with diisobutylaluminium hydride:

A solution of DIBAL in heptane (1cm^3) was injected into a solution of diene 100, (50mg, mmol) in ether (10cm^3) at 0°C. The mixture was stirred for 15min at 0°C and 40min at ambient temperature, then cooled to -20°C. The NMR spectrum of the residue after work up indicated cresol 213 as the only product.

When the reaction was repeated on a NMR scale using DIBAL (after evaporation of heptane) in ether, there was no reaction at temperatures below 0°C. After 1.5h at 0°C, the mixture was worked up in the usual way. The NMR spectrum of the residue indicated 39% unchanged diene 100 and 61% cresol 213.

(c) Reaction with lithium aluminium hydride:

Lithium aluminium hydride (12mg, 0.32mmol) was added to a solution of diene 100, (60mg, 0.26mmol) in ether (2cm^3) at -20°C and the mixture was stirred at -20°C for 2h. The NMR spectrum of the residue after work up indicated the presence of 80% unreacted diene 100 and 20% cresol 213.

Repetition of the above reaction with a large excess of lithium aluminium hydride (3.2 mol) in THF yielded after work up 50% cresol 213 and 50% unreacted diene 100.

7.11.2 Reactions of (Z)-3-bromo-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (101):

(a) Reactions with aluminium hydride:

Aluminium chloride (133.5mg, 1mmol) was added slowly to a stirred solution of lithium aluminium hydride (114mg, 3mmol) in THF (1.5cm^3) under argon at 0°C. The mixture was stirred at room

temperature for 30min and cooled to -20°C. A solution of diene (101, 276mg, 1mmol) in THF (0.5cm^3) was injected into the hydride solution and the mixture was stirred for 1h. The NMR spectrum of the mixture indicated the presence of 15% p-bromotoluene (110), 12% 5-bromo-o-cresol (215) and 73% 4-bromo-1-methyl-1-nitrocyclohexa-2,4-diene (297). Diene 297 was characterized in the mixture by NMR: ^{1}H-NMR (250MHz, $CDCl_3$, -50°C) δ: 2.52 (1H, dd, J=18.98 and 3.50Hz, 6-H), 3.36 (1H, dd, J=18.98 and 5.60Hz, 6'-H), 5.91 (1H, d, J=9.75Hz, 2-H), 6.13 (1H, m, 5-H), 6.20 (1H, dd, J=9.75 and 1.47Hz, 4-H). Irradiation at the centre of the multiplet at 6.13ppm reduced the dd at 2.52ppm to d, J=18.98Hz, and dd at 3.36ppm to d, J=18.98Hz, and the dd at 6.20 to a 9.75Hz-d; ^{13}C-NMR (62.9MHz, $CDCl_3$, -50°C) δ_C:25.7 (CH_3), 35.3 (C_6), 83.4 (C-1), 114.3 (C-4), 124.7 (C-1), 126.2 (C-3), 130.85 (C-2)ppm.

Diene 297 decomposed exclusively to p-bromotoluene 110 on warming to room temperature overnight. When the reaction was repeated with 8 mmol of aluminium hydride an identical product mixture was obtained. A similar reaction with lithium aluminium hydride (4mmol) gave 38% toluene (110) and 62% cresol (213). On decreasing the amount of lithium aluminium hydride to 3 mmol the amount of cresol (215) increased to 84%. With aluminium chloride (1eq) unchanged diene (6) was recovered after 1h at 0°C.

7.11.3 Reaction of (Z)-3-methoxy-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (102):

(a) Reaction with AlH_3:

A solution of diene (102, 227mg, 1mmol) in THF (2cm^3) was added to a well stirred solution of $AlCl_3$ (133.5mg, 0.1mmol) and $LiAlH_4$ (114mg, 3.0mmol) in THF (2cm^3) at -40°C under argon. The reaction mixture was stirred at -40°C for 1h, then diluted with ether (45cm^3) at

-45°C and treated with water ($5cm^3$). The ^{1}H-NMR spectrum of the colorless oil obtained after evaporation of the ether at -45°C indicated the presence of 60% 4-methoxy-1-methyl-1-nitrocyclohexa-2,4-diene (298), 5% 4-methylanisole (112) and 35% 5-methoxy-o-cresol (299). During removal of residual THF on the high vacuum pump at -40°C, some of the diene 298 decomposed to anisole 112. Diene 298 was characterized in a mixture of 35% cresol 299, 40% anisole 112 and 25% diene 298 by ^{1}H-NMR: (250MHz, $CDCl_3$, -50°C) δ: 1.72 (3H, s, CH_3), 2.58 (1H, dd, J=3.26 and 18.25Hz, 6-H), 3.36 (1H, dd, J=5.65 and 18.25Hz, 6'-H), 3.54 (3H, s, OCH_3), 4.74 (1H, br ddd, 5-H), 6.02 (1H, d, J=9.90, 2-H), 6.13 (1H, dd, J=9.90 and 2.15Hz, 3-H). On irradiating the signal at 4.74ppm, the dd at 2.58ppm collapsed to a doublet (J=18.25Hz), the signal at 3.36ppm collapsed to a doublet (J=18.25Hz) and the signal at 6.13ppm collapsed to a doublet (J=9.90Hz).

(b) Reaction with lithium aluminium hydride:

A solution of diene 102 (227mg, 1mmol) in THF ($2cm^3$) was added to a well stirred solution of $LiAlH_4$ (152mg, 4.0mmol) in THF ($5cm^3$) at -40°C and the mixture was stirred for 1h. The ^{1}H-NMR spectrum of the product mixture indicated the presence of 35% anisole 112 and 65% cresol 299.

The cresol 299 was separated from the mixture by extracting with 10% aqueous sodium hydroxide . The aqueous layer was acidified with conc H_2SO_4 and extracted with ether. Evaporation of the ether layer from the dried solution gave pure cresol 299 as a brown oil (59mg, 42% recovered yield). On standing at -20°C, the cresol was obtained as crystals. It had mp 39-41°C (lit[151] 38-40°C); IR (neat): 3400 (OH), 1120 (OCH_3); exact mass: found 138.072 (calculated for $C_8H_{10}O_2$: 138.068); UV (CH_2Cl_2) λ_{max} 279 (ε=596 $m^2 mol^{-1}$); ^{1}H-NMR (250MHz, $CDCl_3$)

δ:2.17 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 4.80 (1H, br s, OH), 6.41 (2H, m, 2-H and 6-H), 6.99 (1H, d, J=8.01Hz, H-5)ppm; ^{13}C-NMR (62.9MHz, $CDCl_3$) δ_C:14.9 (CH_3), 55.4 (OCH_3), 101.6 (C-2), 106.0 (C-6), 115.7 (C-4), 131.2 (C-5), 154.6 (C-3), 159.2 (C-1)ppm.

7.11.4 Reduction of (E)-1,4-dimethyl-4-nitrocyclohexa-2,5-dienyl acetate 80 with lithium aluminium hydride:

Diene 80 (50mg, 0.24mmol) in THF (0.5cm^3) was added to a suspension of lithium aluminium hydride (37mg, 0.96mmol) in THF (2cm^3) at -20°C. The mixture was stirred for 40min during which the temperature was increased to 0°C. The reaction mixture was cooled to -40°C and worked up in the usual way. The NMR spectrum of the residue indicated the presence of (E)-1,4-dimethyl-4-nitrocyclohexa-2,5-dienol (275) as the only product mp 107-8°C (lit[133] 107-8°C).

Similar results were obtained when aluminium hydride (1.9mmol) prepared in the usual way, was employed as the reducing agent.

TABLE 7.11

Crystal data for 101, 190 and 200.

	101	190	200
Crystal system	Orthorhombic	Monoclinic	Orthorhombic
Space group	Pbca (No. 61)	$P2_1/n$ (No. 14)	$Pca2_1$ (No. 29)
a (Å)	27.445(8)	7.386(3)	11.901(5)
b	9.683(3)	7.618(2)	6.758(2)
c	8.335(2)	19.498(6)	11.495(4)
β (°)	90.	92.91(4)	90.
V ($Å^3$)	2215(1)	1095.7(6)	924.5(6)
Mol. Wt.	276.09	276.09	252.5
Z	8	4	4
D_{meas} ($g\ cm^{-3}$)	-	1.67	1.78
D_{calc}	1.656	1.67	1.82
Mounting axis	c	a	a
Standard refls.	18 00, 080, 006	060, 006, 400	200, 006, 020
Meas. range	0-40°	0-30°	0-50°
No. of steps (0.01° in 2θ, 0.25s)	160	200	160
Backgrnd. count (s)	40	50	40
$\mu(cm^{-1})(\lambda=0.71069Å)$	39.25	39.67	49.40
Transmission	0.10-0.53	-	0.17-0.47
R	0.0763	0.1033	0.0551
R_w	0.0941	0.1029	0.0601
Diff. map max.($eÅ^{-3}$)	0.83	1.17	0.58
No. of observations	1033	597	862
No. of parameters	136	61	108

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FORMATION AND REACTIONS OF 1,2-ADDUCTS FROM IPSO-NITRATION OF TOLUENE DERIVATIVES

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SUMIT RAY MAHASAY

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