Formation and Reactions of Ipso Adducts of 2-X-p-xylenes

by

Dan Xi

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[redacted]

(Alfred Fischer)

[redacted]

(Paul R. West)

[redacted]

(Don A. Vandenberg)

[redacted]

(Paul J. Romaniuk)

Superviser: Professor Alfred Fischer

Abstract

The low temperature nitration of 2-X-p-xylenes (X = Cl, Br, $COCH_3$, COC_6H_5) in acetic anhydride has been studied in detail. The nitration of 2-bromo- and 2-chloro-X-p-xylene and 2,5-dimethylacetophenone gives 1,4 adducts exclusively while the nitration of 2,5-dimethylbenzophenone leads to 1,2 adducts only. The yield of these adducts range from moderate to good. The regioselectivity of acetic acid capture appears to be more sensitive to steric effects than to electronic effects. The principle of additivity can qualitatively predict the isomer distribution in the nitration reactions.

Reactions of the 1,4 adducts (X = Cl, Br, $COCH_3$) in different media have been studied. Strong to moderate acid conditions favor the formation of the nitrocyclohexadienyl cation and the competition among three possible pathways (1,2 nitro shift, 1,3 nitro shift and the triene process) is affected by the substituents (X), the acidity and the solvent. In methanol the nitrocyclohexadienyl cation is captured by the solvent to form the dienyl methyl ether. The dominant

reaction of the nitrocyclohexadienyl cation in acetic anhydride is deprotonation to give triene and ultimately, side chain aromatics, while the 1,2 nitro shift process dominates in more strongly acidic media. It is also observed that the more strongly electron withdrawing acetyl group facilitates the 1,2 nitro shift process and, to a lesser extent, the 1,3 nitro shift process. Side chain products are not observed with this substituent. Finally the reactions of 1,4 ipso adducts with methanol in the absence of acid give dienols stereospecifically.

Examiners:

[redacted]

(Dr. A. Fischer)

[redacted]

(Dr. P. R. West)

[redacted]

(Dr. D. A. Vandenberg)

[redacted]

(Dr. P. J. Romaniuk)

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Chapter 1 Introduction

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Chapter 1 Introduction

1.1 Background:

The first known reaction leading to the nitration of benzene was recorded by Faraday[1] in 1825. Then in 1834 Mitscherlich[1] reported the preparation of nitrobenzene by treating benzene with fuming nitric acid. Since these discoveries, electrophilic aromatic nitration has received wide attention and is now regarded as one of the cornerstone reactions of organic chemistry. The establishment of some fundamental principles of organic chemistry have been partly attributed to the investigation of mechanisms of nitration. The main generalizations[2] regarding orientation in electrophilic substitution i.e. ortho/para or meta-directing, and its connection with activation were originally based on extensive data from nitration. Ingold[3] and his coworkers utilised orientation and rate of nitration data in elaborating their original ideas of the electronic theory of the course of organic reactions. Nitration has also played an important role in 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]. Synthetically, nitrations are

valuable because the nitroaromatics obtained are excellent intermediates in the subsequent chemical transformations into useful end products like plastics, pharmaceuticals, dyestuffs, explosives and insecticides. For example, the reduction of the nitro group to an amine, followed by diazotization provides a very convienient way of incorporating a wide variety of funtional groups into the aromatic ring to achieve specific syntheses. The fact that one third of the worldwide organic chemical prodution involves aromatic compounds leads to an ongoing interest in electrophilic aromatic nitration.

1.2 Reagents for Nitration:

Over the years numerous methods have been investigated for effecting nitration. Now nitration can be carried out under a wide variety of conditions in various solvents depending on the solubility and reactivity of the substrate. Dilute nitric acid, solutions of nitric acid or nitrates in oleum, sulfuric, phosphric acid and mineral acids are among the most used nitrating agents, providing a vigorous reaction enviroment. Solutions of nitric acid in organic solvents such as dichloromethane, acetonitrile, acetic acid, acetic anhydride, sulpholan and nitromethane can also be

used for nitration. The relative low acidity and the enhanced solubility of the aromatic subatrates in organic solvents sometimes make these systems more desirable than those involving mineral acid. Some recently developed systems are the solutions of nitronium salts such as nitronium tetrafluoroborate in inert organic solvents[8], alkyl nitrates in the presence of boron trifluoride[9], silver nitrate in the presence of boron trifluoride[10], butyl nitrate or acetone cyanohydrin nitrate with perfluorinated resin as N-nitropyridinium[11] and N-nitroquinolinium salts[12], some of which can effect nitration under essentially neutral conditions. There are some other nitrating agents such as metal nitrates in acetic anhydride[13], alkyl nitrates and sodium alkoxides[14] and ceric ammonium nitrate[15], which are less commonly used.

1.3 Nitration Mechanisms:

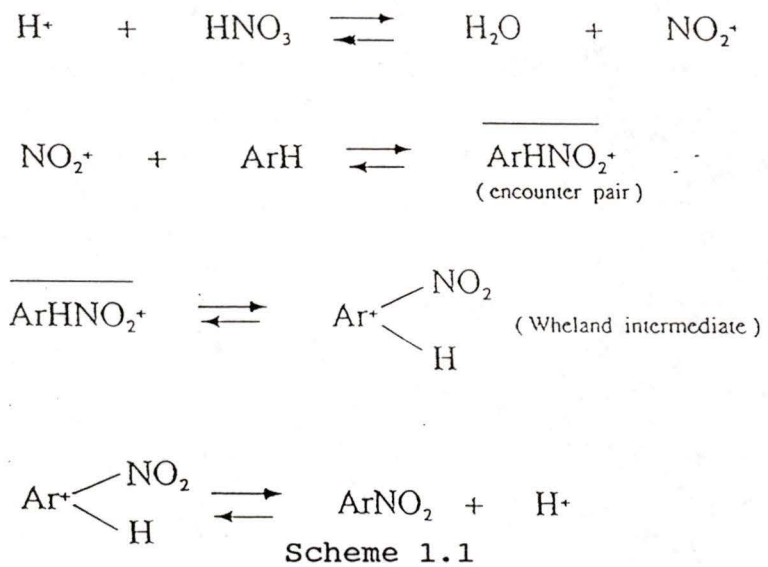
1.3.1 Nitration Involving Ionic Species

Euler[16] proposed as early as in 1903 that the nitronium ion was an intermediate in nitration. Much later the existence of nitronium ion was demonstrated by Raman spectroscopy[17], cryoscopic measurements[18], ultraviolet spectroscopy[19] and conductometric

measurements[20] of solutions of nitric acid in sulfuric acid. Also, nitrations carried out by nitronium salts suggested the strong possibility of nitronium ion as the actual attacking specie. Moreover, kinetic studies[21] of nitrations carried out in inert organic solvents such as nitromethane, chloroform etc., indicated that nitronium ions were involved. For instance, the nitration rates of toluene and its homologues in solutions of nitric acid with nitromethane were found to be independent of the concentration of the aromatic substrates. Therefore, the formation of the reactive specie (nitronium ion) prior to the attack on the aromatic ring was thought to be in the slow step.

The study[22] of kinetic isotope effect in aromatic nitration revealed that the primary hydrogen isotope effect was absent, so the direct displacement mechaniam has no ground to be valid. The insensitivity of product distributions to reaction conditions[23] led to the proposal of a common electrophile, that is the nitronium ion, under most conditions. Based on all of this information a two step mechanism involving the attack of the nitronium ion in the slow step followed fast deprotonation was suggested. Currently, the widely accepted mechanism for aromatic nitration is shown in

scheme 1.1.



Scheme 1.1

The steady-state approximation, applied to the common form of the nitronium ion mechanism represented above gives the following equation as the expression of the reaction rate.

$$\text{Rate} = \frac{k_1k_2k_3k_4[\text{ArH}][\text{HNO}_3]}{k_{-1}[(k_{-2}+k_3)(k_{-3}+k_4)-k_3k_{-3}]+k_2k_3k_4[\text{ArH}]}$$

Any one of the four steps can be rate determining, depending on the substrate and reaction conditions. The formation of the nitronium ion is the slowest step for substrates more reactive than benzene. For these substrates formation of the nitronium ion becomes rate determining and the reaction exhibits zeroth order dependence on the aromatic substrate. Nitration of anthracene with nitronium tetrafluoroborate in

acetonitrile[24] showed a kinetic isotope effect in the proton elimination step (k_H/k_D = 6.1). Steric effects have been suggested for this result. Under normal circumstances the last step in the sequence (step 4) is usually irreversible. However, Olah and his coworkers[25] observed the reversibility of the proton elimination step in some cases.

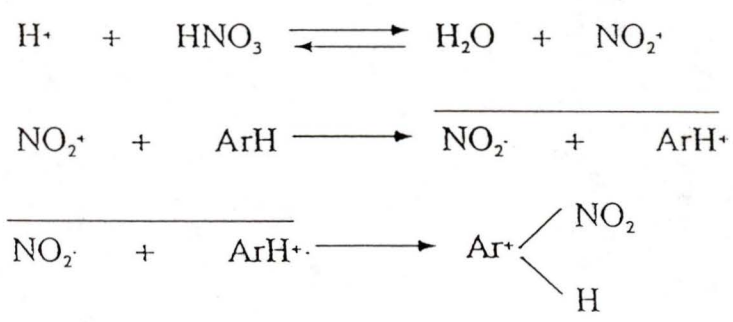
The classical mechanism of aromatic nitration, established on the basis of the extensive contributions of Ingold[26] and Melander[22b], did not distinguish between steps 2 and 3 in scheme 1.1. The nitration reaction was described as an S_E2 one step process involving the slow bimolecular attack by the nitronium ion on the substrate. This picture provided the basis of Brown's selectivity-reactivity principle[27], which states that loss of the substrate selectivity should be accompanied by loss of positional selectivity in competitive processes, both of which depend on the reactivity of the electrophile. The independent observation of the loss of substrate selectivity without the loss of positional selectivity by Schofield[28] and Olah[8] prompted them to propose an intermediate prior to the formation of the Wheland intermediate.

In studies of the reactivity of toluene compared to

that of benzene in the nitration with nitronium salts, Olah[8] found the k_T/k_B value was in the order of 1.15-1.85 as compared to 17-34 observed in nitric acid nitrations, while the positional selectivity was retained. He proposed the formation of a π-complex in the course of nitration prior to the collapse to the Wheland intermediate, to explain the loss of intermolecular selectivity. This suggestion failed to explain the persistence of intramolecular selectivity when intermolecular selectivity was lost. Furthermore, when Rys[29] plotted the relative rates for the nitration of benzene homologues with nitronium salts against the stabilities of the π-adducts, he found a correlation coefficient of only 0.91. This is lower than that which would be expected if formation of a π-complex is rate determining in nitration. The loss of substrate selectivity observed in Olah's experiments was shown to be caused by incomplete mixing[30].

The breakdown of the selectivity-reactivity principle was also observed by Schofield and his coworkers in the study of the nitration of alkyl benzenes in aqueous sulfuric acid and phosphoric acid[28]. Nitration of aromatic substrates with aqueous nitric acid, acetic anhydride, methanesulfonic acid[31] exhibited similar phenomena. Schofield proposed the formation of a non-

interacting encounter pair before the collapse to the Wheland intermediate in order to explain the experimental results. The rate constant for diffusion apart of the components of a non-interacting encounter pair would be in the order of 10^9-10^{10} s^{-1}. In order for the reaction to remain difussion controlled, the collapse rate of the encounter pair has to be larger than the above mentioned value. The upper limit of this rate would be in the order of 10^{12}-10^{13} s^{-1}, the vibrational frequency.The observed positional selectivity between the C-5 and C-6 position in pseudocumene was explained on this basis[32]. However, the proposal of a non-interacting complex failed to explain the intramolecular selectivity in the nitration of durene[33] and pentamethylbenzene[34]. Perrin[35] in alternative proposed the formation of a radical radical-cation interacting encounter pair prior to the collapse to the Wheland intermediates. The mechanism of nitration can be described in scheme 1.2 according to the proposal.



Scheme 1.2

The measurements of anodic half-wave potential for

NO_2 and representative aromatics in acetonitrile showed that the electron transfer to NO_2^+ is exothermic for all aromatics more reactive than toluene. This was the basis of the above proposal. Whenever the electron transfer process is exothermic, it is expected to be encounter controlled. The intramolecular selectivity is explained by Perrin on the basis of non-uniform electron spin density in the aromatic ring with the collapse of the radical-cation and radical occuring at positions of high electron density. In support of the new mechnism Perrin showed that the controlled potential electrolysis of napthalene and NO_2 resulted in the formation of 1- and 2-nitronaphthalene in the same ratio, within experimental error, as that obtained in the nitration of naphthalene in a mixture of of nitric acid and sulphuric acid. Subsequently, Eberson[36] found that the electrochemical nitration actually proceeded through homogeneous nitration of naphthalene by NO_2 catalyzed by anodically generated nitrous acid. Calculations[37] based on Marcus theory of non-bonded electron transfer show that electron-transfer processes as proposed by Perrin can be ruled out for aromatics with E^o lower or equal to perylene.

Recently Kochi and his coworkers[38] have studied the nitration of naphthalene and the methylnaphthalenes by N-

nitropyridium ion upon photoexcitation and have compared the results with those of thermal nitration under otherwise comparable reaction conditions. From the patterns of nitration products the indistinguishability of electrophilic and charge-transfer nitration of naphthalene, 1-methylnaphthalene and 1,4-dimethylnaphthalene can be established. Earlier, Kochi and his coworkers[39,40] demonstrated the formation of a cation-radical complex by charge-transfer excitation using time-resolved spectroscopy. In scheme 1.3, the reaction radical-cation and radical intermediate $ArH^{+}\cdot$ and $NO_2\cdot$ are born within 3 pico seconds as the intimate complex trapped within the solvent cage.(scheme 1.3)

$$[\,ArH,\ C(NO_2)_4\,] \xrightarrow[CT]{h\nu} [ArH^{+}\cdot,\ NO\cdot,\ C(NO_2)_3^{-}]$$

Scheme 1.3

Thus, Kochi again explained the positional selectivity on the basis that the attack of $NO_2\cdot$ occurs at the ring carbon of the radical cation with the highest odd electron spin density during the fast collapse of the radical-cation and radical pair.

At the present time, it appears that there is no universal proposal for the explanation of positional selectivity in aromatic nitration. It is possible that

product distribution is not a very sensitive function of mechanism in the case of nitration.

1.3.2 Nitration in Acetic Anhydride

A mixture of nitric acid and acetic anhydride is a good nitrating medium for studying aromatic nitration because most aromatic compounds are soluble in acetic anhydride and the reaction takes place under relatively mild conditions. It was thought that nitration in acetic anhydride would have a mechanism different from the classical nitronium ion mechanism. Several distinguishing features of nitration carried out in this solvent were responsible for that belief: (a) abnormally high ortho:para ratios in the nitration of anisoles and acetanilides[41]; (b) the requirement of a higher concentration of mesitylene to observe the zeroth order kinetics compared to that required in other media[42]; (c) accompanying acetoxylation in the course of nitration[43].

Vapor pressure measurements[44] of nitric acid (0-0.5 mole ratio) and acetic anhydride mixtures indicated the presence of acetyl nitrate, acetic acid, and the excess of acetic anhydride; when nitric acid is mixed with equal amount (molar ratio) of acetic anhydride, only acetyl

nitrate and acetic acid are present in the solution; when the amount of nitric acid was more than that of acetic anhydride, dinitrogen pentoxide was found. Results from Raman[45] and IR[46] spectra of the mixtures of nitric acid and acetic anhydride confirmed and extended these conclusions. Hence, the following two equilibria was proposed for the HNO_3-Ac_2O mixture (scheme 1.4).

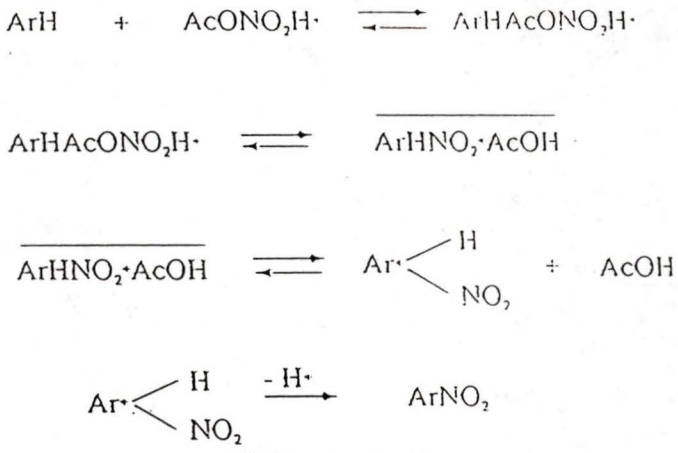
$$Ac_2O + 2HNO_3 \rightleftharpoons N_2O_5 + 2AcOH$$

$$N_2O_5 + Ac_2O \rightleftharpoons 2AcONO_2$$

Scheme 1.4

Species such as acetyl nitrate, protonated acetyl nitrate, dinitrogen pentoxide and nitronium ion have been proposed as the actual effective electrophiles in the nitrating system of HNO_3 and Ac_2O. The insensitivity of the ratio k_T/k_B to changes in the nitrating medium implies that there is a common nitration electrophile in all media. Thus it is considered very probable that nitronium ion is the reactive specie in HNO_3-Ac_2O mixture since there is very strong evidence for the effectiveness of the nitronium ion in other solvents. The observation of a non-zeroth order reaction rate at the encounter rate

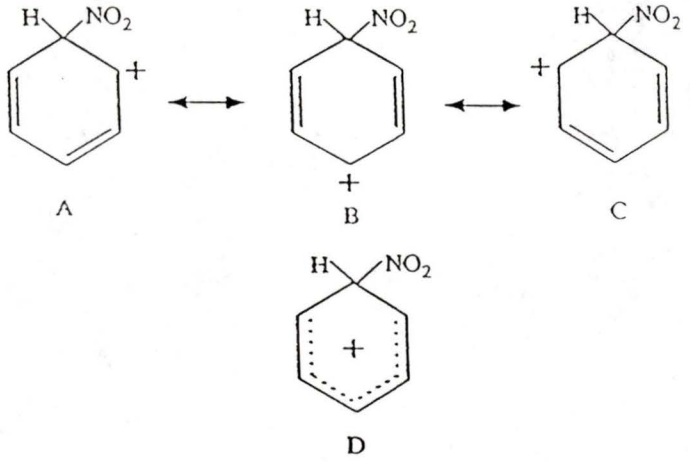
in the nitration of mesitylene serves as the only noteworthy objection to this suggestion. The presently accepted formulation of the nitration sequence in acetic anhydride is that the nitronium ion, if it is actually the active electrophile, is formed from the protonated acetyl nitrate, inside the encounter pair, as shown in scheme 1.5:



Scheme 1.5

1.4 The Wheland Intermediate:

The collapse of the encounter pair (scheme 1.1) leads to the formation of the Wheland intermediate. The structure of the Wheland intermediate can be represented as shown in scheme 1.6.



Scheme 1.6

Although the positive charge is not to be regarded as evenly distributed among the five carbon atoms of the ring, the intermediate is most conveniently written as struture D. Since Wheland[47] first used such structures to represent the transition states, they are called Wheland intermediates. It is also called a σ-complex because of the way in which the electrophile is attached to the ring. Other names used are arenium, aronium, arenonium or cyclohexadienyl cation, and Pfitzer complex. The following experimental evidence demonstrated the existence of Wheland intermediates:

1. The observation by NMR of the formation of a stable

intermediate in the nitration of hexamethylbenzene, trifluoromesitylene, and halopentamethylbenzene in superacid solutions at low temperature[48].

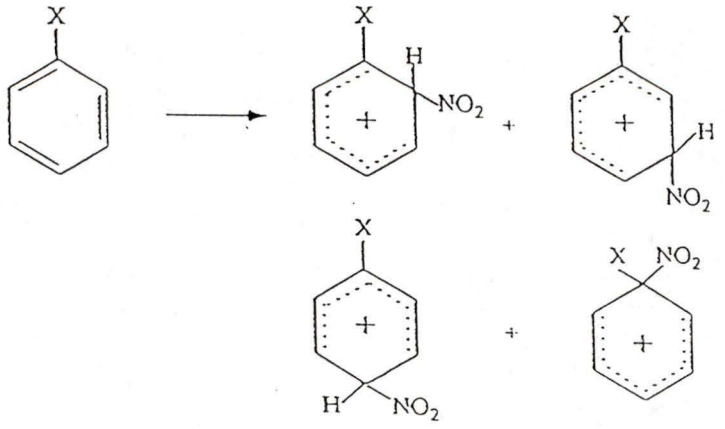
2. There is no primary kinetic isotope effect in the nitration of deuterated and tritiated aromatic compounds[21].

3. Solvent polarity effects on nitration kinetics[50].

4. The observation of an appropriate low-intensity UV absorption spectrum[49] for the intermediate which changes slowly to that of 9-nitroanthracene, in the nitration of anthracene by nitronium tetrafluoroborate in sulpholan.

5. The formation of ipso adducts (section 1.5), which points to the formation of ipso Wheland intermediates followed by capture by nucleophile from thr reaction media.

There are potentially four isomeric Wheland intermediates (Ws) formed on the nitration of a monosubstituted benzene (scheme 1.7).



Scheme 1.7

Normally, the Wo, Wm and Wp intermediates undergo rapid proton loss resulting in the formation of the corresponding nitro compounds. However, the ipso Wheland intermediate (Wi), which bears both nitro group and substituent on the same carbon, is associated with an enormous amount of chemistry. Thus these intermediates are considered separately (section 1.5).

1.5 Ipso Attack in Aromatic Nitration

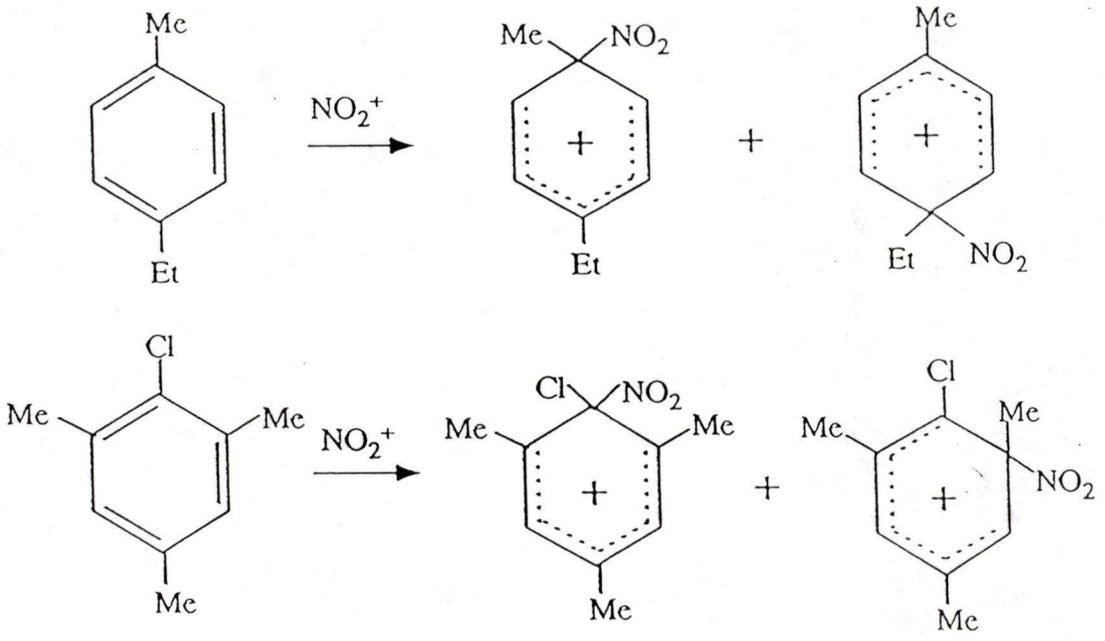
Ipso attack in aromatic nitration has been known for a long time from one of its consequences, namely ipso substitution[51]. The prefix ipso (latin: itself) was introduced by Perrin and Skinner[52] to represent the attack of an electrophile on the substituted position of a benzene ring. Ipso Wheland cations are relatively more stable than other Wheland intermediates arising from the attack on the unsubstituted positions. As a result ipso Wheland intermediates exhibit interesting chemistry. The following list summarizes the consequences of ipso attack:

1. Ipso substitution.
2. Migration of the original substituent.
3. Migration of the ipso nitro group.
4. Capture of the ipso cation by a nucleophile.

5. substituent modification in the ortho or para position.
6. loss of the ipso nitro group, i.e, no net reaction.

In the main substituent effects at the ipso position reflect steric and inductive effects. Resonance effects are unimportant. The ability of a substituent to donate or withdraw electrons affects the ipso position in the same way as it does the ortho, meta and para positions. Fischer and coworkers[53] have obtained the partial rate factors for the nitration of toluene and for other alkylbenzenes relative to toluene. For toluene the values are O_f=44, M_f=2.1, P_f=54 i_f=4.7, and for other alkylbenzenes[54] relative to toluene the values are i_f^{Me} : i_f^{Et} : $i_f^{i\text{-}Pr}$: $i_f^{t\text{-}Bu}$ = 1 : 0.3 : 0.2 : 0. Similarly Perrin[52] has measured the ipso partial rate factors for halogen substituents from the nitration of haloanisoles (i_fI=0.18, i_fBr=0.079, i_fCl=0.061). The methyl substituent activates the ipso position compared to other substituents, but the ipso position is about ten times less reactive than the ortho and para positions. Activating substituents positions ortho and para to an ipso position significantly increase the extent of ipso attack. Thus the extent of ipso attack is 60% in the nitration of o-xylene[55], 75% for p-xylene[56], and 100% for p-tolyl acetate[57]. Ipso attack at a particular position is enhanced if the position is ortho or para to another

activating substituent, which is itself not activating towards ipso attack. Competitive ipso attack arises if the second substituent has a +I and/or a +R effect as in cases of p-ethyltoluene[58] and chloromesitylene[59] (scheme 1.8).



Scheme 1.8

1.5.1 Capture of the Ipso Wheland Intermediate by a Nucleophile

An ipso Wheland intermediate can be captured by either external or internal nucleophiles to form the ipso adducts. The first isolated ipso adducts were observed by Fischer and his coworkers[34].

a. External Capture

Nitration with acetyl nitrate of aromatics is the most studied reaction condition for the nucleophilic capture of Wheland intermediates. The acetic acid generated by the mixing of nitric acid with acetic anhydride acts as the nuleophile and leads to nitrocyclohexadienyl acetates on the capture of Wheland intermediates. These captures can result in the formation of either 1,4-adducts or 1,2-adducts. Attack of the nuleophile at the 4-position with respect to the nitro group results in the formation of 1,4 adducts, normally as a pair of diastereomers. Some examples are shown in Table 1.1.

Selected examples of 1,4-adducts

Compoud	R	R_1	R_2	R_3	R_4	R_5	Ref.
1	Me	H	H	H	H	H	54
2	Me	H	H	Me	H	H	56
3	Me	Me	H	H	H	Me	60
4	Me	H	Me	H	H	Me	60
5	Me	H	H	Et	H	H	50
6	Et	H	H	Me	H	H	50
7	Me	H	H	iPr	H	H	61
8	Me	H	H	tBu	H	H	62
9	Me	Me	H	OMe	H	H	63
10	Me	Me	CN	H	H	H	64
11	Cl	Me	H	Me	H	Me	65
12	Me	H	NO_2	H	H	Me	66

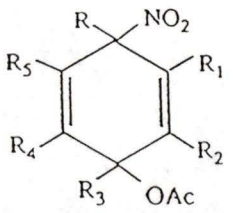


Table 1.1

1,2-adducts can be formed if the attack occurs at the 2-position and in most of the cases only a single diastereomer has been isolated. Table 1.2 lists some of the adducts obtained.

Selected examples of 1,2-adducts

Compound	R	X	Y	Ref.
13	Me	F	H	67
14	Me	Cl	H	67
15	Me	Br	H	67
16	Me	OMe	H	67
17	Me	NHAc	H	67
18	Me	tBu	H	61
19	CPr	OMe	NO_2	68

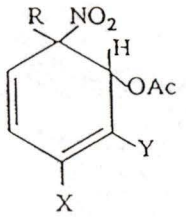
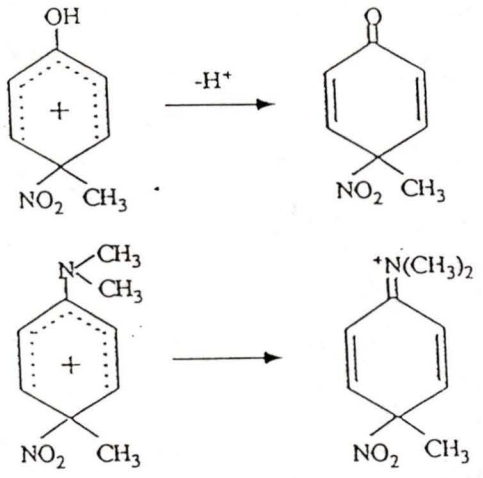


Table 1.2

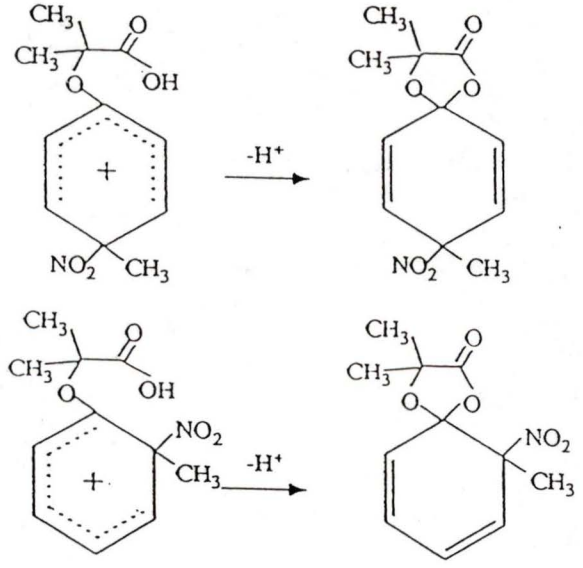
b. Internal Capture

Substituents bearing a lone-pair of electrons such as OH and $N(Me)_2$, present at the ortho or para position with respect to the ipso position, can lead to intramolecular capture of the ipso Wheland intermediate to give dienones[69] and iminium salts[70] respectively (scheme 1.9).



Schemel.9

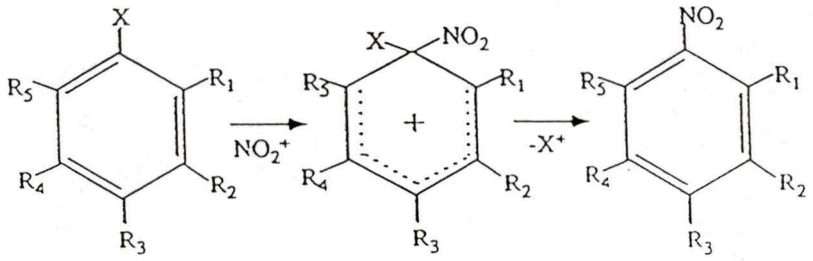
An ipso Wheland intermediate can also be captured by a lone pair on a side chain of a suitable length. This results in the formation of bicyclic spiro compounds[71] (scheme 1.10).



Scheme 1.10

1.5.2 Substitution

Ipso substitution is the longest-known consequence of ipso attack. This process occurs when the original substituent can form a more stable cation than nitronium ion. Substituents like acyl, alkyl, arylazo, aryloxy, carboxyl, halogen, methoxyl, phosphonyl, silyl and sulphonyl are usually lost during the course of nitration as a result of ipso attack[55] (scheme 1.11).

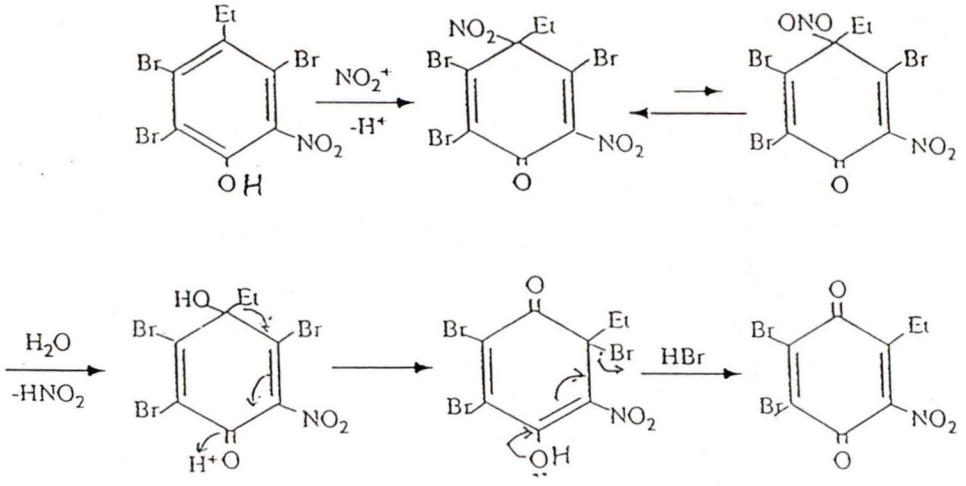


Scheme 1.11

Perrin[72] suggested the following sequence of leaving groups: NO_2 < i-Pr ~ SO_3 < tert-Bu ~ ArN_2 < ArCHOH < NO < CO_2 < $B(OH)_3$, for those that ionize in an S_{N1} process from the Wheland intermediates; The leaving ability of electrophiles by the S_{N2} process follows a different sequence: CH_3 < Cl < Br < D ~ RCO < H ~ I < Hg < Me_3Si. An absolute sequence for all electrophiles cann't be established because of the different nature of the two elimination processes.

1.5.3 Substituent Migration

It has been observed that the ipso attack of the nitronium ion can lead to the migration of the methyl group as in the nitration of polymethylbenzenes. For example, nitration of isodurene[73], dinitroprehnitene[74] and nitropentamethylbenzene[75] gives, in addition to the normal nitration products, a small amount of ketone; nitration of polysubstituted 4-alkylphenols[76] gives 1,4-benzoquinones as well as the normal nitration products. The isolation of the 4-nitrodienone, rearranged 4-nitritodienone and 4-hydroxydienone from the nitration of substituted 4-alkylphenols suggests the intermediacy of these compounds in the formation of 4-benzoquinones. Also, treatment of the 4-hydroxydienone with fuming nitric acid gives benzoquinone. The following mechanism was proposed for the migration of the ethyl group in the nitration of 2,3,5-tribromo-4-ethyl-6-nitrophenol (scheme 1.12).

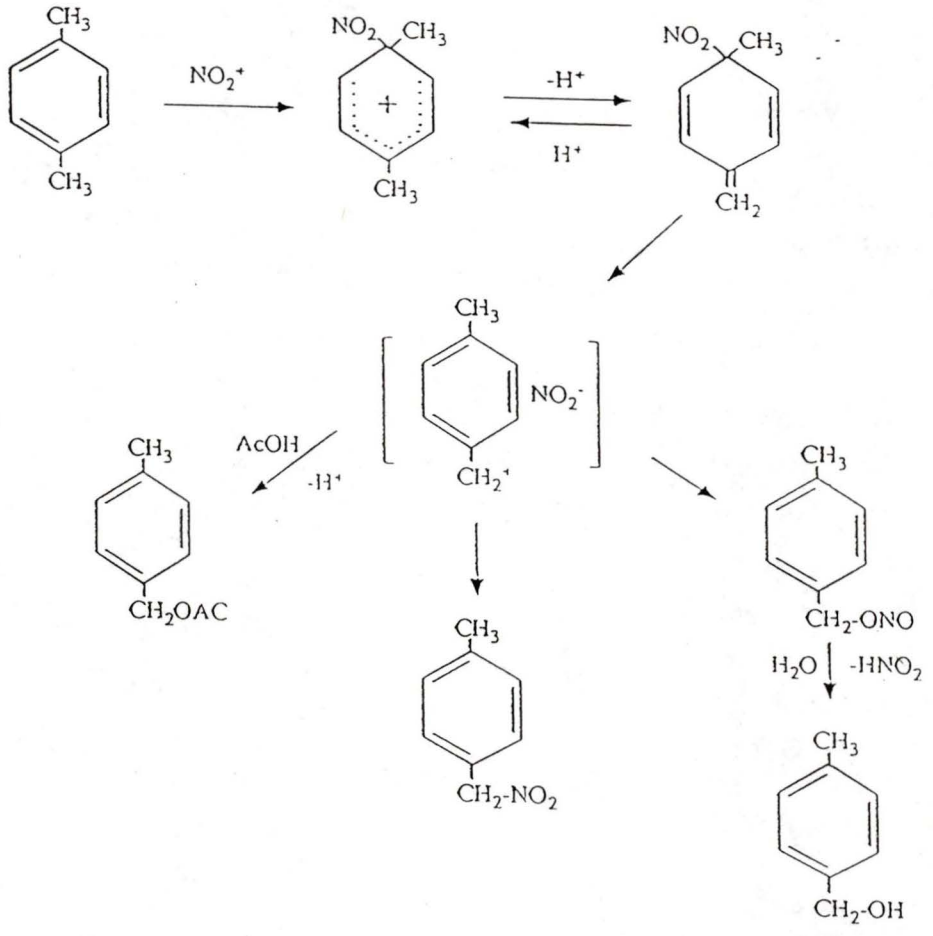


Scheme 1.12

1.5.4 Modification of Substituents

Substituent modification is commonly observed in the nitration of o- and p-substituted benzenes. Substituent groups like hydroxyl, acetoxyl and methoxyl groups at an o- or a p- position, with respect to the ipso position, can be converted to a carbonyl group. This is considered as internal nucleophilic capture and has been discussed in section 1.5.1 (b).

Alkyl groups with an α-hydrogen at an o- or p-position with respect to the ipso position, can be modified, resulting in the formation of side-chain substituted aromatics[77]. Formation of benzyl nitrites, benzyl nitrates and arylnitromethanes has been observed. Normally benzyl nitrates and benzyl nitrites hydrolyse to give benzyl alcohols, or oxidize to give aldehydes or ketones under nitration conditions. In nucleophilic solvents, the capture of the solvent molecule has also been observed. For example, in the nitration of alkylbenzenes in acetic anhydride benzyl acetate is the major product, among side-chain aromatics[78]. These phenomena were explained[76] by the following mechanism (scheme 1.13)

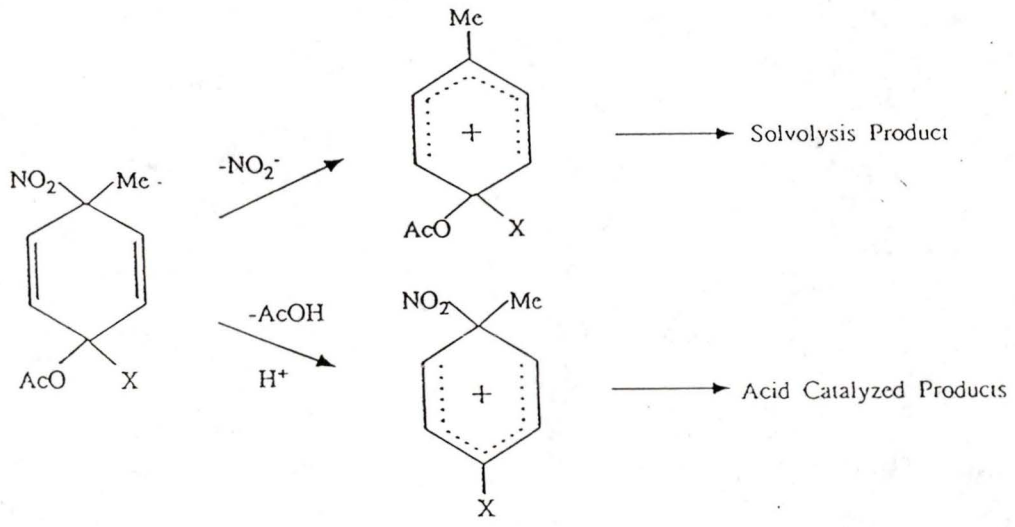


Scheme 1.13

The observation of methyenecyclohexadiene derivatives by Fischer and Goel[79] as an intermediate in the formation of side-chain products in the rearomatization reactions of 1,4-dimethyl-4-nitrocyclohexa-2,5-dienyl acetate and 4-methyl-4-nitro-1-trimethylsilylmethyl-cyclohexa-2,5-dienol provides direct evidence for the proposed mechanism in scheme 1.13.

1.6 Reactions of Ipso Adducts

The current research interest in aromatic nitration is partly due to the isolation and investigation of reactions of ipso adducts. The two major reactions of 1,4 nitronium acetate adducts are: (a) loss of the acetate group as acetic acid in acid media to regenerate the ipso nitro Wheland intermediate; (b) loss of the nitro group as nitrite to generate the ipso acetoxy Wheland intermediate (scheme 1.14).



Scheme 1.14

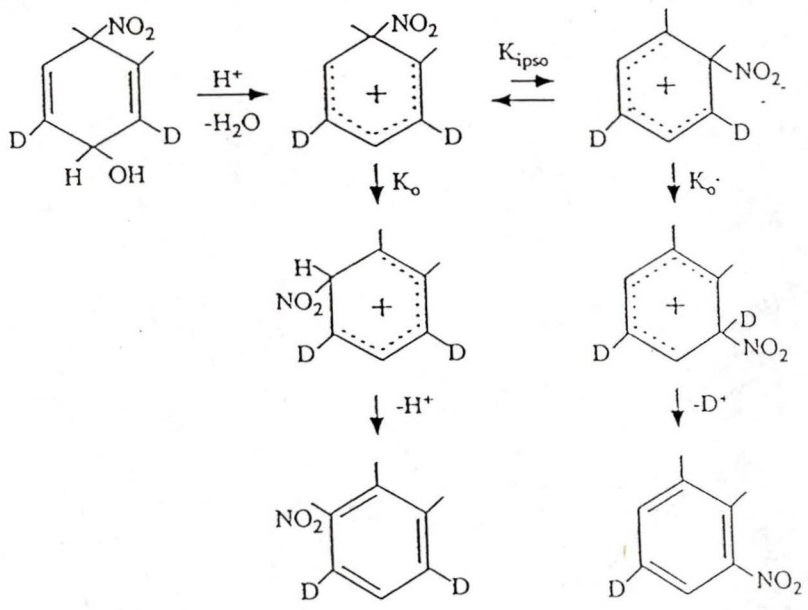
The competitive balance between these two pathways depends on the reaction conditions and the substituents present in the cyclohexadiene ring. Under appropriate conditions, individual Wheland intermediates can be generated or regenerated and their reactions can be studied without undue complications. From the synthetic point of view, these reactions are useful for the regiospecific introduction of functional groups[80].

1.6.1 Nitro Group Migration

The ipso nitro group on the Wheland intermediate is observed to have three modes of migration: intramolecular, extramolecular and intermolecular. In intramolecular migration the nitro group is not completely dissociated from the carbon structure. The 1,2- and 1,3-nitro group shifts provide examples of this type of reaction. In extramolecular migration the nitro group dissociates to form a solvated encounter pair so that the nitro group can either attack another activated position (the extramolecular migration) or can diffuse out of the solvated encounter pair. Intermolecular migration is the process in which the nitro group leaves the original aromatic molecule and diffuses into the solvent to react with another aromatic molecule.

a. Intramolecular Migration

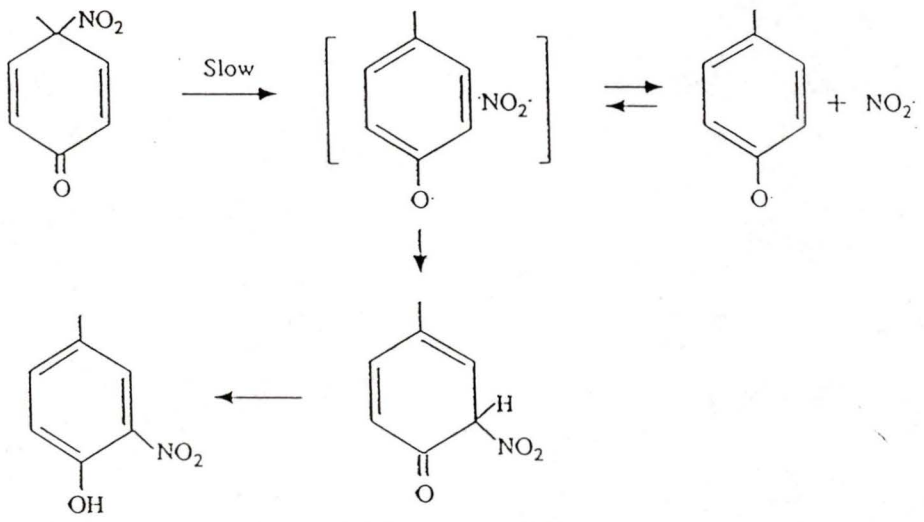
The occurence of intramolecular 1,2-nitro shifts were first observed by Myhre[81] in an investigation of the acidity dependence of the ratio of 3- to 4-nitro-o-xylene produced in the nitration of o-xylene in sulfuric acid[82]. By labelling experiments, Myhre was able to demonstrate that the 1,2-shift of the the nitro group to a substituted position (Scheme 1.15) is 50 times faster than to an unsubstituted position.



Scheme 1.15

Olah and his coworkers[83] observed from the NMR studies that the nitro group in nitrohexamethylbenzenium ion undergoes degenerate 1,2 shifts to all of the ring carbons. The 1,3-intramolecular migration of the nitro group was observed by Fischer and his coworkers[84] in the rearomatization reactions of the ipso adducts of 2,3- and 3,4-dimethylbenzonitriles and 1-chloro-2,3-dimethylbenzene. Due to the absence of 1,2-shift products, the 1,3-shift could not be explained on the basis of successive 1,2-shifts. In the decomposition reactions of 4-alkyl-4-nitrocyclohexa-dienones 1,3-nitro

shifts have also been observed under neutral and acidic conditions. For the uncatalyzed rearrangment of the dienone of p-cresol, Barnes and Myhre[85] proposed a homolytic dissociation to explain the results.(scheme 1.16).

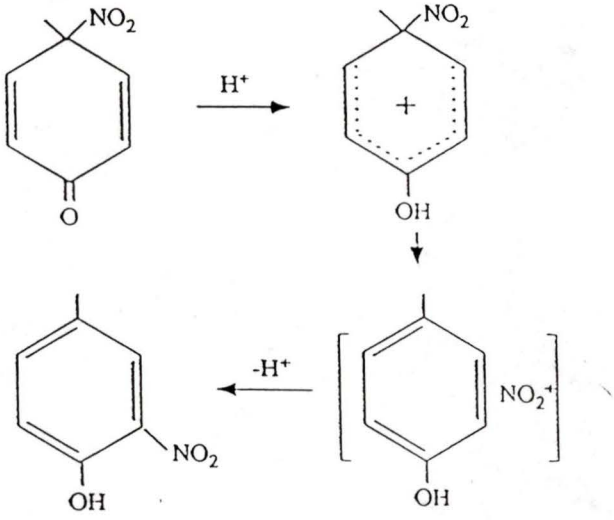


Scheme 1.16

Recent studies[86] by Ridd and his coworkers of the ^{15}N labelled dienones of o- and p-cresols with ^{15}N nuclear polarisation experiments supported such a proposed mechanism. Kaptein's rule[87] permits the information of the phase of nuclear polarisation to be used as a mechanistic study tool. It predicts that the essentially complete combination of the radicals formed could show enhanced absorption in the ^{15}N NMR spectrum of the compound formed and signal enhancement is observed in both the uncatalyzed and the catalyzed reactions of the

dienone of p-cresol indicating a radical intermediate in both cases.

The results of the acid catalyzed reaction of 4-methyl-4-nitro-2,5-cyclohexadienone had been explained on the basis of the formation of the nitronium ion by dissociation[88,89] (scheme 1.17).

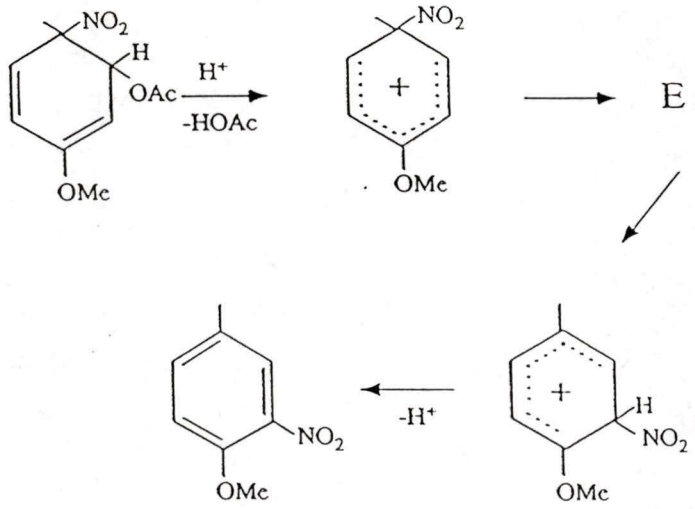


Scheme 1.17

b. Extramolecular Migration

Nitration of the original substrate at the encounter rate provides the setting for extramolecular rearrangement. In that situation the nitronium ion and substrate regenerated from the Wheland intermediate recombine before they have time to diffuse apart. The formation of 4-methyl-2-nitro-anisole in an acid medium from 2-methyl-2-nitro-5-methoxyl-cyclohexadienyl acetate

is thought to proceed through an encounter pair[90] process (scheme 1. 18).



Scheme 1.18

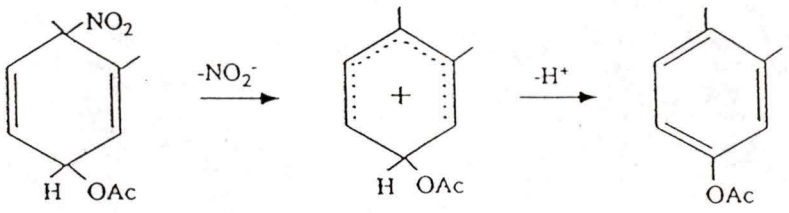
c. Intermolecular Migration

Intermolecular migration occurs when the encounter pair formed from the nitrocyclohexadienyl cation has the chance to diffuse apart, which depends on the reactivity of the substrate. In the case of a deactivated substrate like p-chloroanisole, the nitro group in the encouter pair diffuses into the solvent, and may then encounter a new aromatic molecule and react with it.

1.6.2 Reactions of Acetoxycyclohexadienyl Cation

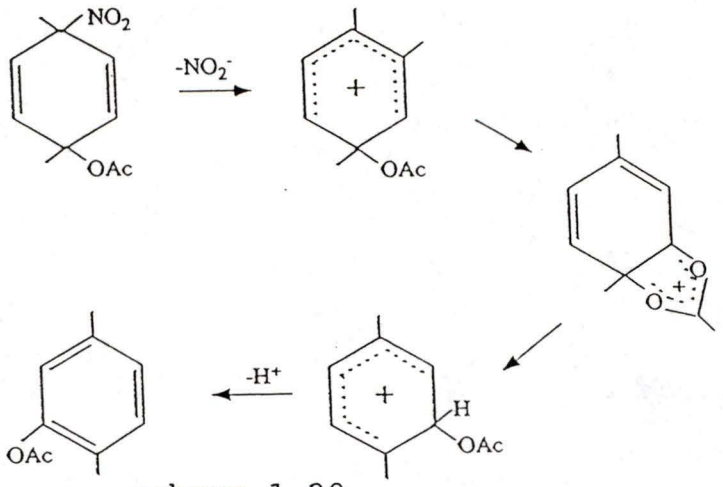
Solvolysis of the nitro group as nitrite from an ipso adduct yields the corresponding acetoxycyclohexadienyl cation. This process is favored in polar solvents

under weakly acidic or neutral conditions. In the case of secondary acetates, the acetoxycyclohexa-dienyl cation undergoes deprotonation to yield an aryl acetate (scheme 1.19).



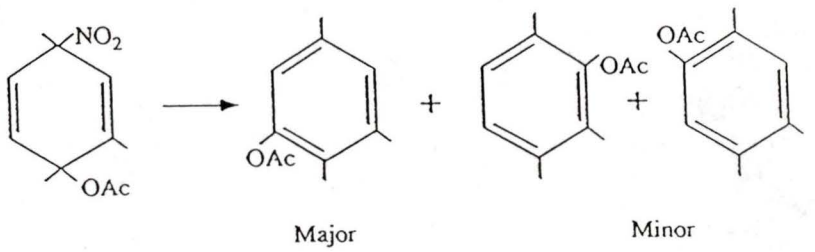
Scheme 1.19

In tertiary acetates, the acetate migrates to an adjacent position to give an isomeric acetoxycyclohexa-dienyl cation, which then loses a proton to yield an aryl acetate. It has been shown that the 1,2-acetate migration is intramolecular[91], presumably occuring via a cyclic transition state (scheme 1.20).



scheme 1.20

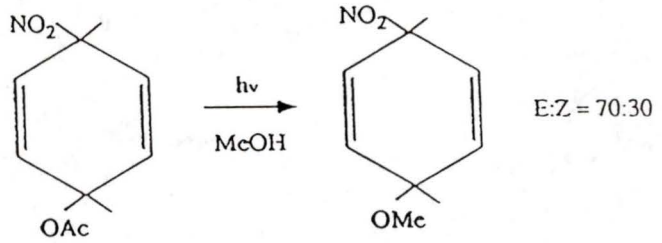
In a few cases 1,3-acetate shifts have been observed. Thus solvolysis of 1,2,4-trimethyl-4-nitro-cyclohexadienyl acetate gave 2,3,5-trimethylphenyl acetate as the major product with minor amounts of 2,3,6- and 2,4,5-trimethylphenyl acetate[92] (scheme 1.21). It is likely that such 1,3-acetate shifts involve the initial formation of the conjugated diene in which the acetate has migrated to its final position (via the ipso nitrocyclohexadienyl cation) and then the aryl acetate is formed by the loss of nitrous acid.



Scheme 1.21

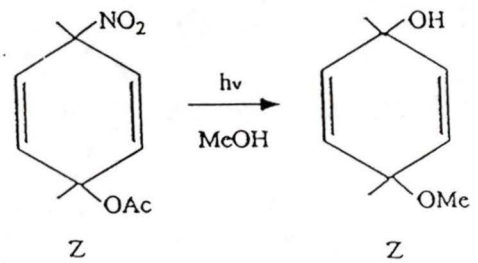
1.6.3 Photochemical Reactions

The photochemistry of the ipso adducts was first reported by Shosenji[93] and his coworkers. They reported that the ipso adducts of p-xylene undergo stereoselective photosolvolysis when photolysed in methanol. (scheme 1.22)



Scheme 1.22

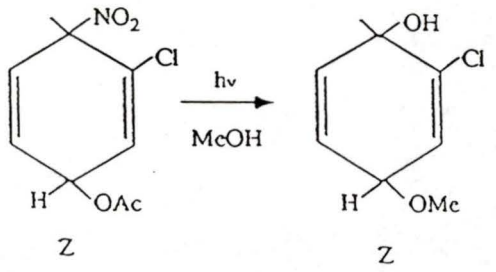
Fischer and his coworkers[94] have recently reinvestigated the same reaction and found different end products. (scheme 1.23)



Scheme 1.23

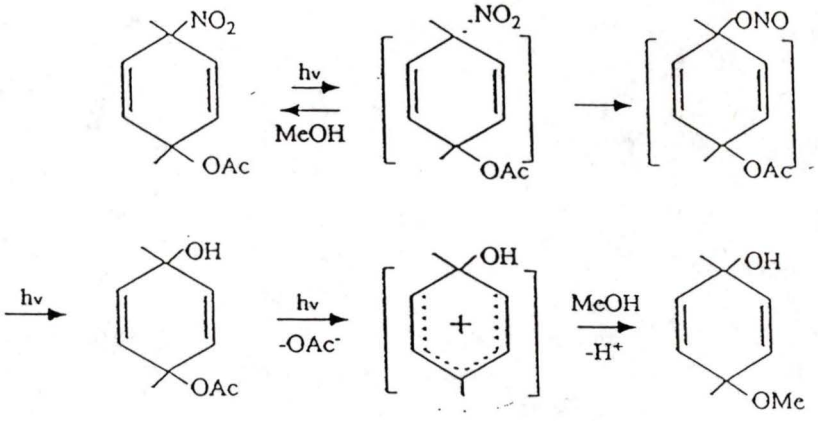
A similar reaction was studied[94], which gave

stereospecific products. (scheme 1.24)



Scheme 1.24

Based on these facts, a nitro-nitrite rearrangement step was thought to be critical for the above chemical transformation and the mechanism for the photochemical process of the adducts from p-xylene was proposed as following: (scheme 1.25)



Scheme 1.25

It is possible that Shosenji and his coworkers misidentified the products from the photolysis. It appears that the photochemistry of the ipso adducts is an interesting field to be explored.

1.7 Objective of the Present Work

Although a considerable amount of information about the ipso nitration of polysubstituted benzenes (both activated and deactivated) and the the reactions of their ipso adducts is available in the literature, there has not been any study on the ipso nitration of 2 substituted p-xylenes.

It has been observed in our laboratory that nitration of p-xylene gave only 1,4 adducts but not 1,2 adducts. In the case of 4-tert-butyltoluene, both 1,4 and 1,2 adducts were formed. The nitration of 4-chloro-, 4-bromo-, 4-methoxy-, and 4-acetomidotoluene gave only 1,2 adduct in each case while in the case of 4-fluorotoluene both 1,2 and 1,4 adducts were obtained. The factors that decide the formation of either 1,4 or 1,2-adducts are not yet clear.

The work described in this thesis involves an investigation of the nitration of a series of 2-X-p-

xylenes(X=Cl,Br are ortho,para directing, X=$COCH_3$,COC_6H_5 are meta directing). The objective was to isolate and characterize the ipso adducts and to investigate the reactions of these adducts in various media. It was hoped this work would yield information concerning the regioselectivity of the capture of the acetic acid.

Chapter 2. Experimental Procedoures

2.1 Instrumentation

Melting points are uncorrected and were determined on a Reichert 7905 melting point apparatus. Infrared spectra of solid samples were determined in potassium bromide discs or in a carbon tetrachloride solution in liquid cells. IR spectra of liquid samples were measured on thin films between sodium chloride plates. ^{1}H NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz) spectrometer or a Bruker WM 250 (250 MHz) spectrometer. Tetramethylsilane was used as the lock signal at 90 MHz, and the solvent deuterium signal was used as the lock signal at 250 MHz. ^{13}C NMR spectra were recorded on a Bruker WM 250 (62.9 MHz) spectrometer using solutions in chloroform-d with tetramethylsilane as the internal standard. In some cases the chloroform-d peak (δc, 77.00 ppm) was used for calibration. Mass spectra were recorded on a Perkin-Elmer-Hitachi RMU-7 spectrometer with 70 ev electron impact ionization, or on a Finnigan 3300 GC-MS 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 typical GC analysis involved injection of 1 ul of methylene chloride solution (1 mg of the sample in 1 cm^3 of the solvent) with the splitter open. The

temperature was held at 70°C for 3 min, then increased to 250°C over a period of 18 min, and held for 15 min. For high performance liquid chromatography a Walters Prep. LC system 500A was used. In a typical experiment a flow rate of 100 cm^3/min and a chart speed of 2 min/cm were used and the relative response (sensitivity) was varied depending on the sample amount. Both the silica column and the solvent reservoir were cooled by circulating ice water. Elemental analyses were performed by Canadian Microanalytical Service Ltd., Vancouver, British Columbia.

2.2 Reagents

The following chemicals were used without futher purification: 2-bromo-p-xylene **21**, 2-chloro-p-xylene **20**, 2,5-dimethylacetophenone **22**, 2,5-dimethylbenzophenone **23**.

Acetic anhydride was certified ACS from Fisher. Trifluoroacetic acid, trifluoroacetic anhydride, and trifluoromethanesulfonic acid were from Aldrich. Fuming nitric acid (Fisher, 600 cm^3) was purified by distilling from urea (20 g) and concentrated sulfuric acid (1000 cm^3) at 100 Pa and at 50°C and stored at -20°C.

The following solvents used for chromatography were distilled before use: petroleum ether (b.p. 30-60°C,

reagent grade, Fisher), Ether (BDH, dried over sodium), and dichloromethane (Van Walters and Rogers Ltd., dried over calcium hydride). Methanol (VWR) was used without purification. The solvent used for NMR was chloroform-d (Aldrich).

Silica gel (60-200 mesh, Davidson Commercial grade H) was used for chromatography. Anhydrous magnesium sulphate was used to dry solvents.

2.3 Nitration Reactions

Reaction conditions for nitration were optimized to yield maximum amounts of ipso-adducts. A series of small scale reactions (2.5 mmol) was carried out with various acid to substrate molar ratios. Typically, the nitrating mixture was added to a stirred solution of the substrate at -78^{o}C, the reaction mixture was transferred into a cooled NMR tube, and the disappearance of the substrate was followed by variable temperature (V.T.) ^{1}H NMR.

2.3.1 Nitration of 2-Bromo-p-xylene 21

Nitric acid (25.2 g, 0.4 mol) was slowly added to acetic anhydride (51 g, 0.5 mol) at -20^{o}C and the solution was cooled to -35^{o}C. This solution was then slowly added to the mixture of the substrate (18.5g, o.1

mol) and acetic anhydride (51g, 0.5mol) which was already cooled to -35^{o}C over a period of 30 min. The reaction mixture was then stirred between -35^{o}C to -30^{o}C for 40 min and cold ether (500 cm^{3}, -60^{o}C) was then added. The excess acid was neutralized by slow addition of aqueous ammonium hydroxide (900 cm^{3}, -20^{o}C) to the reaction mixture at below -40^{o}C. The ether layer was separated , washed with cold brine (50cm^{3}, 0^{o}C), dried over anhydrous magnesium sulphate, and evaporated at 14^{o}C to yield a yellow oil (24.7 g). Separation of this product mixture was carried out by HPLC using ether-petroleum ether (12:88) as eluent. 5-nitro-2-bromo-1,4-dimethylbenzene **31** (59% of the product mixture by NMR) was obtained as yellow needles, mp: 69^{o}C; ^{1}H NMR ($CDCl_3$, 90 MHZ) δ: 2.41 (s, 3H, 1-CH_3), 2.52 (s, 3H, 4-CH_3), 7.54 (s, 1H, 3-H), 7.73 (s, 1H, 6-H) cis-3-bromo-1,4-dimethyl-4-nitro-2,5-cyclohexadienyl acetate **24**(37% of the product mixture by NMR) was obtained as colorless crystals from ether-petroleum ether, mp: 59^{o}C; IR (CCl_4): 1740 (C=O), 1550 and 1360 cm^{-1}(NO_2); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.54 (s, 3H, 1-CH_3), 1.90 (s, 3H, 4-CH_3), 1.98 (s, 3H, $OCOCH_3$), 5.89 (d, 1H, 5-H, J= 9.8 Hz), 6.06 (dd, 1H, 6-H, J = 1.9 Hz and 9.8 Hz), 6.57 (d, 1H, 2-H, J = 1.9 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ_C: 21.6(1-CH_3), 23.5 (4-CH_3), 26.7 ($OCO\underline{C}H_3$), 76.5(1-C), 89.4(4-C), 121.0(3-C), 126.3(2-C), 133.1(6-C), 137.1(5-C), 169.5 (C=O); Trans-3-bromo-

1,4-dimethyl-4-nitro-2,5-cyclohexadienyl acetate **25**(4% of the product mixture by NMR) was obtained as colorless crystals from ether-petroleum ether, mp: 75°C; IR (CCl_4): 1750 (C=O) 1550 and 1350 cm^{-1}(NO2); ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.49 (s, 3H, 1-CH_3), 1.56 (s, 3H, 4-CH_3), 2.03 (s, 3H, $OCOCH_3$), 6.03 (d, 2H, 5-H and 6-H, J = 0.8 Hz), 6.41 (d, 1H, 2-H, J = 0.8 Hz); ^{13}C NMR($CDCl_3$, 62.9 MHz) δ_C: 21.3(1-CH_3), 25.0(4-CH_3), 26.9($OCO\underline{C}H_3$), 76.0(1-C), 87.5 (4-C), 125.2 (3-C), 128.5 (2-C), 131.1 (6-C), 133.2 (5-C), 169.1 (C=O). Anal Calc. for $C_{12}H_{12}NO_4Br$: C 41.67%, H 4.17%, N 4.85%; found for mixture of diastereomers : C 41.68%, H 4.19 %, N 4.87%.

2.3.2 Nitration of 2-Chloro-p-xylene 20

The acetyl nitrate solution prepared from nitric acid (40 g, 0.625 mol) and acetic anhydride (64 g, 0.625 mol) was added dropwise to a stirred solution of 2-chloro-p-xylene (35 g, 0.25 mol) in acetic anhydride (64 g, 0.625 mol) at -25°C over a period of 20 min. The reaction was held for another 40 min at -30°C. Cold ether (300 cm^3, -60°C) was then added to the reaction mixture , followed by the slow addition of cold aqueous ammonium hydroxide (600 cm^3, -60°C) to neutralize the excess acid. The ether layer was separated, washed with brine (50 cm^3) and sodium carbonate solution (50 cm^3), dried over anhydrous magnesium sulfate, and evaporated at 14°C to

yield a yellow oil (43 g). This mixture was separated by preparative HPLC using a mixture of 10% ether and 90% petroleum ether as eluent. 5-Nitro-2-chloro-1,4-dimethyl benzene (66% of the product mixture by NMR) was obtained as pale yellow needles from the first fraction, mp: 80°C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 2.38 (s, 3H, 1-CH_3), 2.53 (s, 3H, 4-CH_3), 7.32 (s, 1H, 3-H), 7.90 (s, 1H, 6-H), cis-3-chloro-1,4-dimethyl-4-nitro-2,5-cyclohexadienyl acetate **26**(34% by NMR) was obtained as colorless crystals from the following fraction, mp: 65°C; IR (CCl_4): 1740 (C=O), 1540 and 1360 cm^{-1}(NO_2); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.53 (s, 3H, 1-CH_3), 1.88 (s, 3H, 4-CH_3), 1.96 (s, 3H, $COCH_3$), 5.85 (d, 1H, 5-H, J = 9.9 Hz), 6.03 (dd, 1H, 6-H, J = 1.9 Hz and 9.9 Hz), 6.26 (d, 1H, 2-H, J = 1.9 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ_C: 21.5 (1-CH_3), 22.1 (4-CH_3), 26.8 (OCO$\underline{C}H_3$), 76.5 (1-C), 88.8 (4-C), 126.4 (3-C), 130.3 (2-C), 132.9 (6-C), 133.2 (5-C), 169.4 (C=O). Anal Calc. for $C_{12}H_{12}NO_4Cl$: C 49.28%, H 4.93%, N 5.75%; found: C 49.02%, H 4.55%, N 5.75% .

2.3.3 Nitration of 2,5-Dimethylacetophenone 22

Nitric acid (9.6g, 0.15 mol) was mixed with acetic anhydride (15.3g, 0.15mol) at -45°C. This acetyl nitrate solution was added dropwise to a stirred solution of 2,5-dimethyl-acetophenone (9g, 0.06 mol) in acetic anhydride

(15.3g, 0.15 mol) over a period of 15 min. The reaction was held between -35°C to -40°C for 45 min, cold ether (200 cm^3, -60°C) was added, followed by the slow addition of cold aqueous ammonium hydroxide (200 cm^3, -60°C) to neutralize the excess acid. More ether (100 cm^3) and 75 cm^3 dichlorometheylene was added to the mixture to enhance the separation. Then the separated organic layer was dried over anhydrous magnesium sulfate, and the organic solvents were evaporated at 14°C to yield a red-brown oil (11.5g). One isomer of trans-2-acetyl-1,4-dimethyl-4-nitro-2,5-cyclohexadienyl acetate **28**(42% by NMR) could be crystallized out from the ether solution of the product mixture at -20°C and had mp 114°C-115°C; IR (CCl_4): 1730 (C=O), 1540 and 1360 cm^{-1}(NO_2); ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.52 (s, 3H, 1-CH_3), 1.81 (s, 3H, 4-CH_3), 1.91 (s, 3H, $OCOCH_3$), 2.34 (s, 3H, $COCH_3$), 5.87 (d, 1H, 6-H, J=10.0 Hz), 5.96 (dd, 1H, 5-H, J = 2.0 Hz and 10.0 Hz), 6.79 (d, 1H, 3-H, J=2.0 Hz); ^{13}C NMR δ_C: 21.3 (1-CH_3), 25.5 (4-CH_3), 26.8 ($OCO\underline{C}H_3$), 27.3 ($CO\underline{C}H_3$), 76.0 (1-C), 85.9 (4-C), 123.7 (6-C), 134.1 (5-C), 135.9 (2-C), 142.5 (3-C), 170.1 ($O\underline{C}OCH_3$), 196.6 ($\underline{C}OCH_3$). The mother liquor was separated on HPLC using 40% petroleum ether and 60% ether as eluent and gave 3-nitro-2,5-dimethyl-acetophenone **39**(14% by NMR) as yellow crystals, mp: 82°C; ^1H NMR ($CDCl_3$, 250 MHz) δ: 2.40 (s, 3H, 5-CH_3), 2.42 (s, 3H, 2-CH_3), 2.55 (s, 3H, $COCH_3$), 7.48 (s, 1H, 6-H), 7.60 (s, 1H, 4-H), and a second

isomer (44% by NMR) of cis-2-acetyl-1,4-dimethyl-4-nitro-2,5-cyclohexadienyl acetate **27** as colorless crystals which had mp: 99-100°C; IR (CCl_4): 1730 (C=O), 1530 and 1370 cm^{-1}(NO_2); ^1H NMR ($CDCl_3$, 90 Mhz) δ: 1.54 (s, 3H, 1-CH_3), 1.83 (s, 3H, 4-CH_3), 2.03 (s, 3H, $OCOCH_3$), 2.38 (s, 3H, $COCH_3$), 5.89 (d, 1H, 6-H, J=9.0Hz), 6.22 (dd, 1H, 5-H, J=2.0 Hz and 9.0 Hz), 7.21 (d, 1H, 3-H, J=2.0 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ_C: 22.8 (1-CH_3), 24.6 (4-CH_3), 26.3 ($OCO\underline{C}H_3$), 29.0 ($CO\underline{C}H_3$), 74.2 (1-C), 83.5 (4-C), 127.5 (6-C), 135.4 (5-C), 138.5 (2-C), 146.7 (3-C), 169.7 ($O\underline{C}OCH_3$), 196.2 ($\underline{C}OCH_3$), Anal. Calc. for $C_{12}H_5NO_5$: C 56.92, H 5.93, N 5.54; found: C 57.10, H 6.03, N 5.57.

2.3.4 Nitration of 2,5-Dimethylbenzophenone 23

The solid substrate (16g, 0.08 cm^3) was dissolved in acetic anhydride (40g, 0.4 mol) and cooled to -5°C. The acetyl nitrate solution, prepared from acetic anhydride (40g, 0.4 mol) and nitric acid (12.6g, 0.2 mol) at -20°C, was added dropwise to the stirred substrate solution. The mixture was held at -5°C for 20 min. Ether (300 cm^3, -15°C) was added to the reaction mixture, followed by aqueous ammonium hydroxide (450 cm^3, -15°C). The ether layer was separated and dried by anhydrous magnesium sulphate and the ether evaporated at 14°C to yield a light brown oil (14g). The dienes could be crystallized

out from ether solution at -20°C. Separation of the two diastereomers by HPLC with ether and petroleum ether and by recrystallization was attempted without success. A 360 MHz ^{1}H NMR spectrum of the diene crystal showed that the methyl peaks of the two dienes were of equal height. In a decoupling experiment the presence of a allylic and two vinylic protons for each diene was evident and a further computer simulation using experimental data confirmed the above conclusion so that the dienes were assigned as 1,2-adduct. Anal. calc. for $C_{17}H_{17}NO_5$: C 64.76, H 5.40, N 4.44; found: C 64.62, H 5.44, N 4.53.

2.4 Shift Reagent Studies

The stereochemical assignments of E and Z to the configurations of the diene adducts were made on the basis of shift reagent studies performed with $Eu(fod)_3$ [tris(1,1,1,2,2,3,3,-heptafluoro-7,7-[$^{2}H6$]-dimethyl-4,6-[$^{2}H3$]-octanedioneto) europium(+3)]. In a typical experiment, to a solution of the diene (20-30mg) in $CDCl_3$ (0.3 cm^3) the shift reagent in $CDCl_3$ (0.045g in 1 cm^3) was added in 0.01 cm^3 increments from a syringe. After each addition the solution was maitained at 0°C for 5 min before the NMR spectrum was taken. The chemical shifts of the hydrogen atoms at C-4 position were plotted against the shift of the acetate methyl or the methoxy group. The results are tabulated in Table 2.1. For each diene

diastereomer with greater relative gradient of the proton shift of the C-4 methyl group was assigned as E and the the other diastereomer was assigned Z.

Table 2.1

Relative gradient of ^1H shifts upon addition of $Eu(fod)_3$) and shift ratios

diene	4-CH_3	1-$OCOCH_3$	shift ratio
25(E)	0.55	1.00	1.3
24(Z)	0.41	1.00	
28(E)	0.17	1.00	2.0
27(Z)	0.083	1.00	
diene	4-CH_3	1-OCH_3	
47(E)	0.33	1.00	1.7
46(Z)	0.19	1.00	
50(E)	0.35	1.00	2.5
49(Z)	0.14	1.00	
51(E)	0.15	1.00	1.4
48(Z)	0.11	1.00	

2.5 Reactions of Ipso Adducts

2.5.1 Reactions of 3-Bromo-1,4-dimethyl-4-nitro-2,5-cyclohexadienyl Acetate 24

a. Reaction with H_2SO_4 in Methanol

The diene (37 mg, 0.13 mmol) was dissolved in a solution (500 ul) of 1% (v/v) H_2SO_4 in CH_3OH solution at ambient temperature. Examination by NMR showed that the

diene reacted completely in 40 min. The acid in the mixture was neutralized by adding 5 cm^3 aqueous ammonium hydroxide, and ether (20 cm^3) was added. The organic layer was washed with brine, separated, and dried over anhydrous magnesium sulfate. The solvents were evaporated to yield a light yellow oil (18 mg). NMR analysis of this mixture indicated that cis-2-bromo-1,4-dimethyl-1-nitro-4-methoxy-2,5-cyclohexadiene **49**(57.5%) ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.30 (s, 3H, 4-CH_3), 1.82 (s, 3H, 1-CH_3), 3.22 (s, 3H, OCH_3), 5.92 (dd, 1H, 5-H, J = 1.9Hz and 9.9Hz), 6.01 (d, 1H, 6-H, J= 9.9Hz), 6.33 (d, 1H, 3-H, J=1.9Hz), and trans-2-bromo-1,4-dimethyl-1-nitro-4-methoxy-2,5-cyclohexadiene **50**(42.5%) ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.41 (s, 3H, 4-CH_3), 1.89 (s, 3H, 1-CH_3), 3.07 (s, 3H, OCH_3), 5.93 (dd, 1H, 5-H, J = 1.9 and 9.9Hz), 6.02 (d, 1H, 6-H, J = 9.9Hz), 6.38 (d, 1H, 3-H, J=1.9Hz), were the only products formed.

b. Reaction with Trifluroacetic acid in Acetic Anhydride

The diene (35 mg, 0.12 mmol) was dissolved in 250 ul of acetic anhydride at ambient temperature and cooled to -75°C, Trifluoroacetic acid (50 ul) was added, and the reaction was examined by V.T. NMR. The diene began to disappear at 5°C and was completely reacted at 15°C. Complete reaction also ensued when the reaction mixture was left at 0°C for 60 min. The acid in the mixture was

neutralized by adding aqueous ammonium hydroxide (30 cm^3) and then ether (30 cm^3). The organic layer was separated and dried over anhydrous magnesium sulphate. After evaporation of the solvent, the product (23 mg) was examined by ^1H NMR, TLC separation and GC-MS which indicated that it contained three side chain products. They are 2-bromo-1-methyl-4-nitromethylbenzene **40**(7%), ^1H NMR ($CDCl_3$, 250 MHz) δ: 2.40 (s, 3H, 1-CH_3), 5.35 (s, 2H, 4-CH_2), 7.28 (s, 2H, 5-H and 6-H), 7.61 (s, 1H, 3-H) and 2-bromo-1-methyl-4-acetoxymethylbenzene **42**(62%), ^1H NMR (CDCl3, 250 MHz) δ: 2.05 (s, 3H, $OCOCH_3$), 2.36 (s, 3H, 1-CH_3), 5.00 (s, 2H, 4-CH_2), 7.18 (s, 2H, 5-H and 6-H), 7.51 (s, 1H, 3-H) and 2-bromo-1-methyl-4-hydroxylmethylbenzene **41**(31%) ^1H NMR ($CDCl_3$, 250 MHz) 2.37 (s, 3H, 1-CH_3), 4.62 (s, 2H, 4-CH_2), 7.18 (s, 2H, 5-H and 6-H), 7.53 (s, 1H, 3-H). In the GC-MS the major mass peak in the mass spectrum was in each case the 186 peak. This corresponds to the benzylic peak formed by cleavage of the side chain substituents.

c. Reaction with Neat Trifluroacetic Acid

The diene (45 mg, 0.16 mmol) was dissolved into 400 ul TFA at -30°C. The colour change in the reaction mixture indicated the reaction occured on mixing. By the time the temperature was raised to 0°C, all of the diene had reacted. The mixture was worked up with 40 cm^3

aqueous ammonium hydroxide and 35 cm^3 ether (see section 2.5.1 b) to yield 30 mg of brown oil. NMR, GC-MS and TLC analysis indicated the presence of 2-bromo-1-methyl-4-nitromethylbenzene **40**(12.5%), 2-bromo-1-methyl-4-acetoxymethylbenzene **42**(6%), 2-bromo-1-methyl-4-hydroxymethylbenzene **41**(18%), 5-nitro-2-bromo-1,4-dimethylbenzene **31**(14.5%), 6-nitro-2-bromo-1,4-dimethylbenzene **32**(49%), ^1H NMR ($CDCl_3$, 90 MHz) δ: 2.35 (s, 3H, 4-CH_3), 2.48 (s, 3H, 1-CH_3), 7.51 (s, 1H, 3-H), 7.59 (s, 1H, 5-H).

d. Reaction with Trifluoroacetic Acid in Chloroform

The diene (60 mg, 0.21 mmol) was dissolved into 250 ul $CDCl_3$ and cooled to 0°C, and 250 ul TFA was then added . The reaction was held at this temperature for 30 min. The TFA and $CDCl_3$ was then pumped off on a rotary evaporator. Analysis of the product mixture (50 mg) by NMR and GC-MS showed the presence of 6-nitro-2-bromo-1,4-dimethyl-benzene **32**(48%), 2-bromo-1-methyl-4-nitromethylbenzene **40**(43%), 2-bromo-1-methyl-4-hydroxylmethylbenzene **41**(9%). Each of these compouds has a major MS peak at 232.

e. Reaction with Trifluoromethanesulfonic Acid in chloroform

The diene (62 mg, 0.21 mmol) was dissolved into 400 ul $CDCl_3$. This solution was cooled to -30°C, and triflic acid (40 ul)was then added. The temperature of this solution was held for 10 min and later raised to 0°C. 40 cm^3 aqueous ammonium hydroxide and 40 cm^3 ether were used for work-up. NMR and GC-MS analysis of the product mixture (20 mg) revealed that three compounds were formed. They are 6-nitro-2-bromo-1,4-dimethylbenzene **32**(67%), 5-nitro-2-bromo-1,4-dimethylbenzene **31**(22%) and 2-bromo-1-methyl-4-nitromethylbenzene **40**(11%).

f. Reaction in Methanol with Tris(hydroxymethyl)-aminomethane

The diene (70 mg, 0.24 mmol) was dissolved in 3 cm^3 of methanol, and 200 mg tris(hydroxymethyl-aminomethane was added. This mixture was mechanically stirred for 48 hrs at ambient temperature before work-up. After evaporation of methanol, ether (50 cm^3) was used to extract products. Tris(hydroxymethyl)-aminomethane in the ether mixture was filtered before the evaporation of ether. The product mixture obtained (53 mg) was applied to a silica TLC plate. Ether and petroleum ether mixture in the ratio of 3:7 was used as eluent. Two bands were observed on the plate. The first one was the starting diene. The second band was 3-bromo-1,4-dimethyl-4-nitro-2,5-cyclohexadienol **52** by ^1H NMR δ:1.46 (s, 3H, 1-CH3),

1.89 (s, 3H, 4-CH3), 5.85 (d, 1H, 5-H, J=9.8 Hz), 6.11 (dd, 1H, 6-H, J= 1.8 Hz and 9.8 Hz), 6.56 (d, 1H, 2-H, J = 1.8Hz).

g. Thermolysis in Chloroform

The diene (67 mg, 0.23 mmol) was dissolved in 300 ul chloroform at ambient temperature, and this mixture was contained in a NMR tube. The NMR tube was then immersed in a water bath, the temperature of which was maintained at 80 ^{0}C. After 10 h, the NMR tube was taken out and the chloroform evaporated. From the analysis of NMR spectra, only one product was formed which was 2-bromo-1-methyl-4-nitromethylbenzene **40**.

2.5.2 Reactions of 3-Chloro-1,4-dimethyl-4-nitro-2,5-cyclohexadienyl Acetate 26

a. Reaction with H_2SO_4 in Methanol

The diene (37 mg, 0.15 mmol) was dissolved in 300 ul 1% (v/v) sulfuric acid in methanol solution at ambient temperature. The reaction was followed by ^{1}H NMR. The diene was completely converted into the methyl ether in 20 min. The acid in the mixture was neutralized by adding 5 cm^3 aqueous ammonium hydroxide, ether (20 cm^3) was added and the organic layer was washed with brine and

separated. After drying over anhydrous magnesium sulphate, the solvent was evaporated to yield a light yellow oil (15 mg). NMR analysis indicated that cis-2-chloro-1,4-dimethyl-1-nitro-4-methoxy-2,5-cyclohexadiene **46**(62%) ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.31 (s, 3H, 4-CH_3), 1.83 (s, 3H, 1-CH_3), 3.20 (s, 3H, OCH_3), 5.89 (dd, 1H, 5-H, J = 1.7Hz and 9.9 Hz), 5.98 (d, 1H, 6-H, J= 9.9 Hz), 6.09 (d, 1H, 3-H, J=1.7 Hz), and trans-2-chloro-1,4-dimethyl-1-nitro-4-methoxy-2,5-cyclohexadiene **47**(38%) ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.42 (s, 3H, 4-CH_3), 1.90 (s, 3H, 1-CH_3), 3.06 (s, 3H, OCH_3), 5.90 (dd, 1H, 5-H, J = 1.5Hz and 9.9Hz), 5.99 (d, 1H, 6-H, J = 9.9Hz), 6.14 (d, 1H, 3-H, J=1.5 Hz), were formed.

b. Reaction with Trifluoroacetic Acid in Ac_2O

The diene (200 mg, 0.82 mmol) was dissolved into acetic anhydride (500 ul) and was cooled to 0^{o}C and TFA (1 cm^3) was added. The mixture was held at 0^{o}C for 30 min. Aqueous ammonium hydroxide (50 cm^3) was added. The product was extracted with ether (50 cm^3) dried over anhydrous magnesium sulphate and the ether evaporated to give a yellow oil (111 mg). The mixture was separated on TLC using a mixture of 25% ether and 75% petroleum ether as eluent. The first band gave 2-chloro-1-methyl-4-acetoxymethylbenzene **45**(75%) ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 2.05 (s, 3H, $OCOCH_3$), 2.33 (s, 3H, 1-CH_3), 5.02 (s,

2H, 4-CH_2-), 7.18 (s, 2H, 5-H and 6-H), 7.35 (s, 1H, 3-H). The second band gave 2-chloro-1-methyl-4-nitromethylbenzene **43**(15%) ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 2.35 (s, 3H, 1-CH_3), 5.30 (s, 2H, 4-CH_2), 7.22 (s, 2H, 5-H and 6-H), 7.40 (s, 1H, 3-H). The third band gave 2-chloro-1-methyl-4-hydroxymethylbenzene **44**(10%). ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 2.33 (s, 3H, 1-CH_3), 4.62 (s, 2H, 4-CH_2-), 7.18 (s, 2H, 5-H and 6-H), 7.35 (s, 1H, 3-H).

c. Reaction with Neat Trifluoroacetic Acid

The diene (48 mg, 0.20 mmol) was dissolved in 400 ul TFA at -30^{o}C. There was a color change in the mixture immediately after the addition of TFA, indicating that reaction occurred. The temperature was gradually raised to 0^{o}C over a period of 20 min. NMR revealed that the diene was completely reacted at 0^{o}C. Ether (35 cm^3) and aqueous ammonium hydroxide (40 cm^3) were added and the product worked up. The brown product weighed 37 mg and NMR, GC-MS and TLC analysis indicated the presence of five compounds. They are 2-chloro-1-methyl-4-nitromethylbenzene **43**(9%), 2-chloro-1-methyl-4-acetoxymethylbenzene **45**(7.5%), 2-chloro-1-methyl-4-hydroxylmethylbenzene **44**(23%), 5-nitro-2-chloro-1,4-dimethylbenzene **34**(17%) and 6-nitro-2-chloro-1,4-dimethylbenzene **36**(43.5%), ^{1}H NMR ($CDCl_3$, 90 MHz) 2.35

(s, 3H, 4-CH_3), 2.46 (s, 3H, 1-CH_3), 7.40 (s, 1H, 3-H), 7.49 (s, 1H, 5-H).

d. Reaction with Trifluoroacetic Acid in Chloroform

The diene (75 mg, 0.31 mmol) was dissolved in 250 ul $CDCl_3$, cooled to 0°C, and 250 ul TFA were then added. The reaction was held at this temperature for 30 min. The TFA and $CDCl_3$ were pumped off on a rotary evaporator to give a brown oil(57 mg). Analysis of the worked-up mixture by NMR and GC-MS revealed three compounds. They are 6-nitro-2-chloro-1,4-dimethylbenzene **36**(33%), 2-Chloro-1,4-dimethyl-4-nitromethylbenzene **43**(46%) and 2-chloro-1-methyl-4-hydroxymethylbenzene **44**(21%).

e. Reaction with Trifluoromethanesulfonic Acid in Chloroform

The diene (71 mg, 0.30 mmol) was dissolved in 400 ul $CDCl_3$, and then cooled to -30°C, followed by addition of 40 ul triflic acid. The mixture was held at -30°C for 10 min. Ether (40 cm^3) and aqueous ammonium hydroxide (40 cm^3) were added and the product worked up (see section 2.5.1 b). The dark brown products weighed 20 mg. NMR and GC-MS analysis of the product (20 mg) indicated the presence of 6-nitro-2-chloro-1,4-dimethylbenzene **36**(72%),

5-nitro-2-chloro-1,4-dimethylbenzene **34**(17%) and 2-chloro-1-methyl-4-nitromethylbenzene **43**(11%).

f. Reaction in Methanol with Tris(hydroxymethyl)-aminomethane

The diene (85 mg, 0.35 mmol) was dissolved in 3 cm^3 of methanol, and 200 mg Tris(hydroxymethyl)-aminomethane was added. This mixture was mechanically stirred for 48 hrs at ambient temperature before work-up. After evaporation of methanol, ether (50 cm^3) was used to extract products. Tris(hydroxymethyl)-aminomethane in the ether mixture was filtered before the evaporation of ether. The product mixture obtained (62 mg) was applied on a silica TLC plate. Ether and petroleum ether mixture at the ratio of 3:7 was used as eluent. Two bands were observed on the plate. The first one was the starting diene. The second band was 3-chloro-1,4-dimethyl-4-nitro-2,5-cyclohexadienol **53** by ^1H NMR δ:1.47 (s, 3H, 1-CH3), 1.88 (s, 3H, 4-CH3), 5.81 (d, 1H, 5-H, J=9.8Hz), 6.09 (dd, 1H, 6-H, J=1.9Hz and 9.8Hz), 6.31 (d, 1H, 2-H, J=1.9Hz).

g. Thermolysis in Chloroform

The diene (75 mg, 0.31 mmol) was dissolved in 300 ul $CDCl_3$ at ambient temperature, and this mixture was

contained in a NMR tube. The NMR tube was then immersed in a water bath, the temperature of which was maintained at 80^{0}C. After 10 h, the NMR tube was taken out and the mixture was evaporated. From the analysis of NMR spectra, only one product was formed which was 2-chloro-1-methyl-4-nitromethylbenzene **43**.

2.5.3 Reactions of 2-Acetyl-1,4-dimethyl-4-nitro-2,5-cyclohexadienyl Acetate 27

a. Reaction with Trifluoroacetic Acid in Chloroform

The diene (53 mg, 0.21 mmol) was mixed with $CDCl_3$ (100 ul) and this mixture was cooled to -30^{o}C followed by the addition of 200 ul of TFA. The temperature was gradually brought up to 0^{o}C and was held there for 1 h. Then the acid was pumped off on the rotary evaporator. The final brown product weighed 50 mg and was analyzed on GC to show the presence of two compounds. Separation by TLC on silica using 20:80 ether and petroleum ether mixture was performed to give 4-nitro-2,5-dimethyl-acetophenone **37**(50%) MS (70ev) M/Z (relative intensity): 193 (100); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 2.43 (s, 3H, 2-CH_3), 2.49 (s, 3H, 5-CH_3), 2.57 (s, 3H, $COCH_3$), 7.53 (s, 1H, 6-H), 7.79 (s, 1H, 3-H), and 6-nitro-2,5-dimethyl-acetophenone **38**(50%), MS (70ev) M/Z (relative intensity): 193 (100); ^{1}H NMR ($CDCl_3$, 250

MHz) δ: 2.29 (s, 3H, 2-CH_3), 2.50 (s, 3H, 5-CH_3), 2.58 (s, 3H, $COCH_3$), 7.21 (d, 1H, H-4, J=8Hz), 7.28 (d, 1H, H-3, J=8Hz).

b. Reaction with Trifluoromethanesulfonic Acid in Chloroform

The diene (130 mg, 0.51 mmol) was dissolved in $CDCl_3$ (800 ul) and the solution was cooled to -70°C, then 80 ul of triflic acid was added. The temperature of this solution was brought to room temperature gradually. Cold CH_2Cl_2 and cold ether (1:5) were added to extract the products. Aqueous ammonium hydroxide (50 cm^3) was used to neutralize the excess acid. After the evaporation of the solvents, the dark brown product weighed 50 mg. ^1H NMR and GC-MS analysis indicated the presence of 4-nitro-2,5-dimethyl-acetophenone **37**(44%) and 6-nitro-2,5-dimethyl-acetophenone **38**(56%) and a trace amount of 2,5-dimethylacetophenone.

c. Reaction with Neat Trifluoroacetic Acid

The diene (180 mg, 0.73 mmol) was cooled to -30°C in a vial, and then reacted with 1 cm^3 TFA. NMR analysis showed that the diene was completely reacted when the temperature was raised to 0°C. Aqueous ammonium hydroxide (60 cm^3) and ether (50 cm^3) were added and the products

worked up. The products weighed 117 mg. Analysis by NMR, GC-MS and TLC of the mixture showed three compounds were present. They are 3-nitro-2,5-dimethyl-acetophenone **39**(33%), 4-nitro-2,5-dimethyl-acetophenone **37**(21%) and 6-nitro-2,5-dimethyl-acetophenone **38**(46%).

d. Reaction with H_2SO_4 in Methanol

The diene (62 mg, 0.25 mmol) was dissolved in 300 ul CH_3OH containing 1% H_2SO_4 (v/v). The diene disappeared in 14 hours at ambient temperature. The acid in the mixture was neutralized by 5 cm^3 of aqueous ammonium hydroxide and products were extracted with 40 cm^3 ether, and the ether separated and washed with brine. After the evaporation of the ether, the products weighed 40 mg. NMR analysis revealed the products were cis-3-acetyl-1,4-dimethyl-1-nitro-4-methoxy-2,5-cyclohexadiene methyl ether **49**(65%) ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.36 (s, 3H, 4-CH_3), 1.82 (s, 3H, 1-CH_3), 2.41 (s, 3H, $COCH_3$), 3.19 (s, 3H, OCH_3), 5.89 (dd, 1H, 6-H, J=10.2 and 1.8 Hz), 5.97 (d, 1H, 5-H, J=10.2 Hz), 6.88 (d, 1H, 2-H, J=1.8 Hz) and trans-3-acetyl-1,4-dimethyl-1-nitro-4-methoxy-2,5-cyclohexadiene methyl ether **50**(35%) ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.55 (s, 3H, 4-CH3), 1.88 (s, 3H, 1-CH_3), 2.41 (s, 3H, $COCH_3$), 3.08 (s, 3H, OCH_3), 5.89 (dd, 1H, 6-H, J=10.2 and 1.8 Hz), 5.97 (d, 1H, 5-H, J=10.2 Hz), 6.88 (d, 1H, 2-H, J=1.8 Hz).

Chapter 3 Results and Discussion

3.1 Nitration Reactions

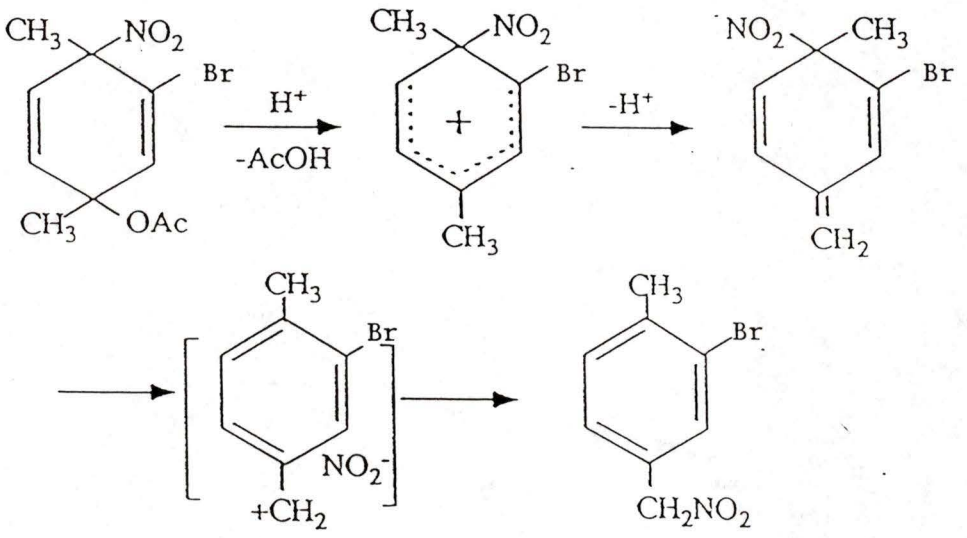
Nitrations of 2-X-p-xylenes were carried out under conditions that led to optimum yields of the adducts, which were determined by carrying out preliminary reactions on a 0.5 mmol scale and following the reactions by variable temperature nuclear magnetic resonance spectroscopy (^{1}H NMR). The nitration conditions for 2-X-p-xylenes are given in Table 3.1

X	T(^{0}C)	t(min)	mole proportion HNO_3	Ac_2O
Br	-35	40	2	5
Cl	-30	40	1	2
$COCH_3$	-35	45	1	2
COC_6H_5	-5	20	1	4

Table 3.1

In the nitration of 2-bromo-p-xylene, the reaction mixture was neutralized by the slow addition of aqueous ammonia at -70^{o}C and during the whole process the temperature of the mixture was monitored not to be higher than -40^{o}C, thus ensuring that the composition of the reaction product isolated after the work-up was the same as that present in the reaction mixture prior to work-up.

If the mixture was not worked up properly, side chain product **40** was observed. This can be explained on the basis of a further reaction of ipso adducts **24**, **25** due to the elevated temperature in some parts of the reaction mixture.(scheme 3.1)



Scheme 3.1

The mixture from the nitration was separated by preparative HPLC at 5°C, using a mixture of ether and petroleum ether as the eluent. The dienes were separated successfully from the nitro-aromatic compound **34** (59% in the worked up mixture as measured by NMR). Since the amount of diene **24** was much greater than that of **25**, diene **24** (37% by NMR) was readily obtained by crystallization from fractions after chomatography. Diene

25 (4% by NMR) was obtained from the chromatography fraction with the lowest ratio of **24:25**, after several recrystallizations.

The same procedures were applied to the nitration of 2-chloro-p-xylene, after work-up and separation diene **26** (34% by NMR) was obtained as was the nitroaromatic compound **32** (66% by NMR).

In the nitration of 2,5-dimethylacetophenone, the reaction mixture was neutralized by the slow addition of aqueous ammonia at -70°C and the temperature kept under -35°C to ensure the maximum yield of diene. The separation was carried out by preparative HPLC and diene **28** (42% by NMR), diene **27** (44% by NMR) and the nitroaromatic **39** (14% by NMR) were obtained.

In the case of 2,5-dimethylbenzophenone, the nitration and work-up procedures were the same as those for 2,5-dimethylacetophenone. However, a complete analysis of the product distribution was not achieved due to the failure to obtain a successful separation by chromatography, although different solvent combinations such as ether-petroleum ether, chloroform-ether, chloroform-petroleum ether, benzene-petroleum ether and

benzene-ether, in various ratios were tried. A 1:1 mixture of the ipso adducts was obtained. This mixture of the dienes could not be separated further.

The electronic substituent effects of the X groups are reflected in the conditions required for the nitration. A longer reaction time, a higher mole-proportion of nitrating agents and a higher temperature are required for less reactive substrates. By making comparisons on the basis of the experimental conditions used, the 2-X-p-xylene series can be arranged in the order of decreasing reactivity as : Br > $COCH_3$ > Cl > COC_6H_5. There is little difference in the reactivity among Br, $COCH_3$, and Cl groups. It is surprising that 2,5-dimethylacetophenone has similar reactivity to the two substrates with Cl and Br substituents.

3.2 Assignment of Spectra of the Dienes

The structure of the dienes **24**, **35**, **26**, **27** and **28** were assigned spectroscopically. Elemental analysis results are consistent with the assigned molecular formulae. The examination of these dienes by infrared spectra confirmed that addition of acetyl nitrate (nitronium acetate) had occurred since all the dienes

obtained exhibited strong absorptions around 1750 (for the $OCOCH_3$ group) and 1550, 1340 cm^{-1} (for the NO_2 group).

Integration of ^1H NMR signals of **24** in the diene region shows the presence of three protons of which two protons are AB quartet coupled exibiting a coupling constant of 9.8Hz and chemical shift of 5.89 and 6.06 ppm respectively, while the other proton is coupled to one of the proton in the AB quartet and has a higher chemical shift (6.57 ppm) and smaller coupling constant (1.9 Hz). This clearly indicates the vinylic proton (6.57 ppm, 1.9 Hz) is adjacent to the bromine atom and the other two vinylic protons are adjacent to each other. The lowest field absorption in the vinylic region is assigned to H-2 and the higher field absorptions are assigned to H-5 and H-6. The resonance signal at 1.90 ppm is assigned to the methyl group ipso to the nitro group while the 1.54 ppm peak is assigned to the methyl group ipso to the acetate group, and the acetate methyl group is assigned to the peak with an absorption at 1.98 ppm. These methyl assignments are consistent with those in other dienes.

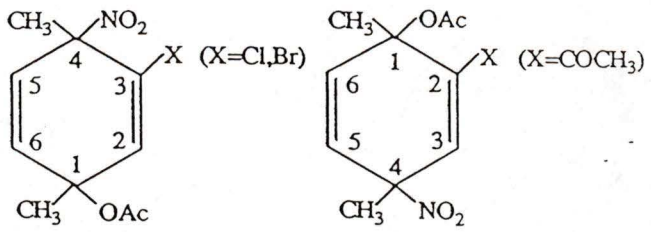
The ^{13}C NMR spectra of **24** gave 3 peaks in the methyl region (21.6, 23.5 and 26.7 ppm). The methyl group ipso to the acetate group is assigned to 21.6 ppm and the methyl group ipso to the nitro group is assigned to 23.5

ppm by comparison with the ^{13}C NMR data in the literature[94] while the 26.7 ppm peak is assigned to the acetate group. There are two saturated ring carbons with absorptions at 76.5 and 89.4 ppm. The 89.4 ppm signal is assigned to the carbon attached to the nitro group by comparison with the literature[95], therefore the 76.5 ppm signal is readily assigned to the carbon attached to the acetate group. The strong absorption at 169.5 ppm is no doubt due to the presence of the carbon atom in the acetate group. The other four unsaturated ring carbons are assigned with reference of the literature[94] and the assignment is listed in Table 3.4.

The ^{1}H NMR and ^{13}C NMR spectra of dienes **25** and **26** are assigned in a similar manner as in the diene **24** and the assignment are listed in Table 3.3 and 3.4.

Compound	X	^{1}H Chemical Shift (ppm)								Coupling Constant(Hz)		
		1-CH_3	4-CH_3	OAc	COMe	H-2	H-3	H-5	H-6	3,5	2,6	5,6
24	Br	1.54	1.90	1.98	-	6.57	-	5.89	6.06	-	1.9	9.8
25	Br	1.49	1.56	2.03	-	6.41	-	6.03	6.03	-	0.8	-
26	Cl	1.53	1.88	1.96	-	6.26	-	5.85	6.03	-	1.9	9.9
27	$COCH_3$	1.54	1.83	2.03	2.38	-	7.21	6.22	5.89	2.0	-	9.0
28	$COCH_3$	1.52	1.81	1.91	2.34	-	6.79	5.96	5.87	2.0	-	10.0

Table 3.3



Compound	X	^{13}C Chemical Shift (ppm)											
		1-CH_3	4-CH_3	OCOMe	COMe	C-1	C-2	C-3	C-4	C-5	C-6	OCOMe	COMe
24	Br	21.6	23.5	26.7	-	76.5	121.0	137.1	89.4	133.1	126.4	169.5	-
25	Br	21.3	25.0	26.9	-	76.0	125.0	133.2	87.5	131.1	128.5	169.1	-
26	Cl	21.5	22.1	26.8	-	76.5	126.4	133.2	88.8	132.9	130.3	169.4	-
27	$COCH_3$	22.8	24.6	26.3	29.0	74.2	138.5	146.7	83.5	135.4	127.5	169.7	196.2
28	$COCH_3$	21.3	25.5	26.8	27.3	76.0	135.9	142.5	85.9	134.1	123.7	170.1	196.6

Table 3.4

From the ^{1}H NMR spectra of diene **27**, three protons in the diene region are found. The one with an absorption at 7.21 ppm is most down field and is assigned to H-3 since this proton shows a doublet peak and is vinylic to the $COCH_3$ group. Another diene proton with an absorption at 6.22 ppm is assigned to H-5 due to the fact that it is coupled to two other diene protons. The diene proton left (5.89 ppm) is assigned to H-6. The ^{1}H NMR also gives four methyl group absorption signals (1.54, 1.89, 2.03 and 2.38 ppm). The 1.54 ppm signal is attributed to the methyl group ipso to the acetate group and 1.89 to the methyl group ipso to the nitro group. Accordingly, the

2.03 ppm absorption is due to the presence of $OCOCH_3$ group and the methyl group in $COCH_3$ is assigned to the peak with a chemical shift of 2.38 ppm. The ^1H NMR spectrum of diene **28** is assigned in the same way. The complete assignments of these two dienes are shown in Table 3.3.

From the ^{13}C NMR spectrum of diene **27**, two saturated ring carbons give absorptions at 74.2 and 83.5 ppm. According to the literature[95], the carbon atom attached to the nitro group is assigned to the peak at 83.5 ppm while the other is readily assigned to the peak at 74.2 ppm. The ^{13}C NMR also shows four peaks in the methyl region (22.8, 24.6 26.3 and 29.0 ppm). The one most down field (29.0 ppm) is assigned to the methyl in $COCH_3$. The 26.3 ppm peak is assigned to the methyl in the $OCOCH_3$ group. With the reference to the literature[94] the 24.6 ppm signal is assigned to the methyl ipso to the nitro group so that the 22.8 ppm peak is assigned to the methyl ipso to the acetate group. There are two carbonyl groups in the adducts giving two absorptions at 196.2 and 169.7 ppm respectively. The 169.7 ppm peak is assigned to $OCOCH_3$ group in accordance with the previous assignment. Therefore the absorption at 196.2 ppm can be assigned to the $COCH_3$ group. The other four unsaturated carbon atoms

are assigned with the reference to the literature[94]. The complete assignments of ^{13}C NMR of dienes **27** and **28** are shown in Table 3.4.

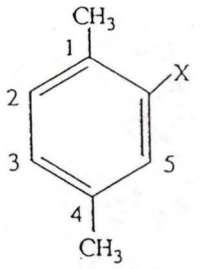
3.3 The relative reactivity of each position on the aromatic ring

The relative reactivity of each position in an aromatic substrate determines the amount of each positional isomer obtained in electrophilic aromatic substitution and such positional selectivity can be assessed by partial rate factors. 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. Once the partial rate factors are known the proportions of the isomers obtained on substitution can be predicted, when two or more groups are present on a ring, by using the principle of additivity[2]. The principle assumes that two or more substituents on a ring each modify the reactivity of a particular position by the same amount as in the corresponding monosubstituted compounds, resulting in an additive influence of effects. The isomer distribution of the products predicted by the principle of additivity and that observed in the

nitration of 2-X-p-xylene are given in the following Table (Table 3.2)

X	1	2	3	4	5	predicted (found)
Cl	33(34)	0(0)	54(66)	1(0)	12(0)	
Br	37(41)	.5(0)	48(59)	1.5(0)	13(0)	
$COCH_3$	14(0)	20(14)	1(0)	57(87)	7(0)	

Table 3.2



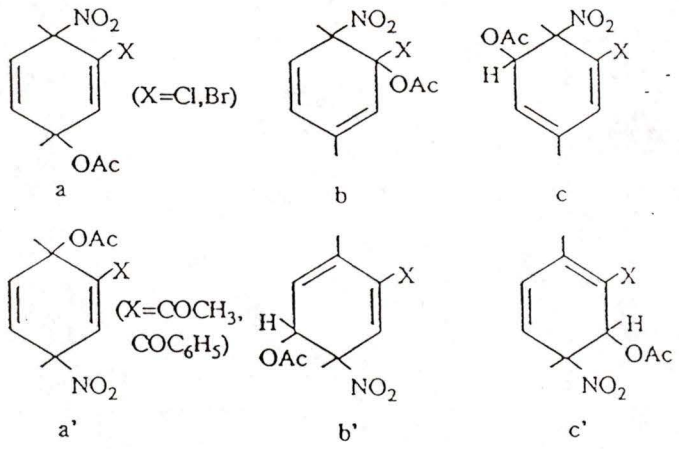
There is qualitative agreement between the observed and predicted reactivities. However, the quantitative agreement is not exact. This may be due to the limitations of the additivity principle, since the principle does not allow for any interaction between the substituents and ignores steric effects. In the case of 2-chloro-p-xylene, there is good agreement between the calculated and observed percentages of the ipso adduct. However the normal nitration product at position 5 was not observed: it is likely that due to the steric effects (buttressing effects) of the CH_3 and Cl groups the amount of nitro compound formed was too small to be separated. In the case of 2-bromo-p-xylene, the situation is similar to that of 2-chloro-p-xylene. The partial rate factors predict well the yield of the ipso adduct but the yield of 5-nitro compound must be less than predicted, again

likely due to steric effects. In the case of 2,5-dimethylacetophenone only one ipso adduct and one nitro isomer were observed. Furthermore the amount of the adduct was substantially more than predicted. Addition of the nitronium ion to the 1-methyl-substituted position would be expected to be hindered by the adjacent acetyl group, thus accounting for the absence of the minor regioisomeric adducts. The amount of the 2-nitro isomer is less than expected reflecting the buttressed steric hindrance at the position. Likewise the 5-position is heavily hindered with two ortho substituents, one of which is buttressed. It is not surprising that none of the product of substituent at this position was observed.

3.4 Regioselectivity in Nucleophilic Trapping

In the ipso Wheland intermediates, the positive charge is delocalized on the two ortho and the para ring carbons (with respect to the ipso methyl group) so that three potential positions are available for nucleophilic capture by the acetate ion. Hence the possible ipso

adducts for 2-X-p-xylenes are:



When X is Cl or Br, nucleophilic capture at C-2 or C-6 leads to the formation of a conjugated 1,3-diene while the capture at C-4 produces a non-conjugated 1,4-diene. The existence of the structure **b** is excluded since such compounds, with an oxygen ipso to a good leaving group, in this case halogen, are not stable and readily form the corresponding dienones. Such a process involving the formation of an intermediate dienone followed by its rearrangement has been used to explain[53] the formation of 4-methyl-2-nitrophenol during the nitration of both 4-methoxytoluene and 4-bromotoluene. As to structure **c**, there should be two vinylic proton signals and one allylic proton signal appearing in the ^{1}H NMR spectrum, and this pattern should be clearly distinct from that for **a**. Moreover in **c** the 4-methyl group should be split by the vinylic proton. Instead three vinylic proton signals

were assigned (section 3.2) and the methyl groups were not split. It is clear from the NMR that structure **a** (1,4-adduct) is the correct structure. The possibility that the isolated dienes have strutures **a'**, **b'**, or **c'** should also be considered. The NMR is consistent with struture **a'** but not with structures **b'** and **c'**. The discussion in section 3.1 leads to the conclusion that when X=Cl, Br position 4 is much less reactive than position 1. The only reasonable conclusion is that the isolated dienes have structures **a** and not structure **a'**.

When x = $COCH_3$, the ^1H nmr spectrum (section 3.2) revealed three vinylic proton signals. Thus structures **b'** and **c'** that have allylic protons are not the correct representation of the ipso adduct obtained and **a'** is assigned as the actual structure for the diene obtained. In this case the 4-methyl position is more reactive than the 1-methyl position and this is the basis for the assignment of **a'** rather than **a** as the structure.

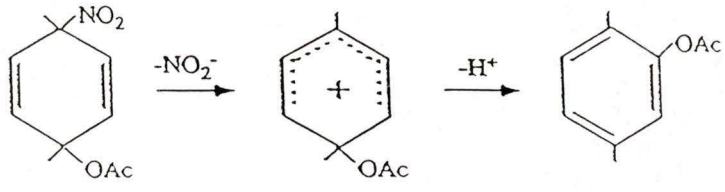
When x = COC_6H_5 group, the ^1H NMR spectrum showed two vinylic proton signals and one allylic proton signal. In this case structure **a'** with three vinylic protons is obviously not the right representation. The possibility of structure **c'** is excluded because no ten Hz coupling constant was observed in the ^1H NMR spectrum. Hence the correct structure must be **b'**.

To summarise the above discussion, it is clear that in the case of 2-chloro- and 2-bromo-p-xylenes, only 1,4 adducts were obtained from the nitration and the nitration of 2,5-dimethylacetophenone also gave 1,4 adduct. However the nitration of 2,5-dimethylbenzophenone gave only 1,2 adducts. The nitrations of 2-chloro-, 2-bromo- and 2,5-dimethylacetophenone do not differ from that of the p-xylene in terms of the regioselectivity of capture of the acetic acid. It is known that formation of the adduct is subject to kinetic control[96] and thus it is the energetics of the transition states for trapping of the ipso cation that determines the preferred adduct. In terms of resonance effects based on electronic theory, the nitrocyclohexadienyl cation obtained from 2,5-dimethylacetophenone and from the corresponding benzophenone is not as stable as those from 2-chloro- and 2-bromo-p-xylenes. Thus for the carbonyl compounds the structure of the transition state for the adduct-forming step should be more similar to the carbocation intermediate than in the case of the halogen compounds. This should lead to less discrimination in the site of addition of the acetic acid for the former. The electronic effects of the acetyl and benzoyl groups are similar and quite different from those of the chlorine and bromine. Thus the explanation for the formation of the 1,2 adduct **b'** in the case where $x=COC_6H_5$ is not to be

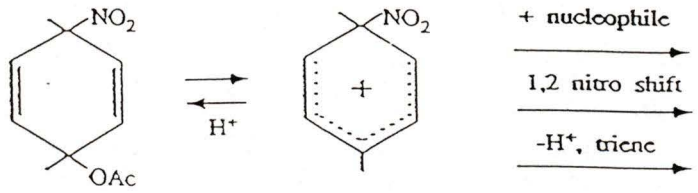
found in electronic effects. On the other hand the steric effect of the benzoyl group would be expected to be larger than that of acetyl and larger again than the halogens. Thus a steric effect may well contribute to the preference for the formation of adduct **b'**. In the transition states for formation of **a'** and **b'** it is clear that an increase in size of the group X will lead to greater interaction between X and the incoming acetate group (steric hindrance) in **a'** and almost no change in the interaction in **b'**. It is however surprising that in going from $X=COCH_3$ to $X=COC_6H_5$ there is such a complete transition of the diene products formation from, apparently, only **a'** to only **b'**. According to the literature[97], a 1,2 adduct was obtained in the case of 4-tert-butyltoluene. Thus it seems that when the substituent group on the benzene ring is bulky enough, steric effects become apparent, at least in the cases when groups are t-Bu and COC_6H_5. As to smaller groups like halogens, Me, OMe and $COCH_3$ it seems there is a subtle joint operation of electronic and steric effects. At the present time we can not predict with reliability the regioseletivity of the acetic acid capture based solely on electronic effects or steric effects.

3.5 Reactions of 1,4 Adducts

The chemistry of 1-acetoxy-4-nitrocyclohexa-2,5-diene adducts has been extensively investigated. There are two main reaction pathways in solutions. Protonation of the acetate group followed by loss of acetic acid gives the nitrocyclohexadienyl cation. Ionisation of the nitro group as nitrite leads to the acetoxycyclohexadienyl cation. These cations may react with available nucleophiles to form dienes or they may rearomatise. The acidity in the solution and the other substituents present on the ring determine the pathways through which the reaction will proceed. In scheme 3.2, pathway **a** is slow, but requires only good ionising conditions. Pathway **b** requires acid catalysis and the presence of good nucleophiles, and may have its rate increased by an increase in the acidity of the reaction medium. The partition of the reactions shown (scheme 3.2) is general for the reactions of diene adducts and, in principle under appropriate conditions the diene can be converted quantitatively to products from one of the pathways only. The partition shown in scheme 3.2 may be affected by other substituents present in the ring.



pathway a



pathway b

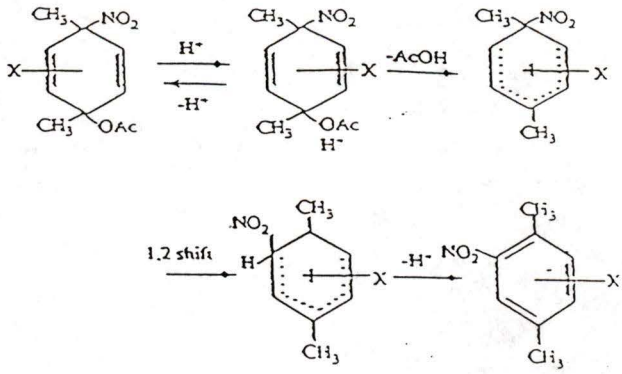
Scheme 3.2

3.5.1 Reactions under Acidic Conditions

Scheme 3.3 summarizes the various reactions observed with 1,4 ipso adducts from 2-X-p-xylenes.

Strong to moderate acid conditions favors the formation of nitrocyclohexadienyl cation. The Wheland cation can recombine with acetic acid at C-1 (reaction 3) to regenerate the original adduct, combine with another nucleophile to give a new diene adduct (reaction 3), undergo deprotonation at the benzylic position to form a triene (reaction 4), undergo a 1,2 nitro shift (reaction 1), or combine with acetic acid at C-6 to form a 1,2 adduct followed by a 1,5 sigmatropic shift (reaction 2) to form the isomeric 1,2 adduct which in turn undergoes loss of acetate to form the isomeric Wheland cation which undergoes deprotonation to give the nitroaromatic compounds. Formation of the products is competitive, partition occuring in the ipso Wheland cation reactions. The outcome of this partition is determined by the substituent and acidity in the solution.

1



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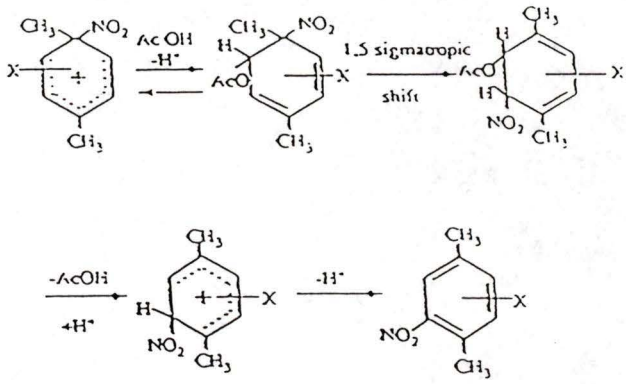

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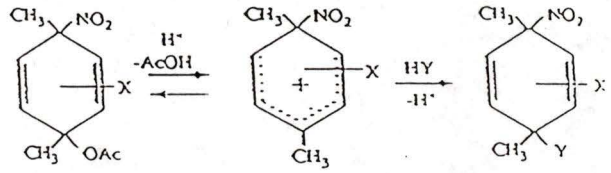

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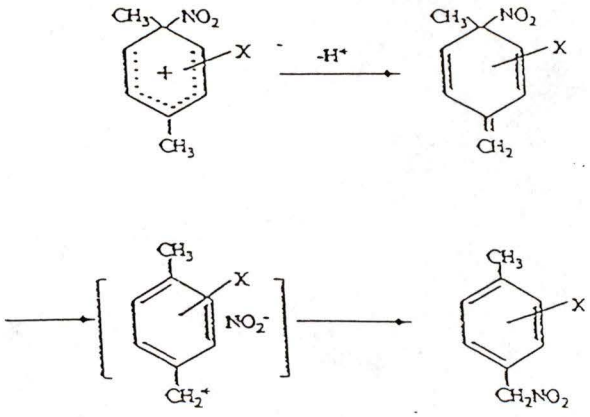
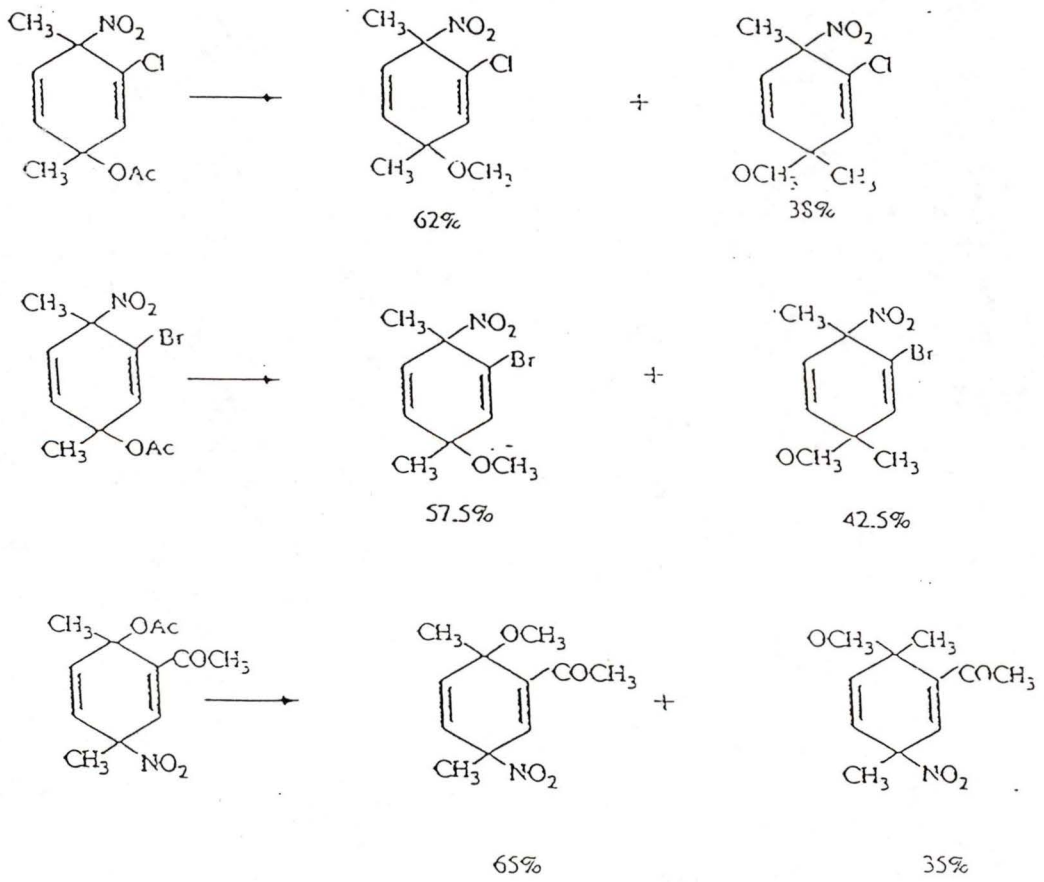


Scheme 3.3

3.5.2 Reactions of 1,4 Adducts with Sulphuric Acid and Methanol

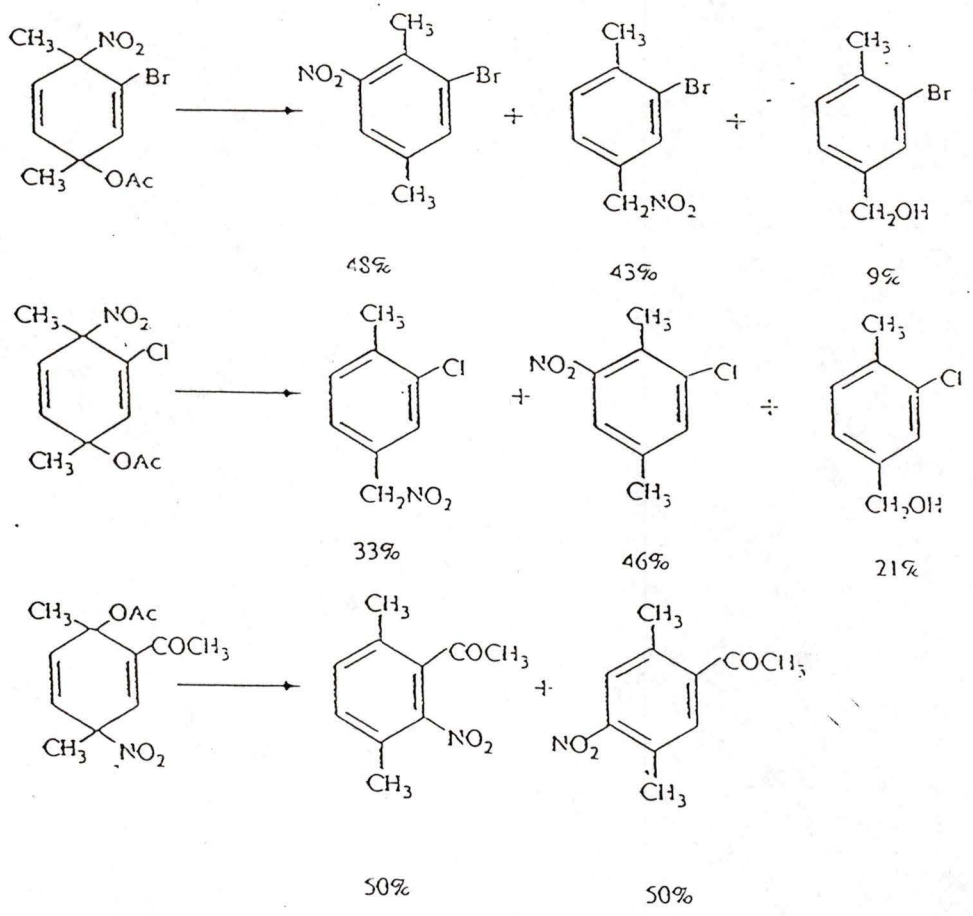
With the catalysis of H_2SO_4 and methanol as a suitable nucleophile, the diene adducts **24, 26** and **27** can be converted to methoxy diene adducts in which the 4-nitro group is retained and the methoxy group at the 1-position has either a cis- or a trans- relationship to the nitro group. Scheme 3.4 gives the reactions and their products. In these reactions, no nitro aromatic compounds were found to be formed indicating weak acidic conditions can well limit the chemical transformation to the exclusive exchange of nucleophiles.



Scheme 3.4

3.5.3 Reactions with Trifluoroacetic Acid in $CDCl_3$

In these reactions dienes **24**, **26** and **27** were reacted with trifluoroacetic acid to give nitro aromatic and side chain compounds (scheme 3.5). Approximately half the amount of products from dienes **24** and **26** are side chain compounds, which are presumably formed via the triene process as depicted in scheme 3.3, while the other half are the nitro aromatic compounds which are formed via the 1,2 nitro shift process (scheme 3.3). In the case of diene **27** nitro aromatic compounds were observed with the complete absence of side chain compounds. Since the reaction condition was the same as for the reactions of **24** and **26** which gave side chain compounds, it seems that the nature of the substituent (X) is the factor that makes the difference. The nitrocyclohexadienyl cations generated by the catalysis of trifluoroacetic acid are destablized by the Cl and Br groups but much less so than by the presence of a $COCH_3$ group on the ring. Therefore the regenerated Wheland intermediate from diene **27** is shorter lived than those from dienes **24** and **26**. Only the inherently faster unimolecular process, the intramolecular 1,2 nitro shift, occurs in the very short lived cation. The triene process, a bimolecular process, becomes competitive when the regenerated cations from dienes **24** and **26** live long enough.

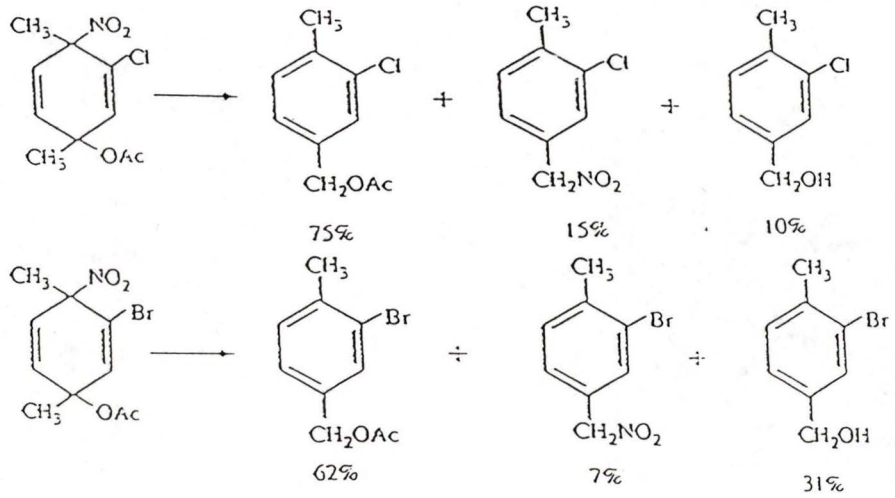


Scheme 3.5

3.5.4 Reactions with Trifluoroacetic Acid in Acetic Anhydride

The reactions of dienes **24** and **26** under catalysis of trifluoroacetic acid in acetic anhydride gave only side chain products (scheme 3.6). This is expected because the change of solvent will change the reaction environment, thus the presence of acetic anhydride tends to accelerate the deprotonation of the nitro cyclohexadienyl cation to

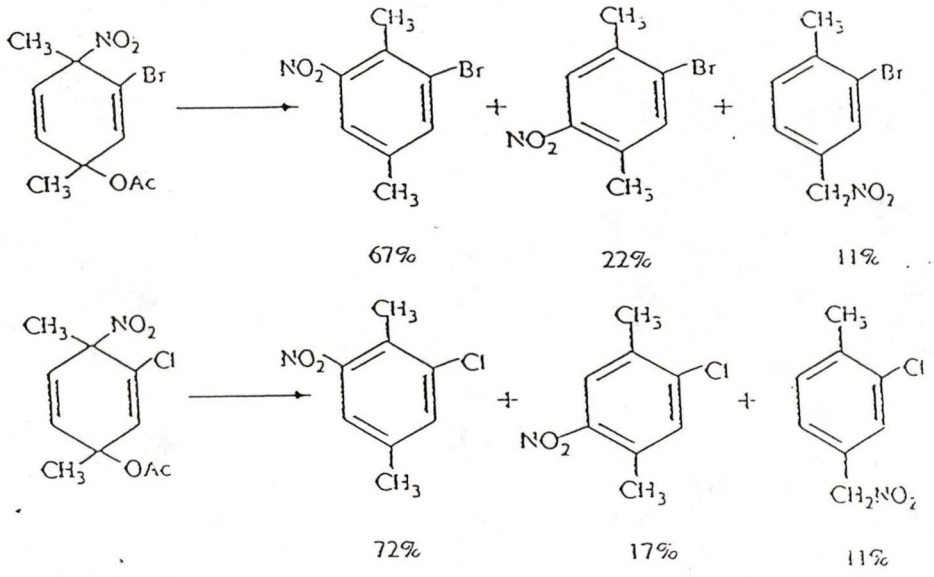
form triene intermediate and ultimately side chain products. Two factors are likely at work here. Acetic anhydride, the solvent with higher dielectric constant, should stablize the cyclohexadienyl cation better than chloroform. Thus the cation should be longer lived in acetic anhydride allowing more opportunity for the bimolecular deprotonation to triene to compete with the unimolecular nitro shift. Deprotonation should be aided by the more nucleophilic solvent. In chloroform the only species which can bring about deprotonation are the acetic acid released in the cation-forming step and present in low concentration and the less nucleophilic trifluoroacetic acid.

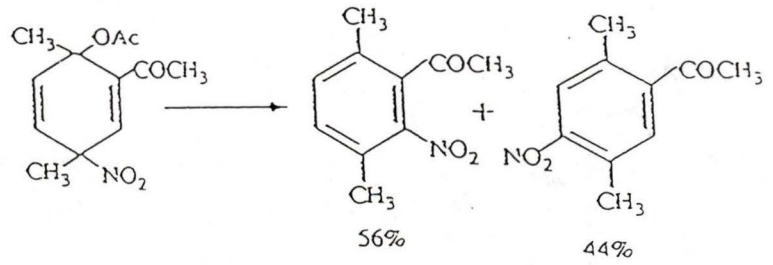


Scheme 3.6

3.5.5 Reactions with Trifluoromethane Sulfonic Acid in $CDCl_3$

The dienes **24**, **26** and **27** are affected under stronger acid condition than that in section 3.4.3. For diene **27** nitro aromatic compounds resulting from 1,2 nitro shift process are the only products found (scheme 3.7). However in the case of dienes **24** and **26** three reaction processes are in competition, of which the 1,2 nitro shift is the dominant one. This is consistent with the results reported in section 3.4.3. The 1,3 nitro shift is actually a two step process as described in scheme 3.3, which is thoroughly discussed in the recent literature[94]. Apparently this is slower than the 1,2 shift and the triene process is the least favored.



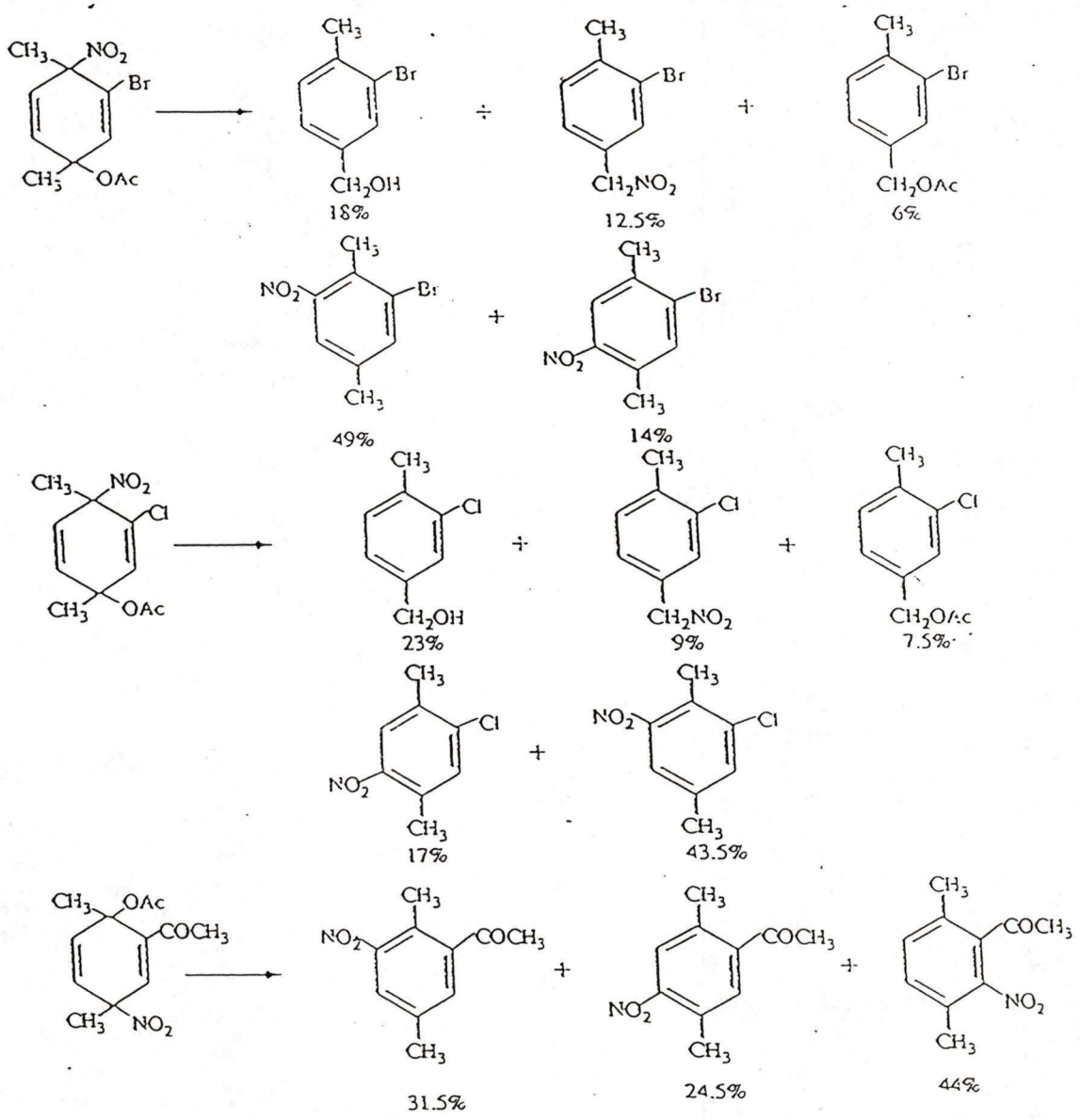


Scheme 3.7

3.5.6 Reactions with Neat Trifluoroacetic Acid

The reactions of dienes **24, 26** and **27** were carried out under the relatively strongly acidic condition of neat TFA. Dienes **24** and **26** give products (scheme 3.8) resulting from all the possible routes (1,2 nitro shift, 1,3 nitro shift and the triene process) among which nitro aromatics from the 1,2 nitro shift process have the highest yield. In the case of diene **27** side chain products were not observed (scheme 3.8). The main products resulted from the 1,2 nitro shift. A significant amount of 1,3 shift products were also found. These results confirmed the observations in the previous sections 3.4.3, 3.4.4 and 3.4.5 that 1,2 nitro shift process is the dominant process under strong to moderate acid conditions for 1,4 ipso adducts while the triene process dominates the reaction course when the solvent is nucleophilic. Substituents on the ring play a significant role in affecting the final product distribution. It is evident that by controlling the reaction conditions the desired compound can be obtained in good yields from the

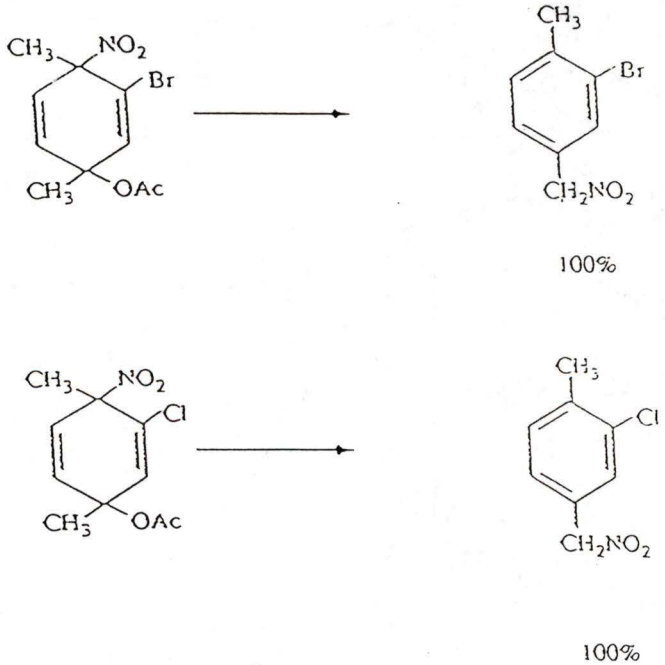
reactions of 1,4 ipso adducts.



Scheme 3.8

3.5.7 Thermolysis in Chloroform

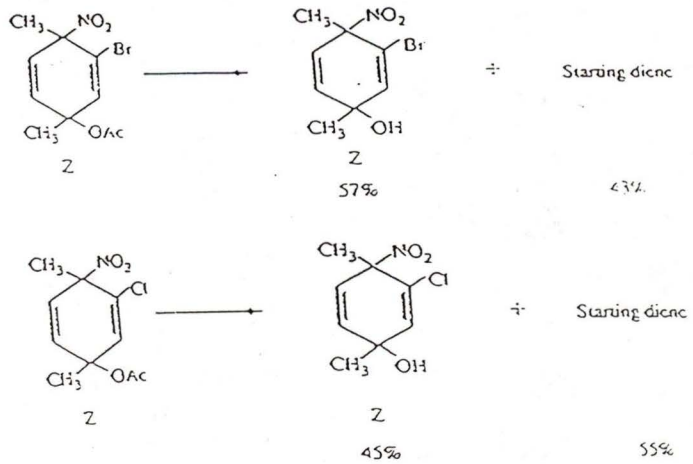
The reactions of dienes **24** and **26** were carried out under elevated temperature and with prolonged reaction time to give two side chain products **40** and **43** (Scheme 3.9) while diene **27** did not react even after 48 h. Hence these dienes are very stable under non-acidic and non-ionising conditions. The yield of side chain product is unexpected. This may be caused by the presence of a minute amount of acidic impurities in the reaction media which at high temperature can serve as a catalyst to lead to the formation of nitrocyclohexadienyl cations and through them the trienes and ultimately the side chain products.



Scheme 3.9

3.5.8 Reactions with Methanol in Tris(hydroxymethyl)-aminomethane

Dienes **24** and **26** can be converted into dienols stereospecifically (scheme 3.10) when for a long time reacted with methanol by the transesterification process (scheme 3.10). The tris(hydroxymethyl)-aminomethane in the media is used to keep the solution slightly basic so that no acid catalysed reaction can occur. The transesterification process is slow and reversible but useful if the dienols are the desired products since they can be readily separated from the unreacted starting dienes. There is a striking substituent effect in this reaction. When the adduct from p-xylene is reacted under these conditions there is a rapid ionization of the nitro group as nitrite leading to the aryl acetate (section 3.4). The acetoxycyclohexadienyl cations formed from **24** and **26** by loss of nitrite are so destablised by the halogen under "neutral" conditions that this ionization process does not occur and the slow transesterification process is dominant.



Scheme 3.10

3.6 Conclusions

This thesis describes the nitration reactions of 2-X-p-xylenes (X=Cl, Br, $COCH_3$, COC_6H_5) and the isolation and reactions of acetoxynitro diene adducts.

The yields of ipso adducts range from moderate to good. The nitration of 2-chloro-, 2-bromo-p-xylenes and 2,5-dimethylacetophenone give 1,4 adducts exclusively while the nitration of 2,5-dimethylbenzophenone leads to 1,2 adducts only. The regioselectivity of acetic acid capture appears to be more sensitive to steric effects than to the electronic effects at least in the 2-X-p-xylene series.

It is confirmed that in the reactions of 1,4 adducts strong to moderate acid conditions favor the formation of nitrocyclohexadienyl cation and the competition among three possible pathways (1,2 nitro shift, 1,3 nitro shift and the triene process) is affected by the substituents (X), the acidity and the solvent. In methanol the nitrocyclohexadienyl cation is captured by the methanol to form the dienyl methyl ether. The dominant reaction of nitrocyclohexadienyl cation in acetic anhydride is the deprotonation to give triene and ultimately, side chain

aromatics while the 1,2 nitro shift process dominates in more strongly acidic media. The more strongly electron withdrawing acetyl group facilitates the 1,2 nitroshift and , to a less extent, the 1,3 nitro shift process. Side chain products are not observed with this substituent. Finally the reactions of 1,4 ipso addducts with methanol give dienols stereospecifically.

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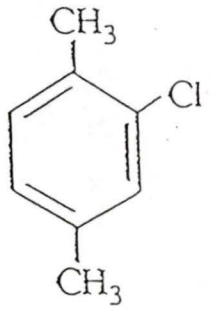
Appendix: Key to the Numbered Structures



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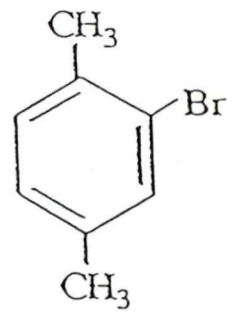

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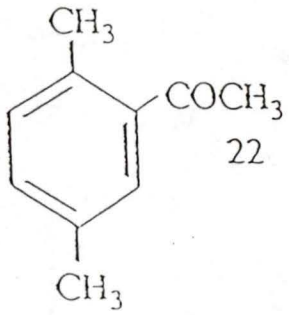

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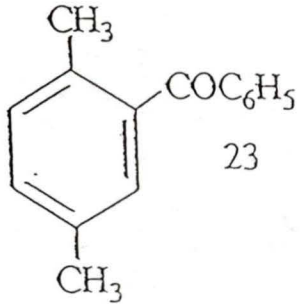

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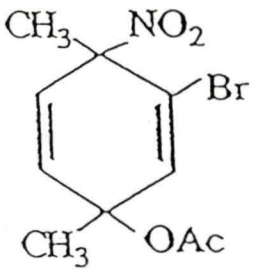

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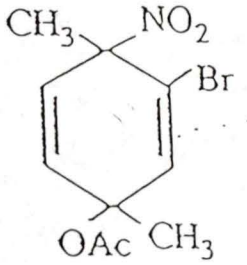

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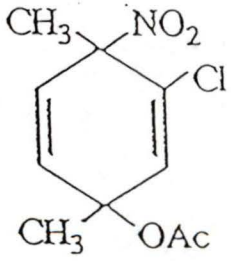

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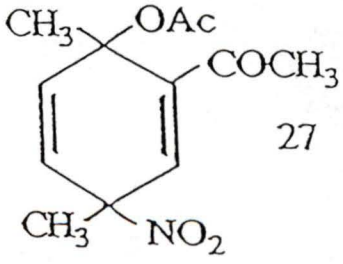

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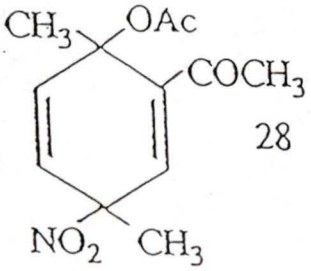

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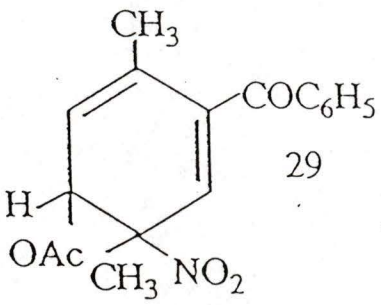

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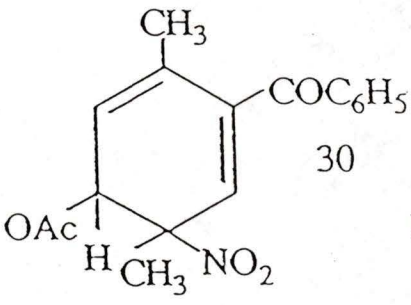

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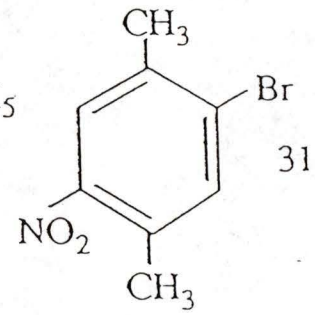

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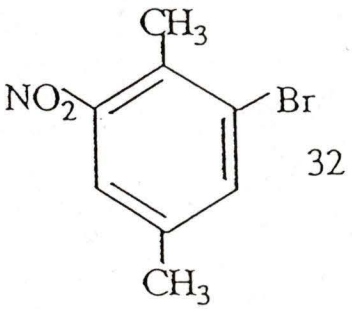

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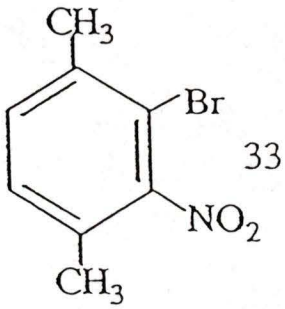

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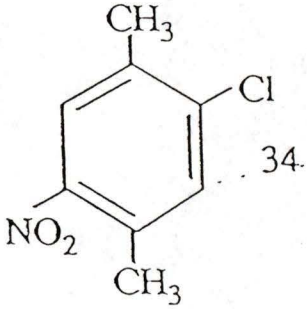

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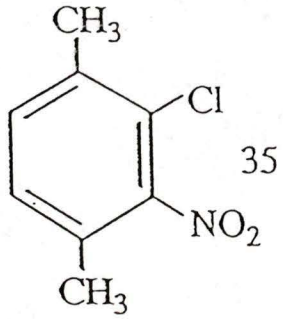

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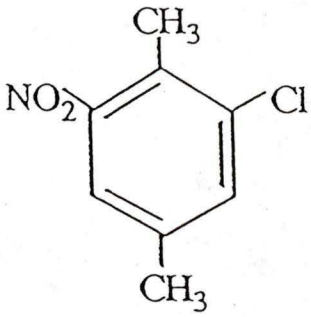

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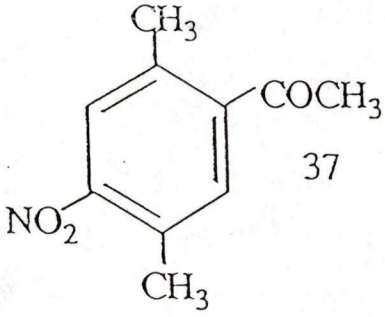

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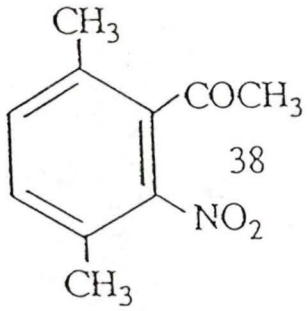

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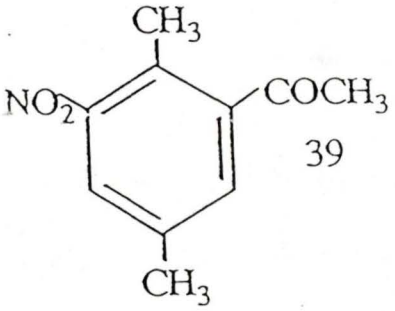

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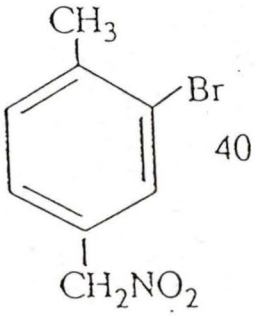

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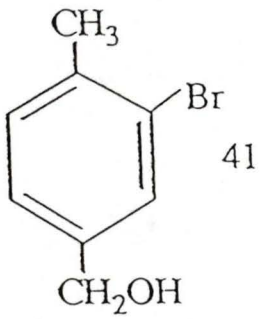

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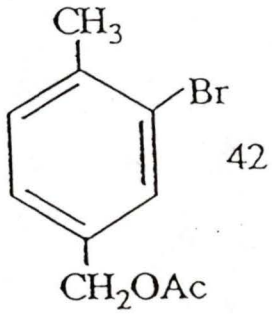

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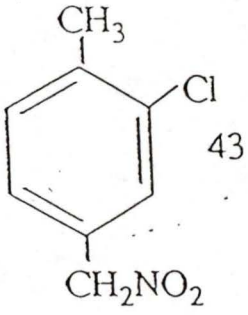

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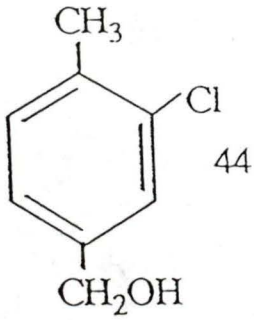

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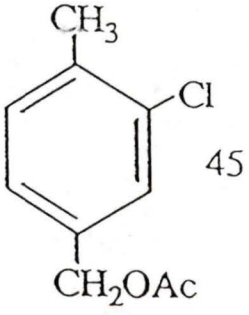

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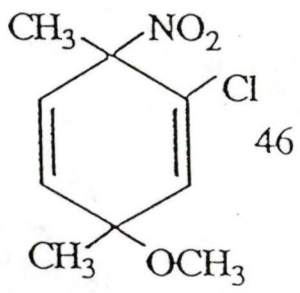

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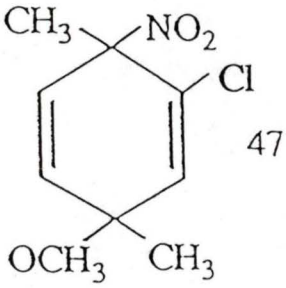

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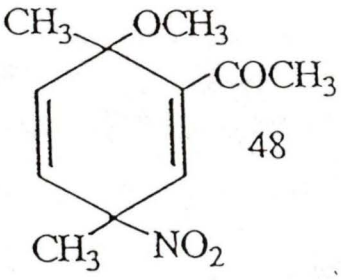

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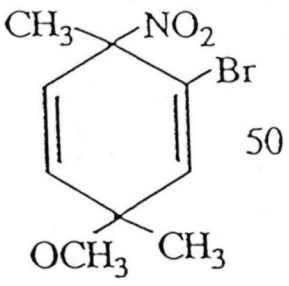

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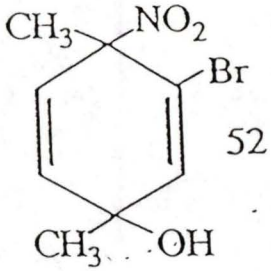

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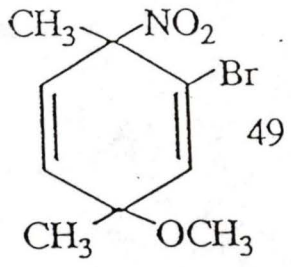

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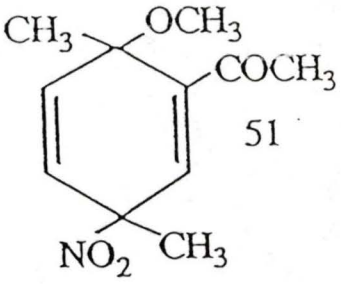

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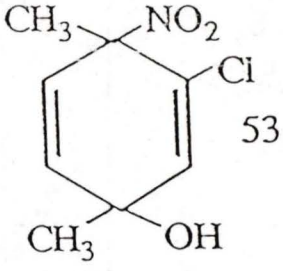

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VITA

First Name: Dan Surname: Xi

Place of Birth: Shanghai, PRC

Date of Birth: March 25,1964

Educational Institution Attended, with dates of entering and leaving:

Fudan University, Shanghai, PRC, 1981-1985

Degrees, Diplomas, Etc., Awarded, with Dates and Names of Institutions

B.Sc. 1985 Fudan University

Publications:

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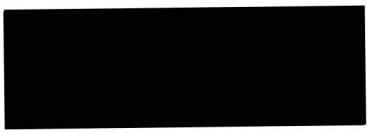

DAN Xi

September 30, 1991