Non-conventional Electrophilic Aromatic Substitutions and Related Reactions

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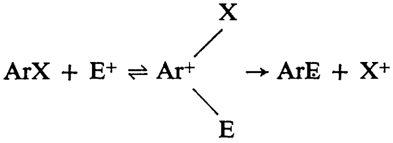
1 Introduction

Electrophilic aromatic substitutions have been studied extensively.[1] The general features of this class of reaction are now well understood and can be explained in terms of the two-step S_E2 mechanism which involves a relatively unstable σ-complex (Wheland intermediate):[2]



$$\mathrm{ArX} + \mathrm{E}^+ \rightleftharpoons \mathrm{Ar}^+\!\begin{smallmatrix}\mathrm{X}\\ \\ \mathrm{E}\end{smallmatrix} \rightarrow \mathrm{ArE} + \mathrm{X}^+$$

There have been attempts to modify this mechanism by introducing additional intermediates (π-complexes),[3] but in general such extensions are thought to be unnecessary.[4]

Until recently most attention was given to those nuclear substitutions in which X = H (or one of its isotopes), *i.e.* conventional electrophilic substitutions, but there is now a growing interest in other types of electrophilic reaction. In particular, there are those substitutions in which X is a group other than hydrogen,[5] and there are those reactions which appear to be initiated by the attack of an electrophile but which give products other than those expected for a conventional substitution.[6] The different types of behaviour may be classified as follows:

(i) *Nuclear substitution.* The electrofugal leaving group may or may not be hydrogen.

(ii) *Side-chain substitution.* This usually involves an alkyl side-chain.

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[1] R. Taylor in 'Comprehensive Chemical Kinetics', ed. C. H. Bamford and C. F. H. Tipper, Elsevier, Amsterdam, 1972, vol. 13.

[2] (*a*) H. Zollinger, *Adv. Phys. Org. Chem.*, 1964, **2**, 163; (*b*) C. K. Ingold, 'Structure and Mechanism in Organic Chemistry', 2nd edn., Bell, London, 1970; (*c*) P. Rys, P. Skrabal, and H. Zollinger, *Angew. Chem. Internat. Edn.*, 1972, **11**, 874.

[3] G. A. Olah, *Accounts Chem. Res.*, 1971, **4**, 240.

[4] D. V. Banthorpe, *Chem. Rev.*, 1970, **70**, 295.

[5] (*a*) C. L. Perrin, *J. Org. Chem.*, 1971, **36**, 420; (*b*) C. L. Perrin and G. A. Skinner, *J. Amer. Chem. Soc.*, 1971, **93**, 3389; (*c*) P. B. Fischer and H. Zollinger, *Helv. Chim. Acta*, 1972, **55**, 2139.

[6] E. Baciocchi and G. Illuminati, *Progr. Phys. Org. Chem.*, 1967, **5**, 1.

(iii) *Rearrangement.* Initiated by an electrophilic reagent.

(iv) *Electrophilic addition.*

(v) *Other reactions.* Examples include the formation of dienones, quinones, and products of coupling.

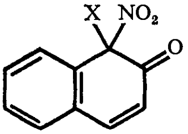
These reactions all appear to be closely related mechanistically and the pathway followed in a particular reaction may depend upon the reaction conditions, the structure of the substrate, and the nature of the leaving group. The reactions of class (ii) have been called non-conventional electrophilic substitutions;[6] the term non-conventional will be applied in this review to all of the above processes other than nuclear substitutions in which hydrogen is the leaving group.

It should be emphasized that a reaction need not be confined to a single pathway, and indeed rearrangements and additions frequently accompany substitution, sometimes with evidence for a common reaction intermediate. Because of the number of pathways available, complicated mixtures of products are often obtained and it is perhaps for this reason that non-conventional reactions have been overlooked in the past, since minor components of reaction products have not always been characterized.

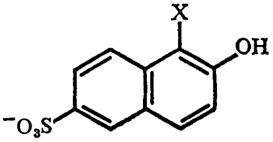
2 Electrofugal Leaving Groups other than Hydrogen

Many electrophilic substitutions in which the leaving group is other than hydrogen have been reviewed.[1] The different types of reaction are well established and interest now lies in finding an order for the leaving abilities of the different electrofugal groups.[5] One recent attempt to establish such an order, based on the magnitudes of hydrogen isotope effects, has led to the following sequence for increasing leaving ability:[5a] $Cl^+ \approx NO_2^+ \approx R^+ < Br^+ < D^+ \approx ArN_2^+ \approx SO_3 \approx RCO^+ < NO^+ \approx H^+ \approx I^+ < Hg^{2+} < Me_3Si^+$.

It has been suggested[5a] that the compound (1; X = Cl) should be a good model for a σ-complex. The reactions of (1) should therefore give some information about the behaviour of the Wheland intermediates involved in non-conventional electrophilic substitutions. In mixtures of acetic acid and acetic anhydride (1) decomposes by loss and migration of NO_2^+ rather than Cl^+, suggesting that NO_2^+ is a better leaving group than Cl^+; with the corresponding bromo-compound, however, Br^+ rather than NO_2^+ is lost. Similarly, the re-



(1)



(2)

arrangement of 1-chloro-1-methyl-2-keto-1,2-dihydronaphthalene in acetic acid[7] indicates that Cl^+ is a better leaving group than Me^+; the sequence of leaving abilities $Me^+ < Cl^+ < NO_2^+ < Br^+$ is suggested by these results.

In the diazodehalogenation of (2) the ease of displacement of halogen is found to be $Cl^+ < Br^+ < I^+ < H^+$.[5c] It was pointed out that this represents only an apparent order of leaving ability, because in the case X = Br the reaction is catalysed by thiosulphate ions, but such catalysis is not observed in the other cases. The rates of bromination of certain phenols provide another means for estimating relative leaving abilities.[8]

The general agreement among the various methods is encouraging, but several difficulties remain. One problem, illustrated by the results for diazodehalogenation, is that the loss of the electrofugal group may involve interaction with a nucleophile. Relative leaving abilities might therefore show some variation with the reaction conditions depending upon the mechanism by which the electrofugal group is removed from the σ-complex. Such a consideration implies that a single order of leaving abilities may be inappropriate. Another problem concerns the identity of the actual electrophilic reagent, which appears to be in question for certain reactions. For example, in the nitrodeiodination of 4-iodoanisole the preliminary step is thought to involve nitrosodeiodination.[9]

Substituent effects on the reactivity of an aromatic compound towards conventional electrophilic substitution are expressed quantitatively in terms of partial rate factors,[2b] which give the reactivity of a ring position, *ortho*, *meta*, or *para* to the substituent, relative to a single position in benzene. For the types of reaction discussed in this section it is necessary, in addition, to have a measure of the reactivity of the ring position at which the substituent is attached; the name *ipso* has been suggested for this position, and an *ipso* partial rate factor (i_f^R) has been defined for this purpose:[5b]

$$i_f^{R} = \frac{k_{ArR} \times \%\ \text{attack at } ipso \text{ position in ArR}}{k_{ArH} \times \%\ \text{attack at corresponding position in ArH}}$$

In this expression k_{ArR} represents the rate constant for total reaction of ArR, the system of interest, and k_{ArH} that for the corresponding system in which the substituent R is replaced by hydrogen. A limited number of *ipso* partial rate factors have been determined and these are collected in Table 1.

The choice of name for the term i_f^R is unfortunate since partial rate factors are generally understood to be measures of reactivity relative to a position in benzene. The definition of i_f^R, however, means that these factors do not express reactivities relative to benzene, or indeed, to any single reference compound.

3 Electrophilic Side-chain Halogenation

The side-chain halogenations of polymethylbenzenes under certain conditions

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[7] K. Fries and K. Schimmelschmidt, *Annalen*, 1930, **484**, 245.

[8] L. G. Cannell, *J. Amer. Chem. Soc.*, 1957, **79**, 2932.

[9] A. R. Butler and A. P. Sanderson, *J.C.S. Perkin II*, 1972, 989.

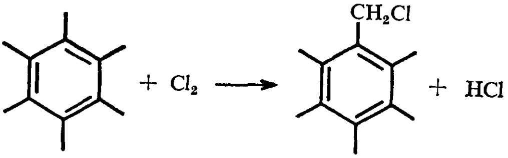
Table 1 ipso *Rate factors* (i_f^R) *for some electrophilic substitutions*

Reaction	R	i_f^R	*Ref.*
Protodesilylation	Me_3Si	*ca.* 10^5	*a*
Bromodesilylation	Me_3Si	*ca.* 10^8	*a*
Diazodesilylation	Me_3Si	< 1	*a*
Protodeboronation	$B(OH)_2$	*ca.* 4	*b*
Bromodemethylation	Me	0.29	*c*
Bromode-t-butylation	Bu^t	0.25	*c*
Bromine exchange	Br	$< 2 \times 10^{-7}$	*c*
Protodecarboxylation	CO_2H	2×10^{-3}	*d*
Nitrodehalogenation	I	0.18	*e*
	Br	0.079	*e*
	Cl	0.061	*e*
Diazodehalogenation	I	0.149	*f*
	Br	0.0089*	*f*
	Cl	0.0070	*f*

* Apparent *ipso*-factor, see text and ref. *f*.

[a] C. Eaborn, 'Organosilicon Compounds', Butterworths, London, 1960; [b] H. G. Kuivila and K. V. Nahabedian, *J. Amer. Chem. Soc.*, 1961, **83**, 2159; [c] E. Baciocchi and G. Illuminati, *J. Amer. Chem. Soc.*, 1967, **89**, 4017; [d] J. L. Longridge and F. A. Long, *J. Amer. Chem. Soc.*, 1968, **90**, 3092; C. L. Perrin and G. A. Skinner, *J. Amer. Chem. Soc.*, 1971, **93**, 3389; [f] P. B. Fischer and H. Zollinger, *Helv. Chim. Acta*, 1972, **55**, 2139.

appear to be electrophilic reactions.[6,10] Thus hexamethylbenzene and molecular chlorine react together rapidly in acetic acid, in the absence of light and catalyst, to give mainly chloromethylpentamethylbenzene (3);[10a, 11] it is known that



(3)

reaction by a free-radical mechanism under similar conditions occurs only slowly. The kinetic orders and relative reactivities observed with other hexa-substituted benzenes (C_6Me_5X) suggest that the slow step in side-chain chlorination is electrophilic in character. The relative rates given in Table 2 show the similarities between side-chain reactions and conventional electrophilic substitutions.

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[10] (*a*) E. Baciocchi and G. Illuminati, *Tetrahedron Letters*, 1962, 637; (*b*) G. Illuminati and F. Stegel, *Ricerca scient.*, 1964, **34**, 458; (*c*) E. Baciocchi and G. Illuminati, *Ricerca scient.*, 1964, **34**, 462.

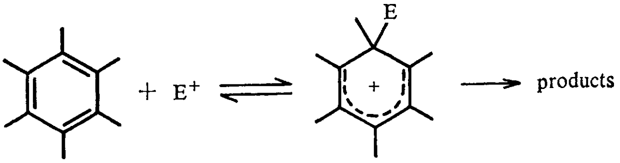
[11] E. Baciocchi, A. Ciana, G. Illuminati, and C. Pasini, *J. Amer. Chem. Soc.*, 1965, **87**, 3953.

Table 2 *Relative rates for some different chlorination reactions*[a]

Reaction	k_{Me}/k_{Cl}	k_{Me}/k_{CN}
Substitution (side-chain), C_6Me_5X	*ca.* 3×10^3	*ca.* 1.4×10^6
Electrophilic substitution (nuclear), C_6H_5X	0.8×10^3	12.8×10^6
Radical substitution (side-chain), C_6Me_5X	2.2	4.3

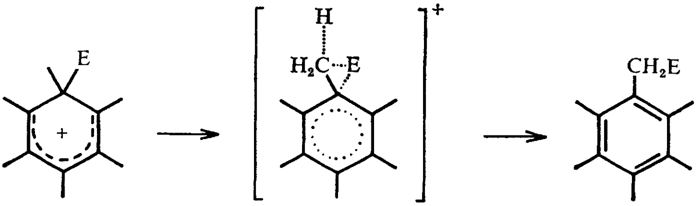
[a] E. Baciocchi, A. Ciana, G. Illuminati, and C. Pasini, *J. Amer. Chem. Soc.*, 1965, **87**, 3953.

The kinetics of the reactions of hexamethylbenzene with bromine in acetic acid[10c,12] and with iodine monochloride in carbon tetrachloride[13] are also of the forms expected for electrophilic processes. The similarities between side-chain and conventional electrophilic substitutions have led to the suggestion that the slow step in the former type of reaction is the formation of a σ-complex. It is assumed that an electrophile may initially attack any activated position of the aromatic system (Scheme 1), regardless of whether a substituent is present and regardless of whether a nuclear displacement will subsequently occur. Little is known about the steps following the slow step, although several mechanisms have been suggested for the formation of side-chain products.[6,10c,11]



Scheme 1

In one view the electrophile migrates to the methyl group attached to the position initially attacked (Scheme 2); a process analogous to the quinobenzilic rearrangement observed with many dienones.[14] Another suggestion (Scheme 3) is that the electrophile migrates to an *ortho*-methyl group. Since the σ-complex



Scheme 2

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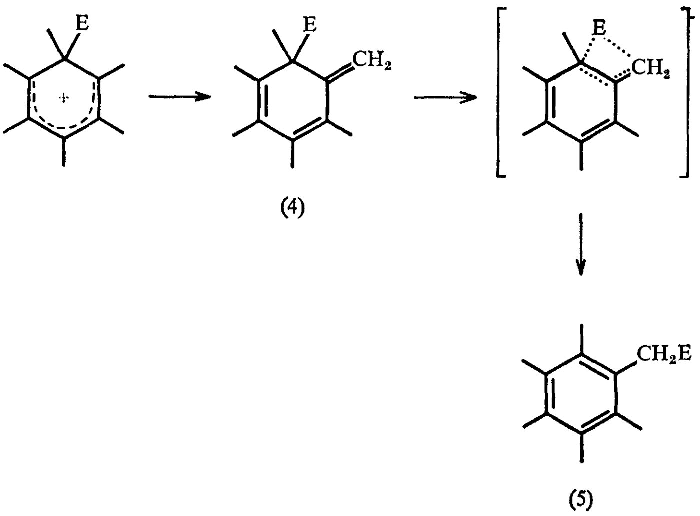
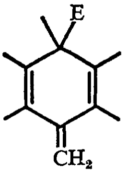
[12] E. Baciocchi, M. Casula, G. Illuminati, and L. Mandolini, *Tetrahedron Letters*, 1969, 1275.
[13] R. M. Keefer and L. J. Andrews, *J. Org. Chem.*, 1966, **31**, 541
[14] V. V. Ershov, A. A. Volod'kin, and G. N. Bogdanov, *Russ. Chem. Rev.*, 1963, **32**, 75.

is an acidic species,[15] it first loses a proton to give (4) which then rearranges to give side-chain product (5). Both mechanisms assume that the rearrangement is intramolecular in order to explain the high retention of halogen that is observed. The chlorination of hexamethylbenzene in acetic acid gives mainly chloromethylpentamethylbenzene and only a small amount (*ca.* 5%) of solvolysis product, apparently formed by solvent capture of a reaction intermediate.[11] Bromination under the same conditions gives bromomethylpentamethylbenzene with no evidence of accompanying solvolysis.[10c] It has been pointed out[11] that the greater tendency for retention in the case of bromine is in the same order as the ability of the halogens to form bridged intermediates. The small amount of solvolysis accompanying chlorination, however, indicates that reaction with an external reagent can compete with the rearrangement.



Scheme 3

Proton loss from the σ-complex can lead to (6),[10c] but (4) is thought to be the



(6)

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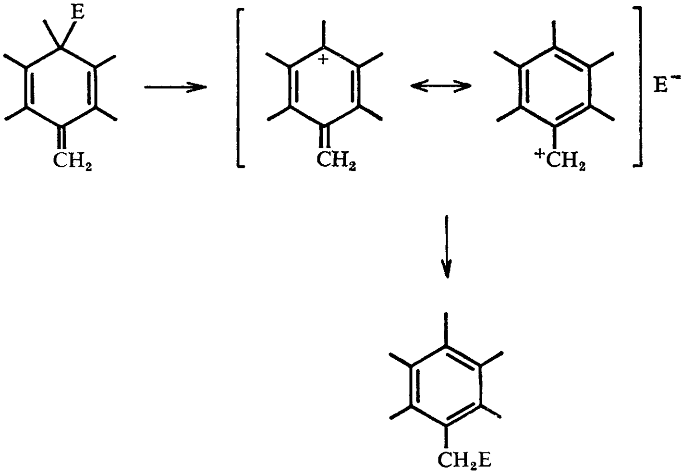
[15] W. von E. Doering, M. Saunders, H. G. Boyston, H. W. Erhart, E. F. Wadely, W. R. Edwards, and G. Laber, *Tetrahedron*, 1958, **4**, 178.

more probable intermediate, presumably because rearrangement of (6) is expected to be an intermolecular process and so does not explain the high retention of halogen. However, under the usual reaction conditions it is probable that the ionization of (6), or (4), does not lead to kinetically free (*i.e.* fully dissociated) ions;[16] rearrangement may then occur at an ion-pair stage with no appreciable intervention by external nucleophiles (Scheme 4), although such intervention (by anion exchange) need not be totally excluded.



Scheme 4

Some support for ionic intermediates in the rearrangement comes from the observation that in the chlorination of hexaethylbenzene[17] the amount of solvolysis accompanying side-chain substitution (*ca.* 15%) is significantly larger than the 5% found in the case of hexamethylbenzene. This difference can be explained in terms of the greater stability of the secondary carbonium ion involved in the former rearrangement, which provides more opportunity for interference by external nucleophiles.

There is no direct evidence at present about which reaction pathway is important in side-chain halogenation; kinetic arguments are inapplicable, and product studies are ambiguous. Thus in the chlorination of isodurene, substitution occurs almost exclusively in the methyl group at the 5-position (7).[18] Of the σ-complexes possibly involved, (8) and (9), in which the positions attacked are both activated by two *ortho*-methyl groups and one *para*-methyl group, appear to be the most likely. Such a consideration seems to eliminate the mechanism

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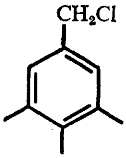
[16] S. Winstein, B. Appel, R. Baker, and A. Diaz, *Chem. Soc. Special Publ.*, No. 19, 1965, p. 109.

[17] G. Illuminati, L. Mandolini, E. M. Arnett, and R. Smoyer, *J. Chem. Soc.* (*B*), 1971, 2206.

[18] G. Illuminati, L. Mandolini, and A. Patara, *Tetrahedron Letters*, 1972, 4161.

involving rearrangement into the *gem*-methyl group, but does not distinguish between the other possibilities.



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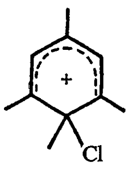

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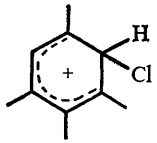

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4 Electrophilic Addition Accompanying Halogenation

Addition is known to accompany the chlorination and bromination of many polycyclic aromatic hydrocarbons.[19] Most examples refer to chlorination by molecular chlorine in acetic acid,[20] although other solvents have been used,[20c] and other chlorinating agents, such as sulphuryl chloride[21] and hypochlorous acid,[22] have been investigated. Fewer results are available for bromination, but the conditions studied include molecular bromine in methanol,[23] in aqueous acetic acid,[24] and in carbon tetrachloride.[25]

A general difficulty in studying these additions arises because the initial product often undergoes further reactions, leading to complicated products and product mixtures.[19] This difficulty may be minimized by a suitable choice of substrate, such that the structure limits the nature of the products obtained. The chlorination of phenanthrene by molecular chlorine in acetic acid shows second-order kinetics and gives the following mixture of products:[20c] (12), 35%; (13), 38%; (14), 10%; (15), 5%; (16), 12%. The reaction shown in Scheme 5 has been proposed.[19]

The addition of lithium chloride increases the amount of *trans*-dichloride (14) but does not affect appreciably the amount of *cis*-dichloride (13). The addition of sodium acetate increases the amount of acetoxy-chloride products and also increases the ratio of *cis*- to *trans*-dichloride. These effects are readily explained if two intermediates are assumed to be involved in the reaction. Capture of (11)

[19] P. B. D. de la Mare and R. Bolton, 'Electrophilic Addition to Unsaturated Systems', Elsevier, Amsterdam, 1966.

[20] (*a*) P. B. D. de la Mare, M. D. Johnson, J. S. Lomas, and V. Sanchez del Olmo, *J. Chem. Soc.* (*B*), 1966, 827; (*b*) P. B. D. de la Mare, G. Cum, and M. D. Johnson, *J. Chem. Soc.* (*C*), 1967, 1590; (*c*) P. B. D. de la Mare, A. Singh, E. A. Johnson, R. Koenigsberger, J. S. Lomas, V. Sanchez del Olmo, and A. Sexton, *J. Chem. Soc.* (*B*), 1969, 717.

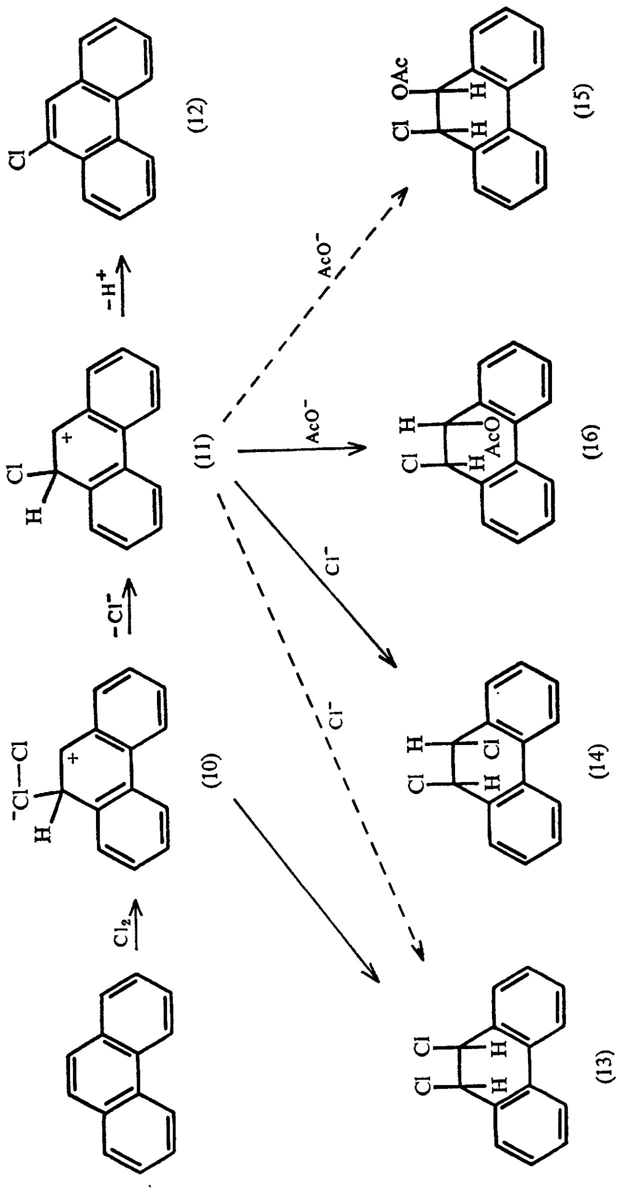
[21] (*a*) R. Bolton, P. B. D. de la Mare, and H. Suzuki, *Rec. Trav. chim.*, 1966, **85**, 1206; (*b*) P. B. D. de la Mare and H. Suzuki, *J. Chem. Soc.* (*C*), 1967, 1586.

[22] P. B D. de la Mare and L. Main, *J. Chem. Soc.* (*B*), 1971, 90.

[23] J. van der Linde and E. Havinga, *Rec. Trav. chim.*, 1965, **84**, 1047.

[24] L. Altshuler and E. Berliner, *J. Amer. Chem. Soc.*, 1966, **88**, 5837.

[25] F. R. Mayo and W. B. Hardy, *J. Amer. Chem. Soc.*, 1952, **74**, 911.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⁻Cl—Cl
H
+
(10)
-Cl⁻
H
Cl
+
(11)
-H⁺
Cl
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AcO⁻
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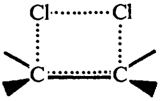
H
(13)
Cl
H
H
Cl
(14)
Cl
OAc
H
H
(15)
Cl
H
H
AcO
(16)

Scheme 5

by added nucleophiles gives predominantly, though not necessarily entirely, *trans*-addition products. The insensitivity of the yield of *cis*-dichloride (13) to the presence of added salts indicates that the major part of this product is produced from another intermediate (10) without the intervention of external reagents. Although *cis*-addition could be a one-step reaction involving a cyclic transition state (17), the dependence of the rate of addition on the polarity of the solvent indicates that a transition state with ionic character is involved.[20c] This is represented by (10), but the ion pair (18) might be an alternative representation; internal return[16] from (18) could give *cis*-dichloride, whereas further dissociation would give (11).



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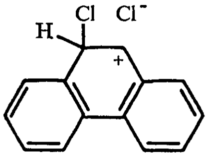

(18)

Similar considerations can be used to explain the chlorination of naphthalene, although in this case there is the additional complication of the further reaction of the initial products.[20a,c] Addition accompanies the chlorination of 1-methylnaphthalene, and in this case a small amount of side-chain substitution (*ca.* 6%) also occurs.[20b]

5 Other Non-conventional Processes in Halogenation

The bromination of 1,3,5-tri-t-butylbenzene in acetic acid is accompanied by acetoxylation, but the latter reaction does not occur in the absence of bromination. The results suggest that bromination and acetoxylation involve common reaction intermediates, and a mechanism (Scheme 6) including addition–elimination pathways has been proposed.[26] The yield of aryl acetates is increased by the addition of sodium acetate, which suggests that acetoxylation depends on the ability of acetate ions to capture these intermediates [(19) and (20)]. In the case of the σ-complex (19) capture by acetate ion competes with proton loss, which implies a relatively slow proton transfer in the pathway leading to (21), a circumstance confirmed by the observation of a primary hydrogen isotope effect.[26,27] The formation of products (22) and (23) shows that the t-butyl group is a good electrofugal leaving group under these conditions. This example illustrates how conventional and non-conventional processes can be closely related.

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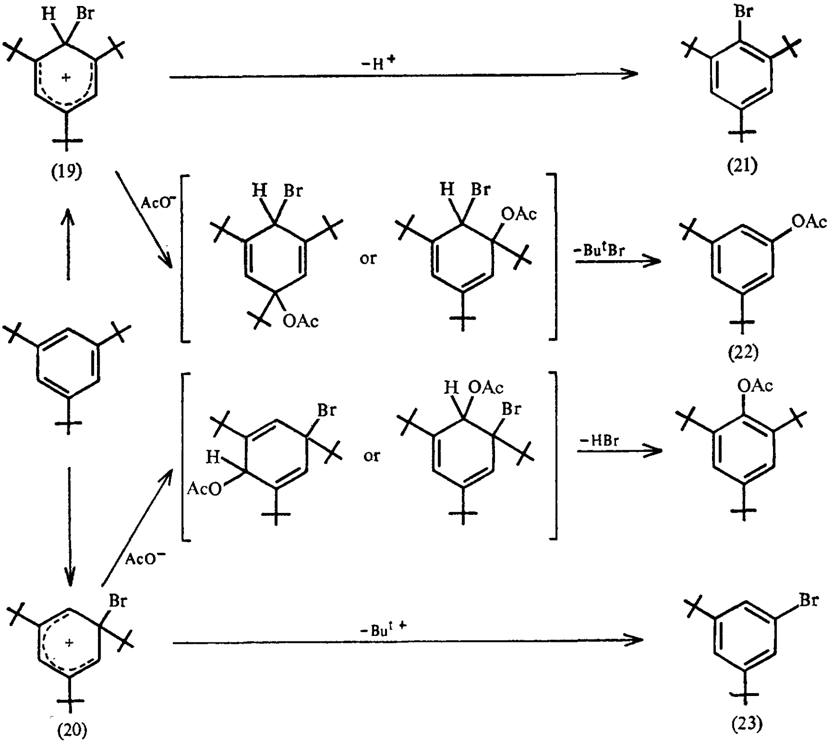
[26] P. C. Myhre, G. S. Owen, and L. L. James, *J. Amer. Chem. Soc.*, 1968, **90**, 2115.
[27] P. C. Myhre, *Acta Chem. Scand.*, 1960, **14**, 219.



Scheme 6

6 Non-conventional Processes in Nitration: Side-chain Substitution

Reports of anomalous nitrations are to be found in the early literature.[28,29] Recently, interest has revived in certain of these reactions, particularly in substitution occurring in an aromatic side-chain. The results of product and kinetic studies indicate that these reactions, like the side-chain halogenations, involve ionic rather than radical processes. Thus the nitration of substituted pentamethylbenzenes (24) by fuming nitric acid in dichloromethane at low temperatures exhibits high positional selectivity.[30] Substitution (to give side-chain nitrates) takes place almost exclusively at the *ortho*-position (25) with the strongly electron-withdrawing substituents X = NO_2, CO_2H, or CO_2Me.[30b] With the substituents X = Cl, Br, or I some substitution occurs at the *meta*-position, in

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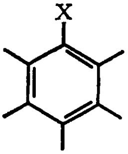
[28] D. V. Nightingale, *Chem. Rev.*, 1947, **40**, 117.

[29] A. V. Topchiev, 'Nitration of Hydrocarbons and other Organic Compounds', Pergamon, London, 1959.

[30] (*a*) H. Suzuki, *Bull. Chem Soc. Japan*, 1970, **43**, 481; (*b*) H. Suzuki and K. Nakamura, *ibid.*, 1971, **44**, 227.



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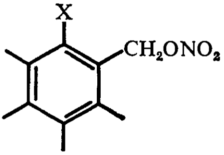


(25)

addition to predominant *ortho*-substitution, whereas with the electron-releasing groups X = OH, OMe, or NHCOMe substitution occurs mainly at the *meta*-position (although complications arise owing to reactions involving the substituents).[30b]

The kinetic data for the substituted pentamethylbenzenes also support the idea of an ionic (electrophilic) reaction pathway and are given in Table 3. The

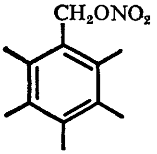
Table 3 *Relative rates of nitration for some side-chain and nuclear substitutions*[a]

Compound	X			
	Me	H	Br	NO_2
C_6Me_5X	1	2×10^{-2}	4×10^{-4}	3×10^{-6}
C_6H_5X	1	10^{-1}—10^{-2}	10^{-3}	10^{-5}—10^{-8}

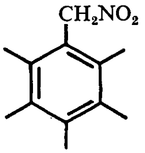
[a] K. Nakamura, *Bull. Chem. Soc. Japan*, 1971, **44**, 133.

similarities between the substituent effects in the series C_6Me_5X and C_6H_5X indicate that side-chain substitution and conventional nuclear substitution are mechanistically similar and suggest that both processes have similar rate-controlling steps, presumably the formation of a σ-complex (*cf.* side-chain halogenation). The stabilities of the σ-complexes might account for the positional selectivity observed,[31] although this has also been discussed in terms of the slow step in proton removal from the side-chain.[32]

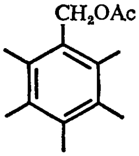
One interesting feature of side-chain nitrations is that the products obtained often depend upon the reaction conditions. The nitration of hexamethylbenzene by fuming nitric acid in dichloromethane at 5 °C gives a variety of products which mostly appear to be derived from the initial product (26).[33] Nitration by



(26)



(27)



(28)

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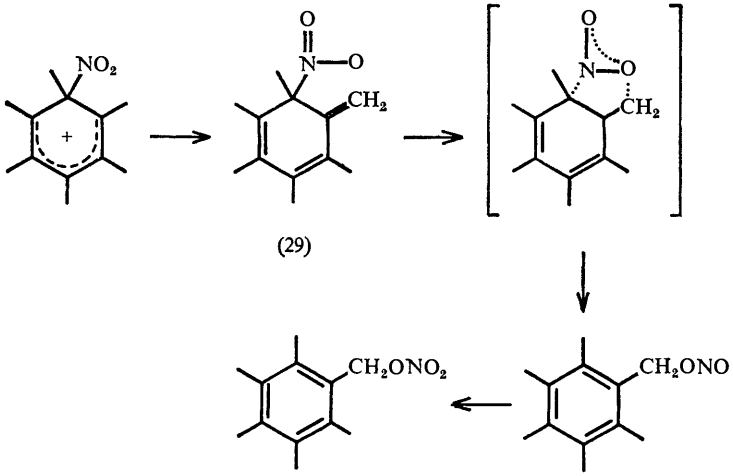
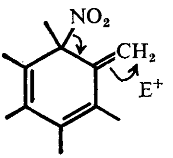
[31] S. R. Hartshorn and K. Schofield, *Progr. Org. Chem.*, 1973, **8**, 278.
[32] K. Nakamura, *Bull. Chem. Soc. Japan*, 1971, **44**, 133.
[33] H. Suzuki, *Bull. Chem. Soc. Japan*, 1970, **43**, 879.

an equimolar amount of nitric acid in acetic anhydride at 0 °C, however, gives (27) as the major product, together with smaller amounts of the acetate (28) and the nitrate (26).[34]

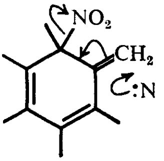
It has been suggested that the nitrate is formed by an intramolecular cyclic rearrangement (Scheme 7), in which the initially formed nitrite ester is readily oxidized to nitrate under the reaction conditions, and that the nitro-compound is formed by some other mechanism.[34] Presumably the importance of the different reaction pathways depends upon the substrate and the reaction conditions. The formation of acetate (28) indicates that side-chain substitution can involve an external reagent, as for example the capture of the cyclohexadiene intermediate (29) by an electrophile (30) or nucleophile (31). Cyclohexadiene intermediates with the *ortho*-quinoid structure have been considered, although it has been pointed out that those with the *para*-quinoid structure (32) might be expected to be more likely.[35]



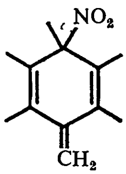
Scheme 7



(30)



(31)



(32)

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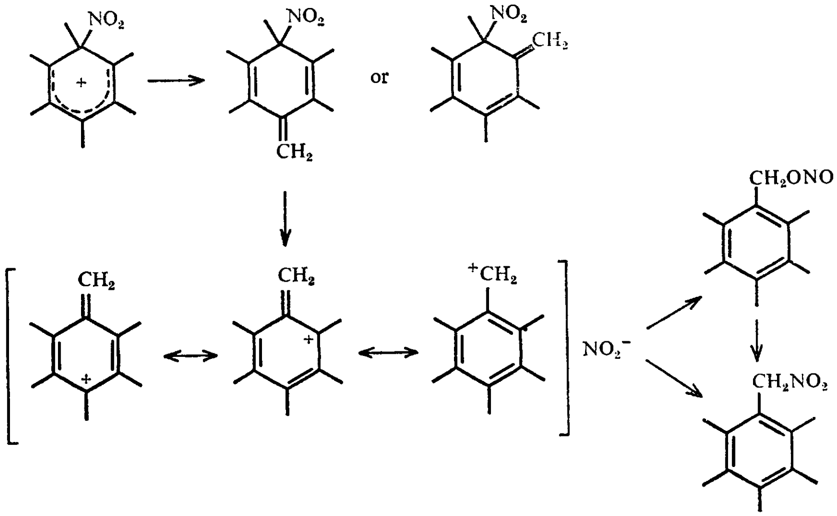
[34] R. Astolfi, E. Baciocchi, and G. Illuminati, *Chimica e Industria*, 1971, **53**, 1153.
[35] E. Hunziker, J. R. Penton, and H. Zollinger, *Helv. Chim. Acta*, 1971, **54**, 2043.

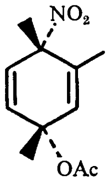
There is some evidence to suggest that the nitro-compound is only formed in the presence of a nitrating agent (see next section) and thus involves electrophilic attack; however, a nucleophilic pathway cannot be excluded on the present evidence. One such mechanism involves rearrangement within an ion pair (Scheme 8);[32,36] since the nitrite anion is an ambident nucleophile[37] both side-chain nitrates and nitro-compounds can be produced. Although there has been much speculation, little is actually known about the reaction pathways leading to side-chain products.



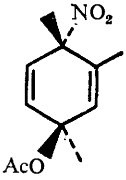
Scheme 8

7 Non-conventional Processes in Nitration: Addition–Elimination

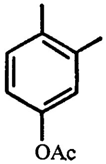
The moderately stable *cis*- and *trans*-acetoxynitrodimethylcyclohexadienes (33) and (34) have been isolated during the nitration of *o*-xylene by nitric acid in



(33)



(34)



(35)

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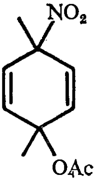
[36] H. Suzuki, K. Nakamura, and M. Takeshima, *Bull. Chem. Soc. Japan*, 1971, **44**, 2248.

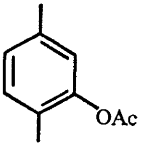
[37] D. H. Rosenblatt, W. H. Dennis, jun., and R. D. Goodin, *J. Amer. Chem. Soc.*, 1973, **95**, 2133.

acetic anhydride.[38] The structures of these adducts have been determined by spectroscopic methods and it is found that the characteristic absorptions observed in the ^{1}H n.m.r. spectrum in the region 3.5—4.6τ provide a particularly convenient method for detecting the formation of adducts in nitrating solutions.

The adducts (33) and (34) readily decompose, either on heating or in aqueous acidic media, with loss of nitrous acid to give the aryl acetate (35). It therefore appears that the acetoxylation that accompanies the nitration of many methylbenzenes in acetic anhydride occurs by an addition–elimination pathway.[31,39] In the case of *p*-xylene, the adduct* (36) isolated from the nitration mixture is found to decompose, by an apparently intramolecular mechanism, to give acetate (37) by a 1,2-migration of the acetoxy-group.[38]



(36)



(37)

A number of adducts have now been isolated (Table 4) and still others have been detected as reaction intermediates. Two features appear to be common to all of the adducts: first, the nitro-group is always attached to a ring position substituted by a methyl group or other alkyl side-chain; secondly, only 1,4-adducts are formed and these occur as pairs of *cis*- and *trans*-isomers. This last observation suggests that a two-step mechanism is involved in adduct formation.

The extent of acetoxylation accompanying nitration depends upon the structure of the aromatic substrate.[39] Appreciable amounts of aryl acetates are produced with substrates such as *o*-xylene, *p*-xylene, and hemimellitene, but not with those such as toluene and *m*-xylene. There is no reason to doubt that, in general, ring nitration occurs by conventional electrophilic substitution, and acetoxylation probably by addition–elimination. The proportion of acetoxylation to nitration can therefore be explained in terms of the extent to which the formation of a σ-complex by *ipso*-attack competes with the formation of conventional σ-complexes (Scheme 9).[31,39] Apparently the former process only provides an important reaction pathway if the *ipso*-position concerned is activated by at least one *ortho*- or *para*-methyl group or an equivalent activating substituent.

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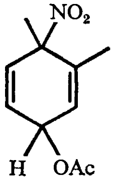
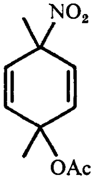
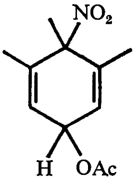
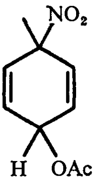
* In the following it is implicit that all adducts occur as *cis*/*trans*-isomers.

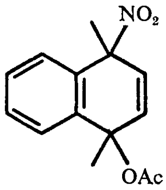
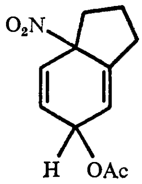
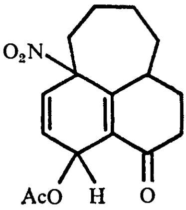
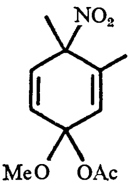
[38] D. J. Blackstock, J. R. Cretney, A. Fischer, M. P. Hartshorn, K. E. Richards, J. Vaughan, and G. J. Wright, *Tetrahedron Letters*, 1970, 2793.

[39] D. J. Blackstock, A. Fischer, K. E. Richards, and G. J. Wright, *Austral. J. Chem.*, 1973, **26**, 775.

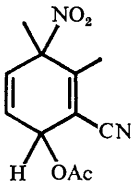
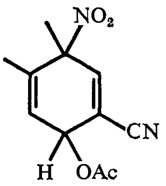
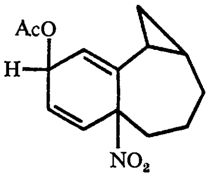
Table 4 1,4-*Adducts isolated from nitrations in acetic anhydride*

Ref. *a*, *b* *b* *b* *c*

Ref. *d* *e* *f* *g*

Ref. *h* *h* *i*

[a] D. J. Blackstock, A. Fischer, K. E. Richards, J. Vaughan, and G. J. Wright, *Chem. Comm.*, 1970, 641; [b] D. J. Blackstock, J. R. Cretney, A. Fischer, M. P. Hartshorn, K. E. Richards, J. Vaughan, and G. J. Wright, *Tetrahedron Letters*, 1970, 2793; [c] A. Fischer and J. N. Ramsay, *J.C.S. Perkin II*, 1973, 237; [d] A. Fischer and A. L. Wilkinson, *Canad. J. Chem.*, 1972, **50**, 3988; [e] A. Fischer, C. C. Greig, A. L. Wilkinson, and D. R. A. Leonard, *Canad. J. Chem.*, 1972, **50**, 2211; [f] A. Fischer and D. R. A. Leonard, *Canad. J. Chem.*, 1972, **50**, 3367 ;[g] A. Fischer and D. R. A. Leonard, *J.C.S. Chem. Comm.*, 1973, 300; [h] A. Fischer and C. C. Greig, *J.C.S. Chem. Comm.*, 1973, 396; [i] R. C. Hahn and M. B. Groen, *J. Amer. Chem. Soc.*, 1973, **95**, 6128.

Addition–elimination is also thought to provide an important pathway for side-chain substitution. The nitration of 1,4-dimethylnaphthalene by nitric acid in acetic anhydride gives (38). If the reaction is carried out at −40 °C and the reaction mixture quenched at that temperature with ammonia, the main product, isolated by low-temperature chromatography over alumina, is the adduct (39).[40] This decomposes in acetic acid at 30 °C to give 1,4-dimethyl-2-naphthyl acetate

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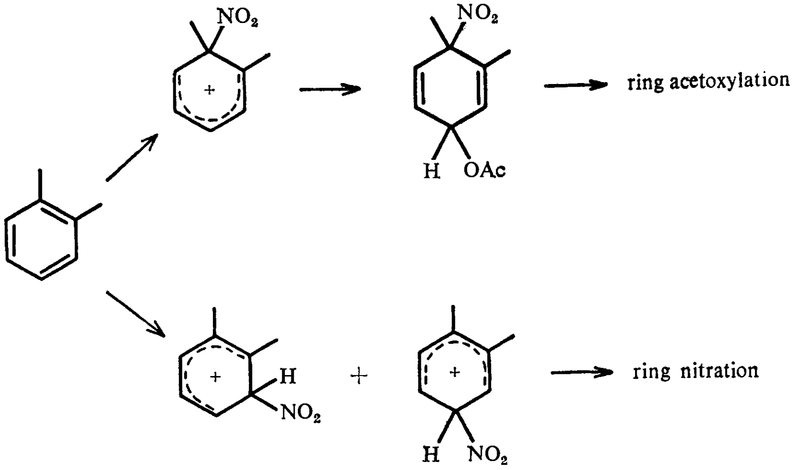
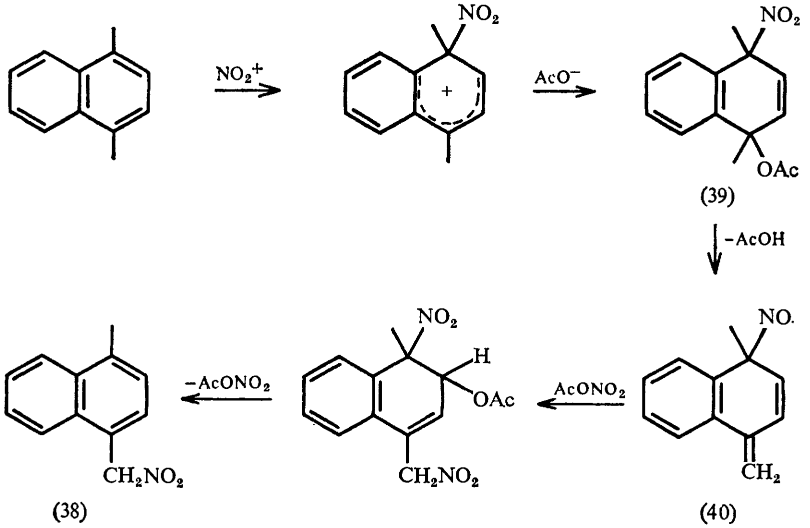
[40] A. Fischer and A. L. Wilkinson, *Canad. J. Chem.*, 1972, **50**, 3988.



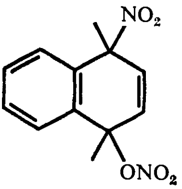
Scheme 9

(*cf.* behaviour of *p*-xylene) together with small amounts of the nitromethyl compound (38). In contrast, the adduct decomposes in acetic anhydride containing nitric acid to give (38) as the main product. The mechanism shown in Scheme 10 has been proposed for the side-chain nitration.



Scheme 10

When the nitration is performed at −60 °C an adduct is obtained whose n.m.r. spectrum is similar to, but not identical with, that given by (39); the structure (41) has been suggested.[40] As the temperature increases the adducts (39) and (41) are found to interconvert. It is relevant that nitration by nitric acid in deuteriated dichloromethane, in the absence of acetic anhydride, also gives the nitromethyl product (38), and the adduct involved is presumed to be (41). On the basis of these observations it is not certain which adduct, (39) or (41), is a necessary intermediate.



(41)

Some uncertainty also surrounds the supposed intermediate (40). Contrary to earlier suggestions,[41] there now appears to be no evidence for the formation of (40).[40] This observation does not necessarily exclude such an intermediate, but it does imply that if involved it must be more reactive than other intermediates in the reaction pathway.

The nitration of 1,4-dimethylnaphthalene in acetic anhydride,[40,42] in nitromethane,[42] and in dichloromethane[43] gives the side-chain nitro-compound. The nitration of hexamethylbenzene in acetic anhydride also gives mainly the nitro-compound, but in dichloromethane the nitrate is formed. As already mentioned, the different products might be produced by different reaction pathways, the nitrate by an intramolecular mechanism and the nitro-compound by an intermolecular mechanism, *e.g.* the addition–elimination pathway, although other possibilities have been considered. The difference in behaviour between hexamethylbenzene and 1,4-dimethylnaphthalene then presumably arises from a structural effect on the partitioning of some reaction intermediate between the different pathways. Some clarification of the processes involved is required.

8 The Formation of Dienones and Quinones

Nitration of the 4-X-*o*-xylenes and of the 5-X-hemimellitenes (42; X = Br, OAc, or OMe, R = H or Me) with nitric acid in acetic anhydride gives the corresponding nitrocyclohexadienones (43) in addition to conventional substitution products.[44] In the case of 3,4-dimethylanisole, the adduct (44) has been isolated and shown to decompose readily to 3,4-dimethyl-4-nitrocyclohexa-2,5-

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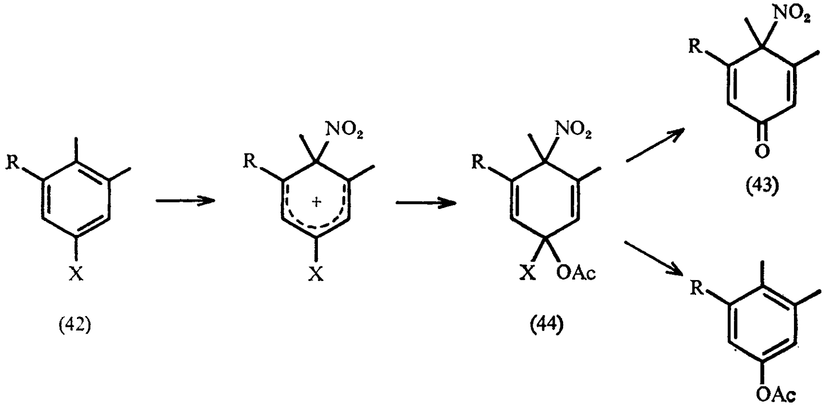
[41] R. Robinson, *J. Chem. Soc.* (*B*), 1970, 1289.

[42] R. Robinson and H. W. Thompson, *J. Chem. Soc.*, 1932, 2015.

[43] H. Suzuki and K. Nakamura, *Bull. Chem. Soc. Japan*, 1971, **44**, 303.

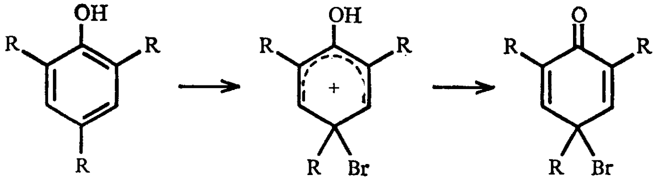
[44] D. J. Blackstock, M. P. Hartshorn, A. J. Lewis, K. E. Richards, J. Vaughan, and G. J. Wright, *J. Chem. Soc.* (*B*), 1971, 1212.

dien-1-one.[45] In the absence of the substituent X the only major products, apart from those of conventional substitution, are aryl acetates.[39] Apparently the mode of decomposition of the adduct (44) depends upon the nature of the substituent X. The small amounts of nitrodienones and cyclohexenones sometimes obtained as by-products in other nitrations[46] can probably be accounted for in similar terms, although in some cases the adduct thought to be involved has a structure analogous to (41) rather than to (44).[46a,d]



(42)
(44)
(43)

Dienones are frequently obtained as the products of electrophilic reactions involving phenols and their derivatives.[14] The bromination of 2,4,6-trialkylphenols by molecular bromine in aqueous acetic acid, for example, gives high yields (70—90%) of the corresponding bromocyclohexadienones (Scheme 11).[47] The yield and the stability of the dienone both increase with the size of the



Scheme 11

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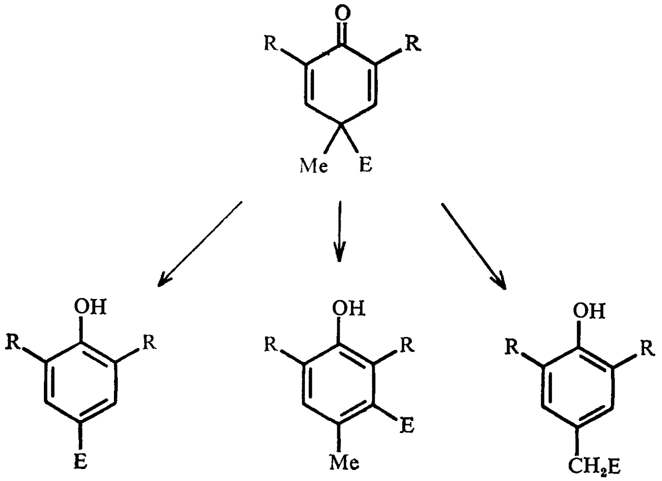
[45] A. Fischer and D. R. A. Leonard, *J.C.S. Chem. Comm.*, 1973, 300.

[46] (*a*) H. Suzuki, M. Sawaki, and R. Sakimoto, *Bull. Chem. Soc. Japan*, 1972, **45**, 1834; (*b*) H. Suzuki and K. Nakamura, *J.C.S. Chem. Comm.*, 1972, 340; (*c*) H. Suzuki, M. Sawaki, and R. Sakimoto, *Bull. Chem. Soc. Japan*, 1972, **45**, 1515; (*d*) H. Suzuki and K. Nakamura, *Bull. Chem. Soc. Japan*, 1972, **45**, 1270; (*e*) A. J. M. Reuvers, F. F. van Leeuwen, and A. Sinnema, *J.C.S. Chem. Comm.*, 1972, 828.

[47] A. A. Volod'kin and V. V. Ershov, *Bull. Acad. Sci., U.S.S.R.*, 1962, 1039.

groups R; with bulky groups (*e.g.* t-butyl or t-pentyl) dienones may be isolated when only the 2- and 6-positions are substituted.[48] Similar results have been obtained for nitration, and nitrocyclohexadienones are readily formed under various reaction conditions.[49]

In many reactions dienones, although not actually isolated, are thought to be reaction intermediates.[14,50] Several modes of decomposition seem probable, including nuclear substitution, substitution with rearrangement, and side-chain substitution (Scheme 12). The last-mentioned reaction is referred to as the quinobenzilic rearrangement and is usually considered to be intramolecular, but some evidence points to an intermolecular pathway under certain conditions.[50a,51]



Scheme 12

Quinones are by-products in many electrophilic reactions,[52] particularly in the nitration of polyphenolic compounds, a circumstance which may be connected with the fact that the reaction conditions employed are favourable for oxidative side reactions.[14] However, the formation of quinones may be an indication that non-conventional electrophilic pathways are involved. Thus the major product from the nitration of 5-X-1,2,3-trimethoxybenzene (X = OMe or OAc) by nitric acid in acetic anhydride is the quinone (45) produced by decomposition of the

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[48] A. A. Volod'kin and V. V. Ershov, *Bull. Acad. Sci., U.S.S.R.*, 1962, 1931.

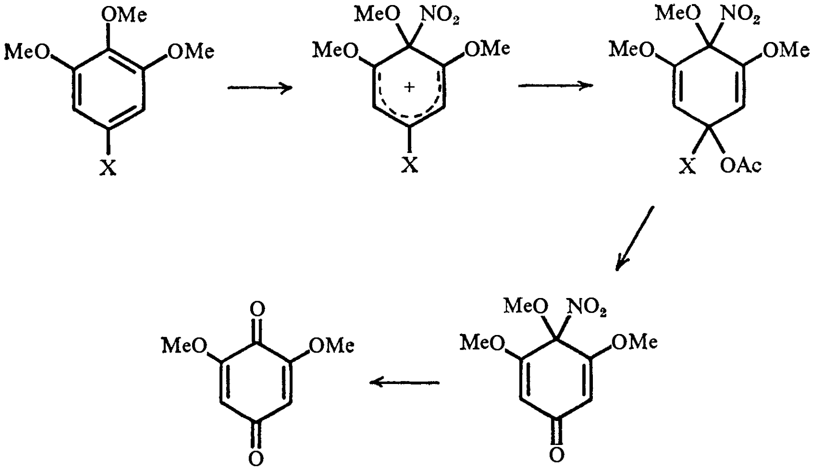
[49] V. V. Ershov and G. A. Zlobina, *Bull. Acad. Sci., U.S.S.R.*, 1963, 1524.

[50] (*a*) V. V. Ershov and A. A. Volod'kin, *Bull. Acad. Sci., U.S.S.R.*, 1962, 1925; (*b*) V. V. Ershov and A. A. Volod'kin, *ibid.*, p. 1935.

[51] G. M. Coppinger and T. W. Campbell, *J. Amer. Chem. Soc.*, 1953, **75**, 734.

[52] (*a*) L. I. Smith and F. J. Dobrovolny, *J. Amer. Chem. Soc.*, 1926, **48**, 1693; (*b*) H. H. Hodgson and J. Nixon, *J. Chem. Soc.*, 1930, 1085; (*c*) C. C. Price and C. Weaver, *J. Amer. Chem. Soc.*, 1939, **61**, 3360; (*d*) K. Ley and E. Müller, *Chem. Ber.*, 1956, **89**, 1402; (*e*) W. F. Gum, M. R. W. Levy, and M. M. Joullie, *J. Chem. Soc.*, 1965, 2282.

dienone (46).[53] A likely mechanism for the formation of (45) therefore involves a non-conventional pathway in which the initial *ipso*-attack of the nitrating agent occurs at a nuclear carbon atom bearing a methoxy-substituent (Scheme 13).



(45) (46)

Scheme 13

9 Coupling Accompanying Electrophilic Substitution

Substituted diphenylmethanes are produced in the nitration of pentamethylbenzene by fuming nitric acid either in chloroform or in dichloromethane,[54] and in the nitration of durene by nitronium hexafluorophosphate in nitromethane.[55] The formation of such compounds may be rationalized in terms of the same types of intermediate used to explain side-chain substitution. A speculative scheme, using pentamethylbenzene as an example, is outlined in Scheme 14; it is assumed that the intermediate involved in side-chain substitution may also react with substrate to give the substituted diphenylmethane.

The positive hydroxylation of polymethylbenzenes by mixtures of peroxytrifluoroacetic acid and boron trifluoride is believed to be an electrophilic process.[56] In addition to the expected phenols, products of rearrangement, disproportionation, and coupling are also frequently obtained. The formation of such products

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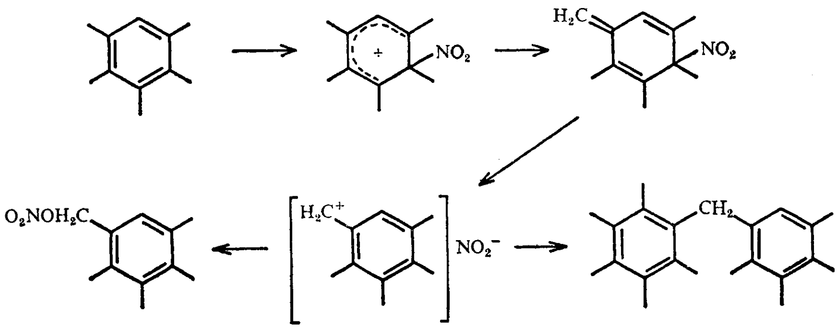
[53] B. A. Collins, K. E. Richards, and G. J. Wright, *J.C.S. Chem. Comm.*, 1972, 1216.

[54] H. Suzuki and K. Nakamura, *Bull. Chem. Soc. Japan*, 1970, **43**, 473.

[55] S. B. Hanna, E. Hunziker, T. Saito, and H. Zollinger, *Helv. Chim. Acta*, 1969, **52**, 1537.

[56] (*a*) C. A. Buehler and H. Hart, *J. Amer. Chem. Soc.*, 1963, **85**, 2177; (*b*) H. Hart and C. A. Buehler, *J. Org. Chem.*, 1964, **29**, 2397; (*c*) H. Hart, C. A. Buehler, A. J. Waring, and S. Meyerson, *J. Org. Chem.*, 1965, **30**, 331.

can again be accounted for by assuming that non-conventional pathways are important.



Scheme 14

Substituted diphenylmethanes have also been reported in the sulphonation of several polysubstituted benzenes under conditions favouring the Jacobsen rearrangement.[57] Thus treatment of 1-chloro-3,4,5,6-tetramethylbenzene with sulphuric acid at room temperature gives chloropentamethylbenzene (by disproportionation) and 3′,4-dichloro-2,2′,3,4′,5,5′,6-heptamethyldiphenylmethane. The formation of diphenylmethanes in this and other electrophilic reactions is of interest in connection with the suggestion that similar compounds may be intermediates in the disproportionation of primary alkylbenzenes under Friedel–Crafts conditions.[58] Diarylalkanes have also been identified among the products of reaction of various monoalkylbenzenes with aluminium chloride[59] and with antimony pentachloride.[60]

Substituted biphenyls are formed as by-products in certain nitrations of alkylbenzenes.[61] The conditions necessary for the optimum yield of biphenyls appear to be the addition of 90% nitric acid to the aromatic at low temperatures (*ca.* −25 °C).[61b] Under such conditions a small amount of 2-nitro-3′,4,4′,5-tetramethylbiphenyl is formed during the nitration of *o*-xylene, in addition to the expected nitroxylenes. The formation of these products of nuclear coupling may be an indication that non-conventional pathways are involved.

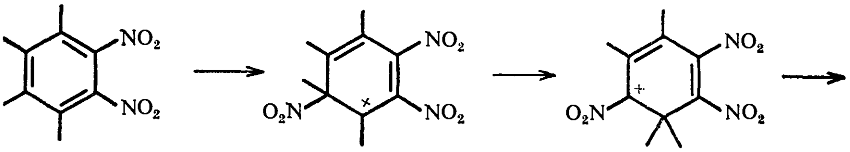
10 Rearrangements Accompanying Electrophilic Substitutions

Rearrangements are of two general types, those involving a change in the structure of the aromatic substrate and those involving the electrophile and

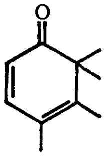
[57] H. Suzuki and Y. Tamura, *Chem. Comm.*, 1969, 244.
[58] A. Streitwieser and L. Reif, *J. Amer. Chem. Soc.*, 1964, **86**, 1988.
[59] R. M. Roberts, A. A. Khalaf, and R. N. Greene, *J. Amer. Chem. Soc.*, 1964, **86**, 2846.
[60] P. Kovacic and A. K. Sparks, *J. Org. Chem.*, 1963, **28**, 972.
[61] I. Puskas and E. K. Fields, (*a*) *J. Org. Chem.*, 1966, **31**, 4204; (*b*) *ibid.*, 1967, **32**, 589.

occurring during the substitution. Among the first type are the well-known migrations of alkyl substituents that occur in Friedel–Crafts and Jacobsen reactions.[62]

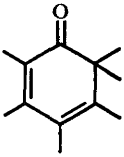
Examples of methyl-group migrations occurring in other electrophilic reactions have been reported more recently in connection with non-conventional pathways. The action of cold fuming nitric acid on 1,2,3,4-tetramethyl-5,6-dinitrobenzene gives a high yield of 2,3,6,6-tetramethyl-2,3,4,5-tetranitrocyclohex-4-enone.[46b] The mechanism proposed for this change (Scheme 15) assumes that the methyl migration occurs after the formation of a non-conventional σ-complex. Such a pathway may also account for the 1,2-methyl migrations observed in the positive hydroxylation of several polymethylbenzenes.[63] Thus the dienone (47) is formed during the hydroxylation of 1,2,3,4-tetramethylbenzene and (48) is formed from hexamethylbenzene.



Scheme 15



(47)



(48)

A more unusual type of behaviour is indicated by the isolation of the products (49) and (50) from the nitration of 2,4,6-tri-t-butyl-1-nitrobenzene.[64] The rearrangement–fragmentations (Scheme 16) are assumed to involve the σ-complex (51) and to be competitive with conventional ring nitration. This mechanism implies that proton loss from (51) be relatively slow, for the non-conventional pathways to compete with the conventional substitution, and indeed the nitration shows a primary hydrogen isotope effect.[65]

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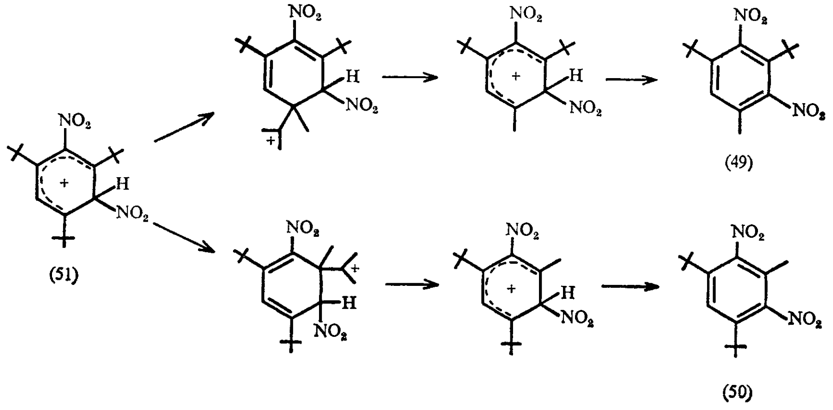
[62] H. J. Shine, 'Aromatic Rearrangements', Elsevier, Amsterdam, 1967.
[63] H. Hart, P. M. Collins, and A. J. Waring, *J. Amer. Chem. Soc.*, 1966, **88**, 1005.
[64] P. C. Myhre, M. Beug, K. S. Brown, and B. Östman, *J. Amer. Chem. Soc.*, 1971, **93**, 3452.
[65] P. C. Myhre, M. Beug, and L. L. James, *J. Amer. Chem. Soc.*, 1968, **90**, 2105.



Scheme 16

The second general type of rearrangement that can occur involves the migration of the electrophile from the nuclear position initially attacked either to another nuclear position or to a side-chain; the latter type of migration has already been discussed. The existence of a pathway involving rearrangement of the electrophile to another ring position may be overlooked, particularly if the final product can also be formed directly by a conventional substitution. However, it is essential to estimate the contribution made by such pathways if reliable information about substituent effects and relative reactivities is to be obtained.

The nitration of *o*-xylene by nitric acid in aqueous sulphuric acid appears to be a normal substitution, although the large change in the isomer proportions as the acidity of the sulphuric acid increases from 50% to 70% is difficult to explain.[66] It has been shown that this change can be accounted for in terms of a contribution from the non-conventional pathway involving the intermediate (52) (Scheme 17).[67] This intermediate can either be captured by the solvent to give phenolic products, or undergo an intramolecular 1,2-migration of the nitro-group to give 3-nitro-*o*-xylene. The former pathway apparently predominates at the lower acidities, whereas rearrangement becomes dominant at higher acidities. The 4-nitro-*o*-xylene is produced only by conventional substitution. The observed change in isomer proportions (3-nitro : 4-nitro) is therefore to be associated with a solvent effect on the partitioning of (52) between solvent capture and rearrangement.

It has also been suggested that some of the product (4-chloro-2-nitroanisole) from the nitration of *p*-chloroanisole is formed by a rearrangement involving a 1,3-migration of the nitro-group.[5b] Similar migrations also seem to be involved

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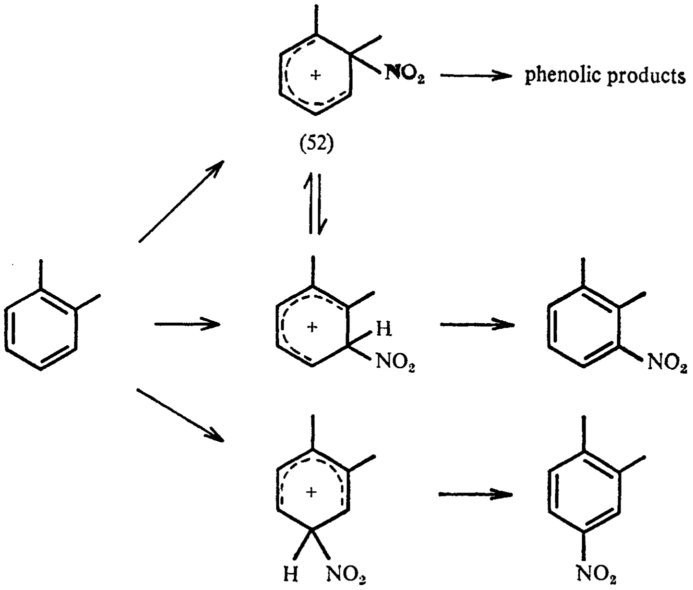
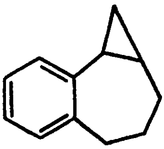
[66] R. G. Coombes and L. W. Russell, *J. Chem. Soc.* (*B*), 1971, 2443.
[67] P. C. Myhre, *J. Amer. Chem. Soc.*, 1972, **94**, 7921.



Scheme 17

in the nitration of (53).[68] Little is known about the mechanism of these migrations except that they appear to be intramolecular,[69,70] and possibly involve successive 1,2-nitro-shifts.[70]



(53)

11 Summary

Electrophilic attack on an aromatic system need not necessarily lead only to the products expected for a conventional substitution. Various non-conventional pathways are available and the examples discussed in this review show that for suitable substrates and reaction conditions products of a surprising variety may be formed.

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[68] R. C. Hahn and M. B. Groen, *J. Amer. Chem. Soc.*, 1973, **95**, 6128.
[69] A. Fischer and C. C. Grieg, *J.C.S. Chem. Comm.*, 1973, 396.
[70] G. A. Olah, H. C. Lin, and Y. K. Mo, *J. Amer. Chem. Soc.*, 1972, **94**, 3667.

The reactions considered can all be rationalized in terms of the initial formation of a σ-complex which can then react by any of a number of available pathways. In outline these seem to be fairly well established, although many details require further clarification.

The establishment of non-conventional reactions has important implications concerning quantitative studies of aromatic reactivity. The demonstration that products of conventional ring substitution can be formed by addition–elimination mechanisms and by a mechanism involving rearrangement of the electrophile suggests that care should always be taken when interpreting results, even for seemingly conventional substitutions. The recognition that an electrophile can attack a substituted ring position also emphasizes the need to consider substituent effects at the *ipso*-position.