ACCOUNTS OF CHEMICAL RESEARCH

VOLUME 7 NUMBER 11 NOVEMBER, 1974

Pathways in Electrophilic Aromatic Substitutions. Cyclohexadienes and Related Compounds as Intermediates in Halogenation

Peter B. D. de la Mare

Chemistry Department, University of Auckland, Auckland, New Zealand

Received April 22, 1974

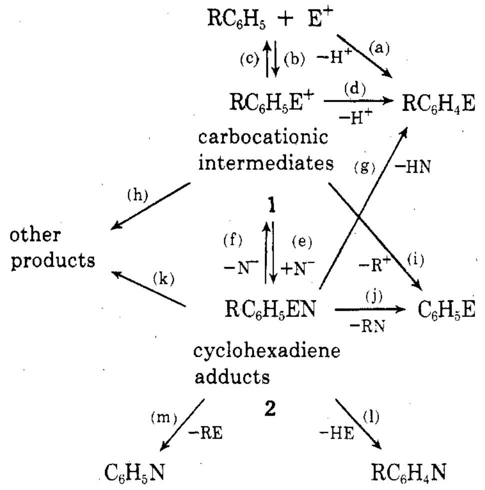
Although an exact definition of the term "aromatic" is elusive,[1] most chemists will acknowledge that derivatives of benzene, pyridine, pyrrole, of naphthalene, quinoline, and indole, and of ring systems structurally related to these in obvious ways may be included in this classification. Electrophilic substitution into such systems is familiar to all students of chemistry. The orientational aspects (or "regiospecificity"), and various experimental approaches toward the identification of the electrophilic reagents available for particular reactions, are equally well known; for example

$$\begin{gathered} 2H_2SO_4 + HNO_3 \rightleftharpoons NO_2^+ + H_3O^+ + 2HSO_4^- \\ NO_2^+ + C_6H_6 \longrightarrow C_6H_5NO_2 + H^+ \\ NO_2^+ + C_6H_5NO_2 \longrightarrow m\text{-}O_2NC_6H_4NO_2 \end{gathered} \qquad (1)$$

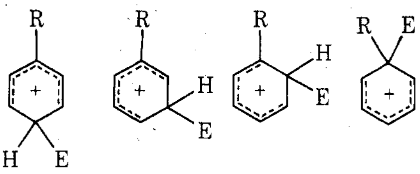
A number of paths are potentially available to effect the actual process of replacement. Free-radical aromatic substitution reactions are well authenticated,[2] and are not further considered in this Account. Among the heterolytic processes which require consideration, those involving removal of the proton by a base prior to attack by the electrophile will also not be discussed. Aromatic substitutions are most familiar when described in terms of Scheme I, with attention confined particularly to reactions a, b, c, and d, and with the possibility of overall reversibility being acknowledged.

The qualitative electronic theory of organic chem-

Scheme I
Some Possible Reaction Pathways for Electrophilic Substitution in a Substituted Benzene by an Electrophile, E, Supplied in the Presence of a Nucleophile, N[a]



[a] (i) Isomeric possibilities for 1



Position of attack: para- meta- ortho- ipso-

(ii) Isomeric possibilities for 2 include positionally and geometrically isomeric products of 1,2 and 1,4 addition. (iii) "Other products" from 1 (reaction h) include those of loss of a proton or of another group from a side-chain center and those of rearrangements. (iv) "Other products" from 2 (reaction k) include those initiated by further reaction with an electrophile ("trapping") and those involving intra- or intermolecular cationotropic or anionotropic rearrangements.

Peter B. D. de la Mare was born in Hamilton, New Zealand, and studied at Victoria University College, Wellington, for his B.Sc. and M.Sc. degrees. After 4 years as an agricultural chemist in New Zealand, he moved to England. He received the Ph.D. degree in 1948 and the D.Sc. degree in 1955 from University College London, and held posts as Lecturer and Reader there before moving to Bedford College (London) in 1960. In 1967 he returned to New Zealand, where he is Professor and Head of the Department of Chemistry at the University of Auckland. His research interests are in the general field of organic reaction mechanisms, where he has made contributions to studies on electrophilic aromatic substitution, additions to olefinic substances, elimination reactions, nucleophilic replacements, and anionotropic and prototropic rearrangements.

---

(1) P. B. D. de la Mare, *Chem. Brit.*, 8, 174 (1972).

(2) G. H. Williams, "Homolytic Aromatic Substitution," Pergamon Press, London, 1960.

istry, cogently put forward by Ingold,[3] focussed attention on the fact that much of the information relating to orientation and reactivity in aromatic substitution can be rationalized by considering the effects of substituents in modifying the electronic structure of the aromatic starting material. The ease of reaction then is determined by the effect of this polarization, which can be augmented by any local effects of polarizability; the detailed structure of the transition state was not at first considered. A synchronous pathway (reaction a) could be consistent with this theory; so could the coordination-heterolysis pathway starting with reaction b to give the carbocationic intermediates **1**.

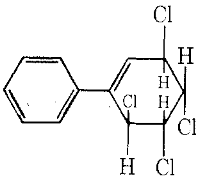
The potential importance of the carbocationic pathway was probably first fully recognized by Pfeiffer and Wizinger.[4] The development of quantum mechanics led to theoretical descriptions[5] in which such intermediates were assumed to provide good approximations to the structures of the transition states for typical aromatic substitutions. Much detailed work followed (for reviews, see, for example, ref 6–8) in which this pathway has been authenticated. The beauty and logic of this work, together with a natural desire to develop quantitative relationships between structure and reactivity, have led to the neglect of other possible mechanisms. Yet the general chemistry of carbocations, no less than the known facts concerning aromatic systems in general, should have prevented this.

Consider, for example, addition–elimination routes from benzene to its substitution product *via* the adducts **2**. One way of realizing such a path is by reactions e, f, and g in Scheme I. These are well-known processes. It is unreasonable to neglect them on the theoretical basis that the thermodynamic stability of aromatic compounds favors reaction d, since carbocationic sequences so often[9] give products of kinetic, rather than thermodynamic, control. Indeed, until 1935 or thereabouts the addition–elimination mechanism of electrophilic substitution was popular.[10] No doubt its disappearance from theory came about in part because adducts such as 2 may sometimes be only temporary repositories for the organic material undergoing reaction. Unless the properties of 2 are fully known, however, there are dangers in this simplification. These dangers have become more apparent now that modern physical methods have enabled analysis of quite complex reaction mixtures. Perhaps no one would be surprised that addition–elimination would need to be resurrected to describe some substitutions in polycyclic and heterocyclic aromatic chemistry. That it can be important in benzenoid systems also is more surprising, but will become apparent from the ensuing discussion, which shows that departures from the "conventional" sequence (reactions b, c, and d, Scheme I) tend to reveal themselves in elaborate sequences in which more than one new reaction type can sometimes become involved.

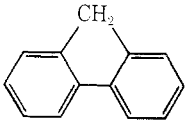
Benzenoid Compounds: Trapping of Cyclohexa-1,3-dienes Formed as Intermediates in Halogenations

Our own contributions in this field were initiated in the belief that chlorinations of simple aromatic compounds by molecular chlorine in acetic acid and related solvents give substitution cleanly, so that partial rate factors for aromatic chlorination, determined from rates and product analyses, give unambiguously the rates of attack of chlorine on particular positions in the aromatic compound.

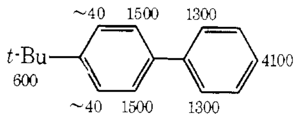
Many workers,[11-13] including ourselves,[14] had used this assumption as a basis for theoretical conclusions, and we were interested in the electronic effects of the phenyl and substituted phenyl substituents on chlorination in the other benzene ring. We found, however, that significant proportions of by-products were formed by addition of chlorine, or of chlorine acetate derived from chlorine and the acetic acid solvent. Some of these products were relatively stable and could be isolated and purified by chromatography; an example is the 1-phenyl-3,4,5,6-tetrachlorocyclohexene (possible stereochemistry **3**) isolated by chromatography of the product of chlorination of biphenyl in acetic acid.[15] Others, as was indicated by the behavior of fluorene (**4**) chlorinated under the same conditions, were very labile and readily decomposed to give a complicated mixture of products.[16]



3



4



5

It will be noted that, in this system, a consequence of the first addition of one molecular proportion of chlorine to the substrate is the production of a phenylhexadiene. This, as expected, is so reactive that it picks up a further molecule of the reagent, and only then is deactivated sufficiently to avoid successful competition with the original aromatic compound for any remaining chlorine. Elimination from the resulting adduct may give a disubstituted derivative of the starting material, and such a reaction can easily be

---

(3) C. K. Ingold, *Chem. Rev.*, 15, 225 (1934); "Structure and Mechanism in Organic Chemistry," Bell, London, 1953.

(4) P. Pfeiffer and R. Wizinger, *Justus Liebigs Ann. Chem.*, 461, 132 (1928).

(5) G. W. Wheland, *J. Amer. Chem. Soc.*, 64, 900 (1942).

(6) P. B. D. de la Mare and J. H. Ridd, "Electrophilic Substitution—Nitration and Halogenation," Butterworths, London, 1959.

(7) E. Berliner, *Progr. Phys. Org. Chem.*, 2, 253 (1964).

(8) H. Zollinger, *Advan. Phys. Org. Chem.*, 2, 163 (1964).

(9) P. B. D. de la Mare, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 17 (1948).

(10) L. Fieser in "Organic Chemistry," Vol. 1, H. Gilman, Ed., 2nd ed, Wiley, New York, N.Y., 1943, p 174 ff.

(11) A. E. Bradfield and B. Jones, *Trans. Faraday Soc.*, 37, 726 (1941).

(12) H. C. Brown and L. M. Stock, *J. Amer. Chem. Soc.*, 79, 5175 (1957).

(13) F. E. Condon, *J. Amer. Chem. Soc.*, 70, 1963 (1948).

(14) P. B. D. de la Mare and P. W. Robertson, *J. Chem. Soc.*, 279 (1943); P. W. Robertson, P. B. D. de la Mare, and B. E. Swedlund, *ibid.*, 782 (1953); P. B. D. de la Mare in "Theoretical Organic Chemistry," Butterworths, London, 1958, p 219.

(15) G. H. Beaven, P. B. D. de la Mare, M. Hassan, E. A. Johnson, and N. V. Klassen, *J. Chem. Soc.*, 2749 (1961).

(16) G. H. Beaven, P. B. D. de la Mare, E. A. Johnson, and N. V. Klassen, *J. Chem. Soc.*, 988 (1962).

realized, either by leaving the crude product to stand for long enough, by heating it, or by submitting it to chromatographic procedures of various kinds.

The lability of some, but not all, of the reaction products makes quantitative study of these systems difficult; however, our experiments with biphenyl and a number of bridged biphenyls of varying reactivity[17] showed that in these examples the amount of addition is not critically determined by the reactivity of the aromatic compound.

Once adducts have been detected as intermediates, it is obvious immediately that interpretation of partial rate factors for such an aromatic substitution requires circumspection. Conclusions derived from the proportions of minor components of the product are especially likely to be unjustified, as, for example, in the case of meta chlorination of biphenyl.[18,19] Unfortunately one is seldom in a position of knowing for certain whether the conventional interpretation of partial rate factors is fully meaningful or not, but the above discussion illustrates the detection of cyclohexadienes formed as intermediates in halogenations and then trapped by further addition of halogen (reaction k, Scheme I) and capable of decomposition to give products of normal substitution.

Electrophilic Attack at the Ipso Position

The isomeric possibilities for the carbocationic intermediate 1 include not only those involving ortho, meta, and para attack by the electrophile but also that involving attack on a position bearing a substituent (see note *a* (i), Scheme I). A convenient terminology is to describe the last-named route as involving attack on the ipso position.[20] With some substituents, and in some circumstances, ipso attack, even if it occurs, does not lead to products, and so is unimportant. However, removal of groups other than hydrogen, sometimes completely swamping normal substitution, is a well-known reaction.[6,21] For the reaction of substituted biphenyls, for example, chloro-de-*tert*-butylation can be significant, as is illustrated in **5**. The value given (600) for the partial rate factor for chloro-de-*tert*-butylation is derived from the rate of chlorination of 4-*tert*-butylbiphenyl relative to benzene and the finding that *ca.* 6% of the product of chlorination is 4-chlorobiphenyl. Clearly such a calculation needs to be treated with reserve; it may represent what is purports to do, but, if the product comes by the addition–elimination sequence from isomers of **2** through route j (Scheme I), then it could have arisen as the result of initial electrophilic attack on any of the other positions, and in these circumstances some or all of this partial rate factor should be added to one or more of the other values to present a realistic estimate of the relative reactivities of the nuclear positions.

Aromatic Hydrocarbons with Annelated Rings

The finding that addition accompanied substitution in the chlorination of relatively simple benzenoid compounds led us to turn to other types of aromatic system in the hope of learning more about the competition between the various pathways. Table I gives some values for the relative reactivities and proportions of addition for some compounds which have been studied in this connection.[15,16,22]

Table I
Chlorination of Some Aromatic Hydrocarbons in Acetic Acid at 25°

Aromatic compound	Relative rate of chlorination	Total addition (% of aromatic compound consumed)
Benzene	1	Not known
Biphenyl	426	9
Triphenylene	6,300	28
Naphthalene	32,600	34
Phenanthrene	280,000	65

In this comparison, in contrast with that made among the bridged biphenyls mentioned above, there seems to be a general tendency for addition to become more prominent as the reactivity of the system increases, but whether further extension of the series would confirm this trend is not known. Addition may be favored also, other things being equal, by thermodynamic factors.[6]

Study of the products of chlorination of phenanthrene showed[23,24] that, if the reaction mixture was examined directly by vapor-phase chromatography, 9-acetoxyphenanthrene appeared to be a significant component of the product. More careful examination, however, showed that this derivative is obtained by decomposition of acetoxy chlorides, formed through electrophilic attack by chlorine followed by capture of acetate ions. The true product composition includes 9-chlorophenanthrene (34%); other chlorophenanthrenes (1%); the *cis*- and *trans*-9,10-dichloro-9,10-dihydrophenanthrenes (48%); and the *cis*- and *trans*-9-acetoxy-10-chloro-9,10-dihydrophenanthrenes (17%). The amount of 9-chlorophenanthrene does not, therefore, measure the total amount of attack on the 9 position, and discussion of partial rate factors must take account of this fact and be restricted to those broad generalities which are not affected by the possibly competing pathways.[22,25]

The formation of acetoxy derivatives as the result of electrophilic attack by chlorine illustrates another possibility for route k (Scheme I) and serves as a reminder that the identification of a substitution product, ArX, formed from an aromatic compound and an electrophilic reagent, does not unambiguously identify X^+ as the electrophilic participant in the reaction pathway. Acetoxylations accompanying nitrations of aromatic compounds in acetic anhydride have recently provided a spectacular illustration of this point, substituted cyclohexadienes being among the intermediates involved.[26,27]

---

(17) P. B. D. de la Mare, E. A. Johnson, and J. S. Lomas, *J. Chem. Soc.*, 5317 (1964).

(18) H. Weingarten, *J. Org. Chem.*, 26, 4347 (1961).

(19) P. B. D. de la Mare and E. A. Johnson, *J. Chem. Soc.*, 4076 (1963).

(20) C. L. Perrin and G. A. Skinner, *J. Amer. Chem. Soc.*, **93**, 3389 (1971).

(21) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, London, 1965.

(22) G. W. Burton, P. B. D. de la Mare, L. Main, and B. N. B. Hannan, *J. Chem. Soc., Perkin Trans. 2*, 265 (1972).

(23) P. B. D. de la Mare and R. Koenigsberger, *J. Chem. Soc.*, 5327 (1964).

(24) P. B. D. de la Mare, A. Singh, E. A. Johnson, R. Koenigsberger, J. S. Lomas, V. Sanchez del Omo, and A. M. Sexton, *J. Chem. Soc. B*, 717 (1969).

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

Table II
Products in the Heterolytic[a] Chlorination of Naphthalene with Molecular Chlorine at 25°

Solvent	HOAc + 0.5 M LiCl	HOAc	$CHCl_3$	$MeNO_2$
Total substitution, %[b]	73	66	57	83
Total addition, %[b]	27	34	43	17
Total acetoxy chloride, %[b]	10	13		
Total α-tetrachloride (7), %[b]	7	13	22	7
Total δ-tetrachloride (8), %[b]	10	8	15[c]	

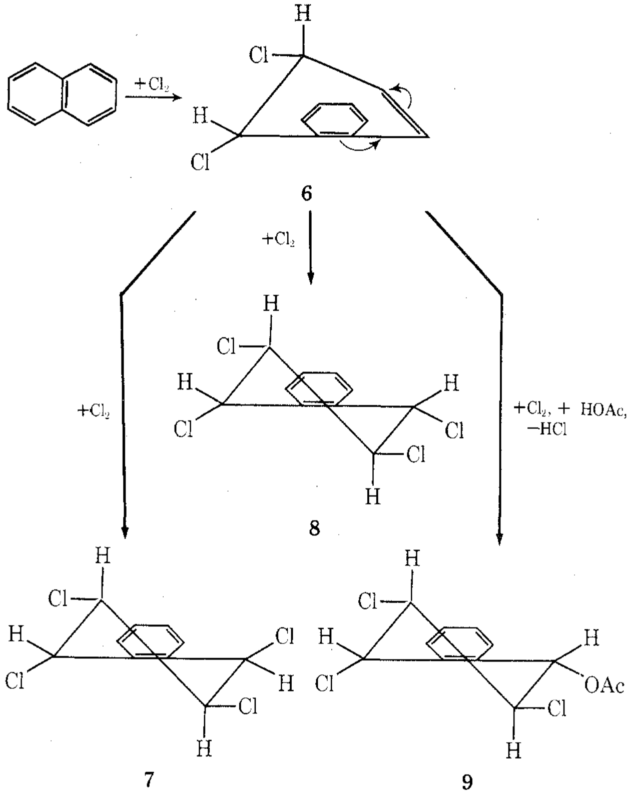
[a] Homolytic chlorination gives other products. [b] Percentage of aromatic compound consumed. [c] Unpublished work of V. Sanchez del Olmo.

Stereochemistry and Orientation of Addition

Addition to benzene or a substituted benzene can in principle give a *cis*- or a *trans*-1,3- or 1,4-cyclohexadiene by 1,2 or 1,4 addition, respectively. Little is known concerning this aspect of the sequences involved in chlorination of simple substituted benzenes. For the chlorination of naphthalene, however, the nature and stereochemistry of the products throw important light on the details of the reaction paths. The significant facts are as follows.[23,28,29]

The chlorination of naphthalene by molecular chlorine in acetic acid is heterolytic in character and gives a mixture of products, all of which are relatively stable under the reaction conditions. The main product of substitution (66%) is, as expected, 1-chloronaphthalene. No naphthalene dichloride can be detected in the product, but a mixture of naphthalene tetrachlorides (21%) is obtained, of which the major component is the α isomer, **7** (Scheme II); it is accompanied by the δ isomer, **8**, and minor amounts of others. A mixture of acetoxy chlorides (13%) is also formed; the major component has structure **9**. The amount of the α tetrachloride **7** is decreased by the inclusion of chloride ions in the reaction medium, while the amount of **8** is increased. The corresponding reactions in dipolar aprotic solvents chloroform or nitromethane also give mixtures of 1-chloronaphthalene and naphthalene tetrachlorides, with the α isomer as the major component. The results are summarized in Table II, and the course taken in the reaction is shown in Scheme II.

Scheme II
Main Reaction Path in the Chlorination of Naphthalene in Acetic Acid at 25°



The products of addition must be formed through an intermediate benzocyclohexadiene (**6**), very reactive in further addition of chlorine. The fact that the addition of chloride ions to the reaction medium does not increase the proportion of the α-tetrachloride **7** in the product indicates that external chloride ion is not concerned in the formation of the main addition product. For this reason, a possible route to **7** *via* trans-1,4 addition in the first stage of chlorination can be excluded; the geometrical requirements for the introduction of the electrophilic and nucleophilic groups would require that reaction with an external nucleophile would for this mode of addition be competitive with paths to other products. We have concluded, therefore, that the cis adduct, **6**, is the first product of addition, and that this then reacts by rapid cis or trans addition, initiated on the side of the molecule remote from the chlorine substituents already present, to give **7** or **8** respectively. Some capture of the solvent is possible also in the second stage of addition and gives mainly the trans acetoxy chloride **9**, with stereochemistry determined as for the δ tetrachloride **8** and orientation directed by the electronic movements shown by the arrows in **6**.

These conclusions are supported and extended by results for phenanthrene, acenaphthylene, and other aromatic and olefinic substrates[30] and throw new light on the details of the reaction paths encountered in molecular chlorination. In particular, these results provide evidence supporting a view put forward earlier on other grounds[14] that an intermediate zwitterion, of stoichiometry ArH,X_2 and probably related in structure to the trihalide ions through containing bivalent halogen, is important in these halogenations. The particular role of the intermediate in the present context is that, occurring as it must rather early in the reaction path, it holds the potentially

---

(26) A. Fischer, J. Packer, J. Vaughan, and G. J. Wright, *Proc. Chem. Soc., London*, 369 (1961); A. Fischer, J. Vaughan, and G. J. Wright, *J. Chem. Soc. B*, 368 (1967); J. Vaughan, G. J. Welch, and G. J. Wright, *Tetrahedron*, 21, 1665 (1965).

(27) D. J. Blackstock, A. Fischer, K. E. Richards, J. Vaughan, and G. J. Wright, *Chem. Commun.*, 641 (1970).

(28) P. B. D. de la Mare, M. D. Johnson, J. S. Lomas, and V. Sanchez del Olmo, *J. Chem. Soc. B*, 827 (1966).

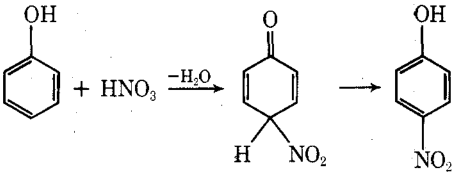
(29) P. B. D. de la Mare and J. S. Lomas, *Recl. Trav. Chim., Pays-Bas*, 86, 1082 (1967).

(30) P. B. D. de la Mare, M. A. Wilson, and M. J. Rosser, *J. Chem. Soc., Perkin Trans. 2*, 1480 (1973).

nucleophilic chloride ion near to the carbocationic center, which then can capture the departing nucleophile and so bring about cis addition. This we have shown to be prominent in the heterolytic chlorinations of phenanthrene and naphthalene; in these examples, the stereochemistry of reaction is clearly differentiated from that found in the corresponding homolytic chlorinations. Electrophilic additions of other reagents to other systems are known to differ also in regiospecificity; for the nitration of *o*-xylene in acetic anhydride, for example, 1,4 rather than 1,2 adducts are known to be prominent products,[27] this reaction probably involving initial attack on the ipso position.

Cyclohexadienone Intermediates; the SE2′ Reaction

Yet another possible fate of a carbocationic intermediate (1, Scheme I) involves loss of a cation from the α atom of the group R and leads potentially to cyclohexadienes bearing unsaturated exocyclic substituents of various kinds. Such reactions, of which the first step of sequence 2 is an example, have been envisaged as possibilities for many years (*cf.* ref 31); they can be categorized formally as bimolecular electrophilic substitutions with rearrangement (SE2′) in the same sense (and with the same reservations) that the more usual reaction path (Scheme I, reactions b, c, d) can be categorized as SE2.

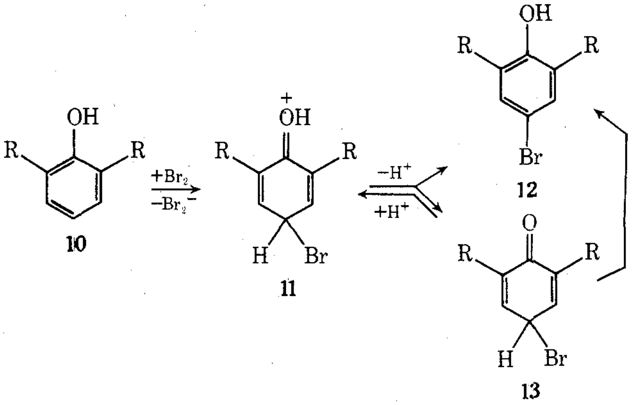


(2)

Our own discussions of such paths derived from the fact that the hydroxyl group is in a number of situations more electron releasing than the methoxyl group. This led to consideration of the possibility that electron release by H–O hyperconjugation is significant,[32,33] and thence to the establishment that DOC_6H_5 is less reactive with bromine in deuterioacetic acid than is HOC_6H_5 in acetic acid.[34,35] This observation establishes, in our view, that H–O bond fission contributes to the rate-determining stage for the bromination of phenol. The dienone **13** (Scheme III; R = H) may be an intermediate in this reaction; therefore, its rearrangement to the substituted phenol (**12**; R = H) would be expected to be rapid.

2,6-Di-*tert*-butylphenol (**10**; R = *t*-Bu) likewise gives a cyclohexadienone which now is sufficiently stable to be isolatable. Illuminati and his coworkers[36] have measured the kinetics of the formation of a number of analogous dienones and have shown that these resemble the kinetics of conventional brominations. We have studied the rearrangement **13** → **12** (Scheme III; R = *t*-Bu) in acetic acid and in aqueous acid.[37,38] This reaction is catalyzed both by acids and by bases.

Scheme III
Possible Reaction Paths in the 4-Bromination of Some Phenols



Under acid catalysis, the rearrangement goes *via* the protonated intermediate **11**, so the bromination of the original phenol (**10** → **12**) normally gives **13** as a temporary repository of electrophilic bromine (the SE2′ reaction) which then ultimately gives the "normal" (SE2) substitution product (**12**) *via* the "normal" intermediate (**11**). When bromination is carried out in acetic acid in the presence of sodium acetate, however, the buildup of the intermediate (**13**) can be shown to occur. Thus with 2,6-di-*tert*-butylphenol (2.21×10^{-4} *M*), bromine (1.07×10^{-4} *M*), and sodium acetate (0.095 *M*) in acetic acid containing water (1 *M*), the buildup and decay of dienone (absorption at 255 nm) at 25° can be shown from the following previously unpublished experimental results of S. Nicolson (time in min after mixing, optical density at 255 nm): 1, 0.683; 2, 0.834; 3, 0.912; 4, 0.921; 5, 0.893; 10, 0.719; 20, 0.390; 40, 0.118; 120, 0.033. Under these particular experimental conditions, rearrangement does not[38] involve **11**, so that a second pathway, **10** → **13** → **12**, can be said to have been established for the aromatic substitution.

A mechanistic pathway of the SE2′ kind is probably available very widely for phenols, naphthols, and related substances. The range of structures over which it can be demonstrated for amines has not been investigated, though evidence exists for sequences in which hydrogen must be lost from nitrogen in electrophilic processes.[39] Interesting cases exemplify the corresponding formation of exocyclic methylene groups, particularly from the work of Illuminati and coworkers[40] on substitution in hexasubstituted benzenes. Our investigations contribute through the demonstration[41] that intermediates bearing exocyclic methylene groups may be trapped by molecular chlorine; thus one of the various polychlorinated products obtained in the reaction of 1-methylnaph-

---

[31] A. Lapworth, *J. Chem. Soc.*, **79**, 1265 (1901).

[32] P. W. Robertson, P. B. D. de la Mare, and B. E. Swedlund, *J. Chem. Soc.*, 782 (1953).

[33] P. B. D. de la Mare, *Tetrahedron*, **5**, 107 (1959).

[34] P. B. D. de la Mare, O. M. H. El Dusouqui, J. G. Tillett, and M. Zeltner, *J. Chem. Soc.*, 5306 (1964).

[35] P. B. D. de la Mare and O. M. H. El Dusouqui, *J. Chem. Soc. B*, 251 (1967).

[36] E. Baciocchi and G. Illuminati, *J. Amer. Chem. Soc.*, **89**, 4017 (1967).

[37] P. B. D. de la Mare, A. Singh, J. G. Tillett, and M. Zeltner, *J. Chem. Soc. B*, 1122 (1971); P. B. D. de la Mare and A. Singh, *J. Chem. Soc., Perkin Trans. 2*, 1801 (1972).

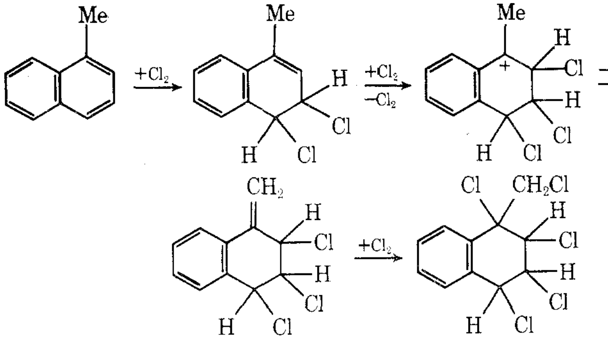
[38] P. B. D. de la Mare and A. Singh, *J. Chem. Soc., Perkin Trans. 2*, 59 (1973).

[39] F. Bell, *J. Chem. Soc.*, 3035 (1953); F. Bell and J. A. Gibson, *ibid.*, 24 (1955).

[40] E. Baciocchi, A. Ciana, G. Illuminati, and C. Pasini, *J. Amer. Chem. Soc.*, **87**, 3953 (1965); G. Illuminati, L. Mandolini, A. Patara, and E. Baciocchi, *Tetrahedron Lett.*, 4161 (1972).

[41] G. Cum, P. B. D. de la Mare, and M. D. Johnson, *J. Chem. Soc. C*, 1590 (1967).

thalene with chlorine in acetic acid under heterolytic conditions is the chlorotetrachloride 14, which we regard as having been formed by such a sequence as is shown in (3).[41]



14

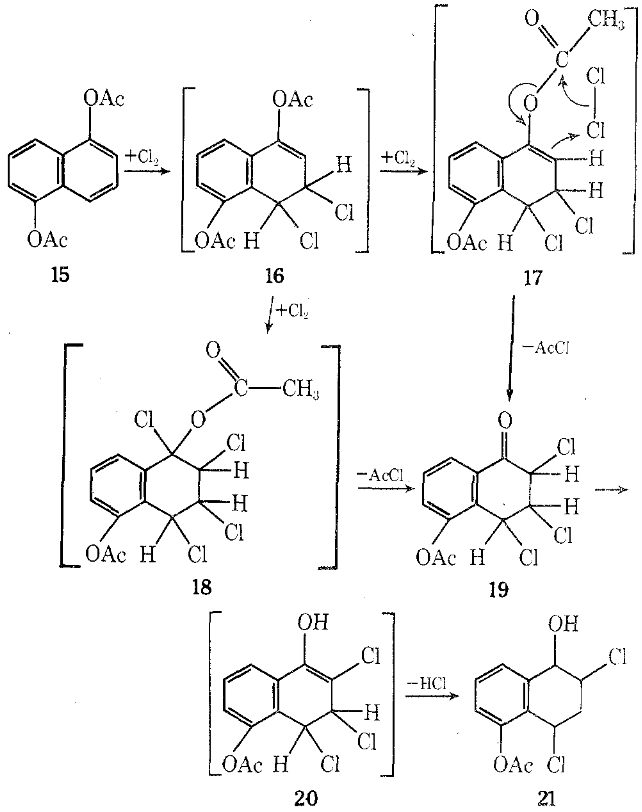
(3)

SE2′ Processes Involving Displacement of Groups Other than Hydrogen

The above discussion, and the papers cited, provide evidence for the importance of path h (Scheme I, note *a* (iii)), with the detailed amplifications: (i) that electrophilic attack on an aromatic molecule can initiate proton loss with double bond rearrangement; (ii) that the seat of proton loss can be from oxygen, nitrogen, or carbon; (iii) that the position of attack can be ortho or para to the substituent from which the proton is displaced; (iv) that attack can be on a position bearing hydrogen or another substituent; and (v) that additions, additions followed by elimination, rearrangements, and other complications of the "normal" (SE2) mode of substitution are equally apparent in paths leading to SE2′ products.

We now turn our attention to related reaction paths in which attack by the electrophile initiates displacement of groups other than hydrogen from the side chain. There are many indications in the literature that such processes are possible; for example, the nitration of anisole is accompanied by the formation of demethylated by-products.[42] Our own studies are limited to displacement of alkyl and acyl groups, and particularly to displacements of $[COCH_3]^+$ and of Me^+ from derivatives of phenols and naphthols. We first studied the chlorination of 1,5-diacetoxynaphthalene (15; Scheme IV), which was known to give the 5-acetoxy-2,4-dichloronaphthol 21.[43] This is difficult to understand in the simplified terms of the qualitative electronic theory of aromatic substitution if it is assumed that only the "normal" (SE2) reaction path is available. We found[44] that the reaction in acetic acid or in chloroform gives an intermediate (19) formed by addition of chlorine and chlorodeacylation with rearrangement (not necessarily in that order). The progressive, fairly rapid but not instantaneous, changes in the ^1H nmr spectrum of the reaction mixtures did not indicate the presence of any other organic intermediate, or any delay in the liberation of acetyl chloride. We presume that addition to give 16 is followed either by synchronous chlorodeacylation with rearrangement through the transition state 17 or by stepwise further addition to give 18 followed by elimination of acetyl chloride. The intermediate 19 can be isolated, and separately allowed to decompose, giving the final product, 21, by dehydrochlorination and rearrangement (again, not necessarily in that order).

Scheme IV
Intermediates in the Chlorination of 1,5-Diacetoxynaphthalene in Acetic Acid and in Chloroform[a]



[a] Square brackets indicate either intermediates postulated but not isolated (16, 18, 20) or transition states (17).

Clearly we are concerned here with a complicated reaction sequence involving stages which include chlorodeacylation, addition, and elimination. Similar results have been obtained for the chlorination of 3,4-dimethylphenol, of 3,4-dimethylphenyl acetate, and of 3,4-dimethylphenyl methyl ether (Scheme V; 22, R = H, Ac, Me, respectively).[45] For the phenol, chlorodeprotonation to 25 followed relatively slowly by rearrangement to 28 (presumably *via* 27) could be established to be a minor reaction path, but the major intermediate, obtained also from the acetate and the ether, was the enone 23, the formation of which involves a stage of addition as well as of substitution. This enone could be isolated and separately allowed to decompose, first to the dienone 24 and then to the mono- and dichlorophenols 28 and 29. Stages of chlorodemethylation and of chlorodeacylation are thus indicated clearly for the appropriate substrates.

Bromination is equally complicated; but here any intermediate adducts are still less stable than in chlorination, so their participation in reaction paths is more difficult to establish directly. Anomalous ori-

---

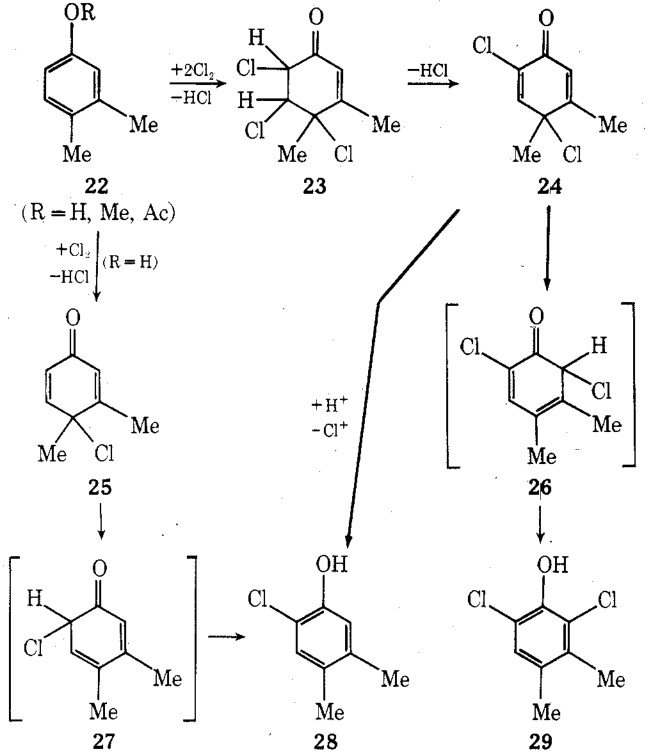
(42) C. A. Bunton, E. D. Hughes, C. K. Ingold, D. I. H. Jacobs, M. H. Jones, G. J. Minkoff, and R. I. Reed, *J. Chem. Soc.*, 2628 (1950).

(43) R. H. Thomson, *J. Org. Chem.*, 13, 371 (1948).

(44) P. B. D. de la Mare, S. de la Mare, and H. Suzuki, *J. Chem. Soc. B*, 429 (1969).

(45) P. B. D. de la Mare and B. N. B. Hannan, *Chem. Commun.*, 1324 (1971).

Scheme V
Reaction Pathways in the Chlorination of 3,4-Dimethylphenol and Its O Derivatives in Acetic Acid[a]



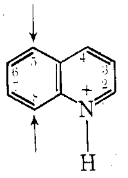
[a] Square brackets indicate intermediates postulated but not isolated.

entations for substitution sometimes allow unconventional reaction paths to be inferred, however. Thus we have shown[46] that the bromination of 2,6-diisopropylphenyl benzoate in nitromethane gives only the 3-bromo derivative, expected if orientation is controlled by the alkyl groups; but 2,6-diisopropylphenyl acetate instead gives a mixture of 4-bromo-2,6-diisopropylphenyl acetate, 4-bromo-2,6-diisopropylphenol, 3,4-dibromo-2,6-diisopropylphenol, and traces of other products. The phenols must be formed by sequences including a bromodeacylation, which we have shown to be catalyzed by added bromide ion. The products of disubstitution presumably arise through sequences which include an addition followed by an elimination.

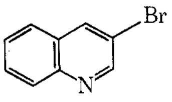
The mechanisms available for the stages of the reactions involving deacylation have been elucidated only in part. We know that this process may be, but is not necessarily, susceptible to catalysis by nucleophiles; we know that enones, rather than dienones, are often produced, but we do not know whether the stage of addition has to precede the deacylation or not; we know that an electrophile can be introduced either ortho or para to the directing substituent, but we do not know whether its attack is followed by capture by halide, by loss of Ac⁺ or Me⁺, or both. Some degree of selection from among the numerous possible transition states can be made for particular cases, but further definition is not yet possible except on intuitive grounds. We hope in further investigations to clarify some details, particularly with regard to the accessibility of cyclic processes, and of routes involving extended conjugation; these are almost certainly available in related processes involving olefinic systems.[47]

Reversibility of Halogenation

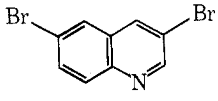
It will be clear from the above account that the formation of adducts and their subsequent decomposition can sometimes be very important in determining the rates and products of halogenation, whether by chlorine or by bromine, and that the chemistry of the adducts formed from any particular aromatic system can be very individual and can lead to specific fates for the substituents. The chemistry of heterocyclic systems provides further examples; here we will refer specifically to substitution in quinoline. This compound reacts with nitric acid in sulfuric acid to give the 5- and 8-nitro derivatives[48] and with bromine in sulfuric acid containing silver sulfate to give the 5- and 8-bromo derivatives.[49] Presumably these are reactions of the quinolinium cation, **30**.



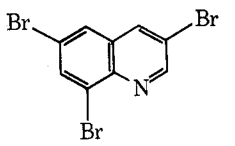
30



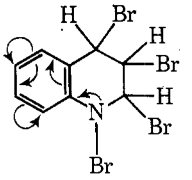
31



32



33



34

With molecular bromine under a variety of other conditions, however, 3-bromoquinoline (**31**), 3,6-dibromoquinoline (**32**), and 3,6,8-tribromoquinoline (**33**) can be identified in various proportions in the products.[49,50,51] These results have been interpreted[52,53] by assuming that adducts (*e.g.*, **34**) are formed reversibly. Loss of bromine and hydrogen bromide then give 3-bromoquinoline (**31**), and this sequence accounts for the unexpected orientation of monobromination. In the adduct **34**, however, the lone pair of electrons has been taken from a situation in which it is not conjugated with the adjoining aromatic ring to one in which it can activate the 6 and 8 positions through the electronic movements shown by the arrows in the formula. Further substitution can then occur in these positions, thus leading ultimately to the characteristic di- and tribrominated products.

Similar results have been recorded for iodination and chlorination.[54] Despite Eisch's reserva-

---

(46) P. B. D. de la Mare and B. N. B. Hannan, *Chem. Commun.*, 156 (1970).

(47) P. B. D. de la Mare and B. N. B. Hannan, *J. Chem. Soc., Perkin Trans. 2*, 1086 (1973).

(48) M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.*, 2521 (1957).

(49) P. B. D. de la Mare, M. Kiamud-din, and J. H. Ridd, *J. Chem. Soc.*, 561 (1960).

(50) W. La Coste, *Ber. Deut. Chem. Ges.*, **14**, 915 (1881); A. Claus and F. Collischon, *ibid.*, **19**, 2763 (1886).

(51) J. J. Eisch, *Advan. Heterocycl. Chem.*, **7**, 1 (1966).

(52) P. B. D. de la Mare in "Rodd's Chemistry of Carbon Compounds," Vol. IIIA, S. Coffey, Ed., 2nd ed, Elsevier, 1971, p 84 ff.

(53) M. D. Johnson and J. H. Ridd, *J. Chem. Soc.*, 291 (1962).

(54) M. Kiamud-din and M. E. Haque, *Chem. Ind. (London)*, 1753 (1964); M. Kiamud-din and M. E. Haque, *Pak. J. Sci. Ind. Res.*, **9**, 30 (1966); M. Kiamud-din and A. K. Choudhury, *ibid.*, **9**, 326 (1966).

tions[51] concerning the above interpretation, it provides the most direct explanation of the experimental observations, and is preferred by the writer. Some support can be derived from the fact that related adducts do in fact undergo 6- and 8-bromination.[53] It is likely that similar reaction paths, available because of the easy reversibility of attachment of halogen to nitrogen, are to be found with related heterocyclic systems.

Reversibility in Aromatic Substitution: Applicability of Linear Free-Energy Relationships Involving Partial Rate Factors for Aromatic Substitution

The qualitative electronic theory of organic chemistry, together with attempts to put this theory in quantitative terms by using linear free-energy relationships or by making molecular orbital calculations concerning the relative availability of transition states, involves a number of assumptions which are not always stated explicitly. One of these is that the rate-determining transition states which are being compared have similar compositions and bonding characters. When this is not so, deviations from predicted rates and orientations are expected as possibilities, though they are not required. Thus it is by no means clear that two aromatic substitutions, one of which shows a primary H–D isotope effect and one of which does not, should give a reasonable linear free-energy relationship between their relative reaction rates. Quite good correlations are, in fact, found in a number of cases,[21] but Berliner and his coworkers[55] have illustrated how reversibility of the first stages of substitution (reactions b and c, Scheme I) can influence the orientation of the products in suitable cases. This provides one example of a number of ways in which the detailed chemistry of the carbocations and other intermediates leading to electrophilic substitution in unsaturated systems can be important in determining the relative rates at which particular products are formed.

This Account has surveyed a number of examples to the understanding of which the writers' coworkers have made contributions; it gives quite inadequate acknowledgment of his personal indebtedness to them, as it does also to the many other groups of workers contributing actively to our knowledge of these reactions.

---

(55) E. Berliner, J. B. King, and M. Link, *J. Org. Chem.*, 33, 1160 (1968); J. B. Kim, C. Chen, J. K. Krieger, K. R. Judd, C. C. Simpson, and E. Berliner, *J. Amer. Chem. Soc.*, 92, 910 (1970).

Prebiotic Chemistry and Nucleic Acid Replication

Leslie E. Orgel* and Rolf Lohrmann

The Salk Institute for Biological Studies, San Diego, California 92212

Received May 28, 1974

The replication of nucleic acids is the central reaction responsible for the transmission of hereditary information in all contemporary organisms. It is widely believed that a similar process, some form of complementary replication of molecules related to nucleic acids, played an important part in the origins of life. In this Account we review our work on some reactions that we believe could have occurred on the primitive earth and played a part in the evolution of a self-replicating system.

Unfortunately, our picture of the conditions that prevailed on the primitive earth is incomplete, so no generally accepted rules can be given that determine whether or not a reaction condition is prebiotic. The following are the guidelines that we have followed in our work.

(a) All primary organic reagents must be derivable as significant products from a reducing atmosphere composed of a selection of the following simple gases: CH_4, CO, CO_2, NH_3, N_2, H_2O. Ultraviolet light, heat, or electric discharges may be used as sources of the energy involved in the synthesis of primary reagents from these elementary gases.

(b) No solvent other than water may be used. Reactions in aqueous solution must be carried out at moderate pH's, preferably between 7 and 9.

(c) Solid-state reactions must occur without excessive drying of the reactants. Solid-state reaction mixtures are preferably obtained by evaporating aqueous solutions that are initially at pH's between 7 and 9.

(d) All reactions must occur under conditions of temperature and pressure that occur on the surface of the earth today. We doubt that volcanos or thermal springs contributed much to the origins of life, so we prefer to carry out solid-state reactions at temperatures below 80°C (surface temperatures up to 90°C have been recorded in California deserts, and we have found that large areas of the desert surface are raised above 65°C for several hours on a typical

Leslie E. Orgel is a Senior Fellow of the Salk Institute for Biological Studies, where he has been since 1964, and an Adjunct Professor of University of California, San Diego. He was born in London in 1927 and received both his B.A. and Ph.D. degrees from Oxford. In 1955, he joined the Chemistry Department at Cambridge University. Dr. Orgel began his career as a theoretical inorganic chemist. However, his interests have turned to biological problems in recent years, and he is now studying the relatively simple chemical reactions which are presumed to have produced the small molecules essential for the origin of life and the evolution of the highly specific interactions between them which form the molecular basis of heredity.

Rolf Lohrmann was born in Germany in 1930, and studied at the Technische Hochschule in Stuttgart. He spent 2 years as Postdoctoral Fellow at the Genetics Foundation of the University of Texas, Austin, with H. S. Forrest, followed by work at the Institute for Enzyme Research, University of Wisconsin, with H. G. Khorana. Dr. Lohrmann has been Senior Research Associate at the Salk Institute since 1965.