Polar and Steric Effects in the Homolytic Amination of Alkylbenzenes and Biphenyl

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Partial rate factors for homolytic amination of alkylbenzenes and biphenyl by *N*-chloroamines have been determined in an acidic medium. The resulting polar effects are by far the highest ever observed in homolytic substitution and are of the order of magnitude of those in the common electrophilic reactions. The reaction is sensitive to steric and polar effects (conjugative and inductive, but not hyperconjugative), as previously observed for hydrogen absractions. The transition state of the reaction is discussed and a hypothesis is put forward on inductive and Baker–Nathan effects on electrophilic substitution.

HOMOLYTIC aromatic amination has a synthetic value omparable with that of the classical electrophilic reactions.[1,2] In fact, the orientation and reactivity are usually similar to those of a highly selective electrophilic reaction. The only exceptions, so far as orientation is concerned, are alkylbenzenes, which are attacked with poor selectivity at the *meta*- and *para*-positions. In order to clarify the mechanism of the homolytic reaction, an investigation of the amination of alkylbenzenes and biphenyl has been undertaken.

RESULTS AND DISCUSSION

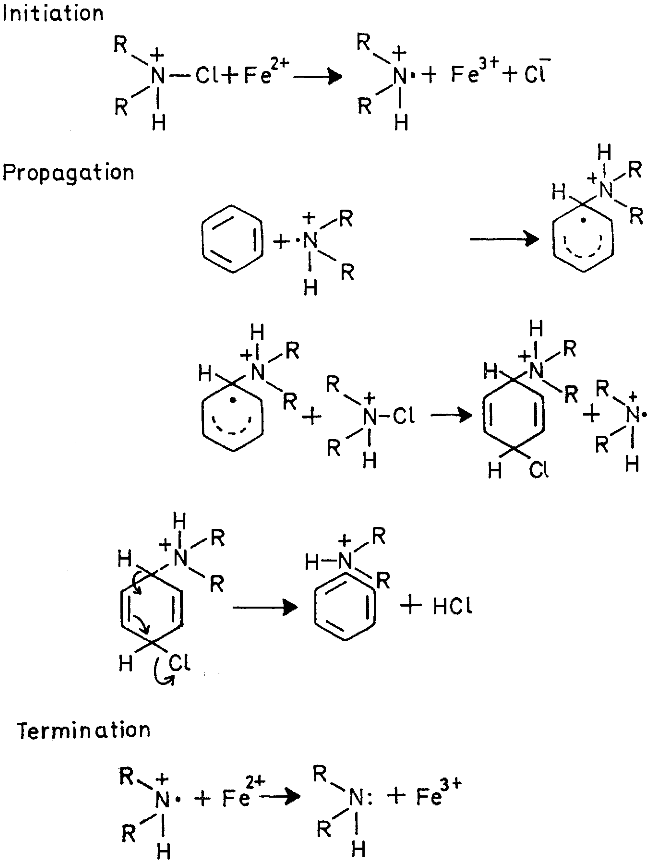
The large influence of polar effects on homolytic amination is clearly indicated by the fact that protonated *NN*-dialkylanilines do not react under conditions in which benzene is aminated easily. This has important synthetic consequences since it is possible to eliminate completely the formation of polysubstitution products.

In order to achieve a quantitative evaluation of the effects of substituents in alkylbenzenes and in biphenyl, partial rate factors have been determined for the homolytic amination of these substrates. A mixture of sulphuric acid, nitroethane, and ferrous lactate proved to be a suitable initiator. Ferrous lactate under the reaction conditions is transformed into ferrous sulphate and the lactate's greater solubility in the reaction medium makes initiation of the radical chain [2] more effective (Scheme 1). We verified that these conditions control the formation of the ammoniumyl cation radicals, by using an alkyl derivative (methyl hexanoate and 1-chloropentane) instead of the aromatic substrate; chlorination of the hydrocarbon chain occurs with extremely high selectivity, substantially identical to that observed under conditions favouring the radical chain process (1) and (2).[2,3] Also benzylic chlorination always takes

$$R^1_2\overset{+}{N}H + R^2H \longrightarrow R^1_2\overset{+}{N}H_2 + \cdot R^2 \qquad (1)$$

$$\cdot R^2 + R^1_2\overset{+}{N}HCl \longrightarrow R^2Cl + R^1_2\overset{+}{N}H \qquad (2)$$

place together with amination. The partial rate factors, determined by the competitive method and the isomer distribution in the amination by dimethylammoniumyl cation radical of toluene, isopropylbenzene, t-butylbenzene, and biphenyl are reported on Table 1. The alkylanilines, under the reaction conditions, do not rearrange and the reaction is catalysed by ferrous, but not ferric salts. Thus it is unlikely that an electrophilic process (*e.g.* the Kovacic reaction[4]) is super-



SCHEME 1

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[1] F. Minisci, *Chimica e Industria*, 1967, **49**, 705; G. Sosnovsky and D. J. Rawlison, *Adv. Free Radical Chem.*, 1972, **4**, 203.

[2] F. Minisci, *Synthesis*, 1973, 1.

[3] N. C. Deno, 'Methods in Free-radical Chemistry,' ed. E. S. Huyser, Dekker, New York, 1972, p. 143.

[4] P. Kovacic, M. L. Lowery, and K. W. Field, *Chem. Rev.*, 1970, **70**, 639.

imposed on the radical process. Moreover with biphenyl, amination takes place without the formation of any *meta*-isomer; the Kovacic reaction gives only this isomer.[4]

TABLE 1

Isomer ratios and partial rate factors for the amination of alkylbenzenes and biphenyl by $.\mathrm{NHMe}_2$

Substrates	Isomer distribution (%) *ortho*	*meta*	*para*	Relative rates $C_6H_6 = 1$	Partial rate factors *ortho*	*meta*	*para*
Toluene	5·6	22·6	71·8	11·8	2	8	51
Isopropylbenzene	1·1	23·4	75·5	9·3	0·3	6·2	42
t-Butylbenzene		14·6	85·4	5·3		2·3	27
Biphenyl			100	200			598

The values reported in Table 1 must therefore reflect a radical process alone. On consideration of the partial rate factors it becomes obvious that meaningful comparisons cannot be made with the only homolytic aromatic substitution, phenylation, for which numerous and accurate data exist for the substrates examined here.[5] Rather, the values of the partial rate factors and the general character of the amination[2] allow a more relevant analogy to be drawn with electrophilic substitution reactions.

The absence of *ortho*-isomers from t-butylbenzene and biphenyl and the low percentage from toluene and isopropylbenzene must be attributed to steric effects; this phenomenon is also confirmed by the results obtained from *o*-xylene (Table 2).

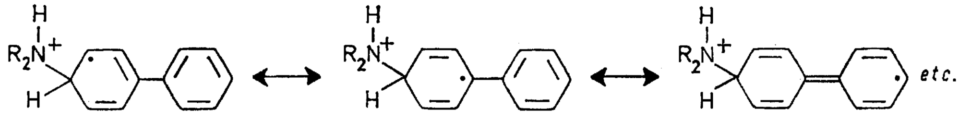
TABLE 2

Isomer ratios and partial rate factors for amination of toluene, t-butylbenzene, and *o*-xylene by ammoniumyl cation radicals

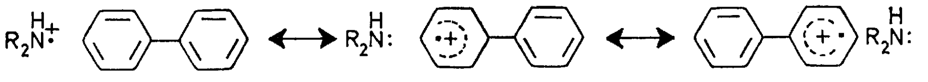
Cation radical	Toluene: Isomer distribution (%) *o*	*m*	*p*	Toluene: Relative rates $C_6H_6 = 1$	Toluene: Partial rate factor *o*	*m*	*p*	t-Butylbenzene: Isomer distribution (%) *m*	*p*	t-Butylbenzene: Relative rates $C_6H_6 = 1$	t-Butylbenzene: Partial rate factor *m*	*p*	*o*-Xylene: Isomer distribution (%) 3	4	*o*-Xylene: Relative rates $C_6H_6 = 1$	*o*-Xylene: Partial rate factor 3	4
$\overset{+}{\cdot}\mathrm{NHMe}_2$	5·6	22·6	71·8	11·8	2	8	51	14·6	85·4	5·3	2·3	27	2·7	97·3	78·8	6·4	230
$\overset{+}{\cdot}\mathrm{NHEt}_2$	2·5	15·4	82·1	13·4	1	6·2	66	15·2	84·8	4·6	2·1	23·5	2·5	97·5	71·2	5·4	205
$\overset{+}{\cdot}\mathrm{NH[CH_2]_5}$ [a]				9·8									0·8	99·2	62·1	1·4	185
$\overset{+}{\cdot}\mathrm{NH[CH_2]_2O[CH_2]_2}$ [b]				33·4									3·6	96·4	218	24	630

[a] Piperidiniumyl. [b] Morpholiniumyl.

As the reactivity of *meta*-positions can be considered to reflect best the effect of the polar nature of the attacking radical, the partial rate factor for *meta*-attack on toluene indicates that the sensitivity of homolytic amination to inductive effects is high, of the order of magnitude of the most selective electrophilic reactions.[6] Such sensitivity to steric and inductive effects of ammoniumyl cation radicals was found for hydrogen abstraction processes.[7] The exceptionally high positional and substrate selectivity for biphenyl may be, in principle, due to two separate causes; either a conjugative polar effect of the phenyl group, as for electrophilic reactions, or to resonance stabilization (3) of the intermediate radical. We feel that the first effect is by far the most important. In the absence of marked polar effects, as in homolytic phenylation, the partial rate factor of the *para*-position has a rather low value (2·5), not differing greatly from those of the *ortho*- (2·1) and *meta*- (1·0) positions.[8] High sensitivity to conjugative polar effects is responsible for great reactivity of anisole, phenol, acetanilide, *etc.*[2] A transition state which is more of a charge-transfer complex



(3)



SCHEME 2

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[5] G. H. Williams, 'Homolytic Aromatic Substitution,' Pergamon, London, 1960; D. H. Hey, *Adv. Free Radical Chem.*, 1967, **2**, 47.

[6] R. O. C. Norman and R. Taylor, 'Electrophilic Substitution in Benzenoid Compounds,' Elsevier, London, 1965.

[7] R. Bernardi, R. Galli, and F. Minisci, *J. Chem. Soc.* (*B*), 1968, 324; N. C. Deno, R. Fishbein, and J. C. Wyckoff, *J. Amer. Chem. Soc.*, 1971, **93**, 2065.

[8] D. H. Hey, S. Orman, and G. H. Williams, *J. Chem. Soc.*, 1961, 565.

than a σ-complex would justify such a high sensitivity to conjugative polar effects (Scheme 2).

The low positional selectivity of the alkylbenzenes, the increase along the series toluene < isopropylbenzene < t-butylbenzene, and the fact that the 4-position of biphenyl is considerably more activated than the corresponding position of toluene can be explained if the reaction is sensitive to polar effects (inductive and conjugative), though not to hyperconjugative ones. But with this interpretation the sequences of the partial rate factors of the *meta*- and *para*-positions of toluene, isopropylbenzene, and t-butylbenzene are inexplicable. However, the exceptional sensitivity to steric effects of dialkylammoniumyl cation radicals [7] leads us to put forward a hypothesis which, in our opinion, overcomes the apparent difficulties. This hypothesis is based on a transition state in which a bond between the radical and the substrate has not yet developed and a contribution from a charge-transfer complex plays an important role in determining the reactivity. The steric effects of the alkyl groups in the benzene ring in such a transition state would affect the reactivity of the substrate.

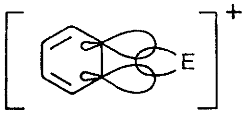
An attempt to verify this hypothesis was made by varying the size of the alkyl groups in the dialkylammoniumyl radical. The use of ethyl instead of methyl gave a small increase in the partial rate factor for the *para*-position and a decrease for the *ortho*- and *meta*-positions of toluene while the partial rate factor was reduced even for the *para*-position of t-butylbenzene (Table 2). These results support the assumption that the steric effects can affect the total reactivity of the substrate. Analytical difficulties prevented the quantitative study of other alkyl groups.

The results for the amination of *o*-xylene (Table 2) show that reactivity of the 4-position is considerably increased relative to the *para*-position of toluene even if it does not reach the value derived from the additivity principle. The partial rate factors of the 4-position of *o*-xylene with different ammoniumyl radicals emphasize the influence of the polarity of the cation radical which, besides being determined by the electronegativity of the nitrogen atom, on which the unpaired electron is localized, and by the presence of a positive charge, is also affected by the nature of the groups bonded to nitrogen. The highest selectivity is obtained with morpholine, the least basic amine used (p*K* 5·6), while the lowest selectivity is observed for piperidine, the most basic (p*K* 2·8), their steric requirements being substantially identical.

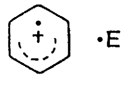
In conclusion all the characteristics observed can be rationalized on the basis of a transition state in which the contribution of a charge-transfer complex produces high sensitivity to steric and polar effects. This conclusion leads us to put forward a new hypothesis on the much discussed Baker–Nathan and inductive orders (the sequence of reactivity in Baker–Nathan order is toluene > isopropylbenzene > t-butylbenzene: the inductive order is opposite) in electrophilic substitutions of alkylbenzenes which were considered among the best defined from a mechanistic point of view.

The transition state may be of the Wheland classical type (I), a π-complex (II) which has been invoked for a number of reactions characterized by low substrate but high positional selectivity,[9] or a charge-transfer complex (III).[10] Complex (III) is certainly present in some interactions between aromatic compounds and electrophiles.

(I)



(II)



(III)

From a general point of view this would indicate a substantially identical mechanism for radical amination, as we have interpreted it, and electrophilic substitution; the rate-determining step in the reaction between an aromatic substrate and an electrophile would be the same, apart from the radical or non-radical nature of the latter. Now, assuming that the transition state of electrophilic substitutions contains contributions from both structures (I) and (III) and that the phenomenon of hyperconjugation is associated with structure (I) but not with (III), the inductive order would be obtained when structure (III) is important and the Baker–Nathan order for a transition state similar to (I). A larger degree of charge development in a transition state similar to (I) would enhance such behaviour.

For the three electrophilic substitutions for which the inductive order holds, *i.e.* hydrogen exchange,[11] bromination in trifluoroacetic acid,[12] and nitration,[13] we observe characteristics which are in agreement with this interpretation. Hydrogen exchange is a common source of aromatic radical cations investigated by e.s.r. spectroscopy [14] and also the formation of aromatic radical cations in the reaction of aromatic substrates with bromine has been recently observed by e.s.r.[15] Furthermore, the possible formation of the charge-transfer complex (III) is related to the stability of the radical •E and this supports our hypothesis in the case of nitration in which the electrophile E^+ is given by the species NO_2^+ and the corresponding radical $\cdot NO_2$ is particularly stable.

EXPERIMENTAL

Materials.—Aromatic substrates and starting amines were pure (by g.l.c.) commercial samples. *N*-Chloro-

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[11] C. Eaborn and R. Taylor, *J. Chem. Soc.*, 1961, 247.

[12] R. A. Wirkkala, *Diss. Abs.*, 1963, **23**, 2329.

[13] Ref. 6, p. 78.

[14] E. T. Kaiser and L. Kevan, 'Radical Ions,' Wiley-Interscience, New York, 1968.

[15] P. D. Sullivan, *J. Amer. Chem. Soc.*, 1973, **95**, 288.

dimethylamine hydrogen sulphate was prepared as described previously;[16] the other *N*-chloroamines were prepared by the general procedure of Coleman,[17] distilled before use, and analysed iodometrically.

TABLE 3

Competitive amination of alkylbenzene

Pairs of substrates	Molar ratios	Cation radical	Relative rates
Toluene–benzene	1 : 1	$\overset{+}{\cdot}\mathrm{NHMe_2}$	11·6
Toluene–benzene	1 : 2	$\overset{+}{\cdot}\mathrm{NHMe_2}$	11·9
Toluene–benzene	1 : 3	$\overset{+}{\cdot}\mathrm{NHMe_2}$	11·9
Toluene–benzene	1 : 1	$\overset{+}{\cdot}\mathrm{NHEt_2}$	13·4
Toluene–benzene	1 : 2	$\overset{+}{\cdot}\mathrm{NH[CH_2]_5}$	9·8
Toluene–benzene	1 : 2	$\overset{+}{\cdot}\mathrm{NH[CH_2]_2O[CH_2]_2}$	33·4
Isopropylbenzene–benzene	1 : 1	$\overset{+}{\cdot}\mathrm{NHMe_2}$	9·4
Isopropylbenzene–benzene	1 : 2	$\overset{+}{\cdot}\mathrm{NHMe_2}$	9·2
t-Butylbenzene–benzene	1 : 1	$\overset{+}{\cdot}\mathrm{NHMe_2}$	5·3
t-Butylbenzene–benzene	1 : 1	$\overset{+}{\cdot}\mathrm{NHEt_2}$	4·7
t-Butylbenzene–benzene	1 : 2	$\overset{+}{\cdot}\mathrm{NHEt_2}$	4·5
Toluene–t-butylbenzene	1 : 1	$\overset{+}{\cdot}\mathrm{NHMe_2}$	2·4
Toluene–t-butylbenzene	1 : 2	$\overset{+}{\cdot}\mathrm{NHMe_2}$	2·3
o-Xylene–benzene	1 : 2	$\overset{+}{\cdot}\mathrm{NHMe_2}$	78·8
o-Xylene–benzene	1 : 2	$\overset{+}{\cdot}\mathrm{NHEt_2}$	71·2
o-Xylene–benzene	1 : 2	$\overset{+}{\cdot}\mathrm{NH[CH_2]_5}$	62·1
o-Xylene–toluene	1 : 1	$\overset{+}{\cdot}\mathrm{NHMe_2}$	6·7
o-Xylene–toluene	1 : 1	$\overset{+}{\cdot}\mathrm{NH[CH_2]_5}$	6·4
o-Xylene–toluene	1 : 2	$\overset{+}{\cdot}\mathrm{NH[CH_2]_2O[CH_2]_2}$	6·5
Biphenyl–toluene	1 : 2	$\overset{+}{\cdot}\mathrm{NHMe_2}$	17·0
Biphenyl–*o*-xylene	1 : 1	$\overset{+}{\cdot}\mathrm{NHMe_2}$	2·6

Determination of Partial Rate Factors. General Procedure.—To a stirred solution of the mixture of two aromatic substrates (0·1 mol) and *N*-chloroamine (0·005 mol) in nitroethane (84 ml) and sulphuric acid (28 ml) was added ferrous lactate (0·005 mol). The solution was kept at 20° in a thermostatted bath for 1 h with stirring. The mixture was diluted with water, basified with 30% NaOH solution, extracted with ether, and analysed by g.l.c. Products were identified as previously described.[18] G.l.c. analyses were performed on a Hewlett–Packard model 5750 G, equipped with a flame ionization detector, using a 6 ft × 1/8 in steel column, packed with 10% D.E.G.S. on Chromosorb W-AW-DMCS, 80—100 mesh and a 6 ft × 1/8 in steel column, packed with 10% U.C.C. W-982 on Chromosorb W-AW-DMCS, 80—100 mesh. The isomer ratios were obtained from analysis of the products of competitive experiments, using pure compounds as standards. The pairs of substrates used in competitive experiments are reported in Table 3. The agreement between direct and calculated values is good. The separation by g.l.c. of the *meta*- and *para*-isomers in the amination of toluene by *N*-chloro-piperidine and -morpholine is not complete, so that only the total relative rates are reported in Table 2. The values reported in Tables 1—3 are the average of at least three independent experiments and agree to within ±5%.

Chlorination of 1-*Chloropentane and Methyl Hexanoate by* N-*Chlorodimethylamine. General Procedure.*—To a stirred solution of 1-chloropentane (or methyl hexanoate) (0·1 mol) and *N*-chlorodimethylamine (0·05 mol) in nitroethane (84 ml) and sulphuric acid (28 ml) was added ferrous lactate (0·05 mol). The solution was kept at 20° for 30 min, diluted with water, extracted with ether, and analysed by g.l.c. as previously[19] described. Only monochloro-derivatives were present.

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