Inductive and Field Effects in Aromatic Substitution. Part IV.[1] The Nitration of 1- and 2-Phenylcyclohexylammonium Ions

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The kinetics and products of nitration of certain 1-phenyl- and 2-phenyl-cyclohexylammonium ions with $^+NMe_3$ or $^+NH_3$ poles are reported for reactions in aqueous sulphuric acid. The comparison of these results with those for the ions Ph[CH$_2$]$_n$$^+NR_3$ (R = H or Me) is used to investigate how the *meta*-deactivation produced by a –C–C–$^+$NR$_3$ substituent depends on the conformation of the carbon chain The comparison provides evidence for a contribution from the direct electrostatic effect of the pole but suggests that other types of interaction are significant when there is only one carbon atom between the pole and the ring.

PREVIOUS studies [2,3] of how the substituent effect of a nitrogen pole depends on its distance from the aromatic ring have dealt mainly with substituents of the type –[CH$_2$]$_n$·$^+$NR$_3$ (R = H or Me). In the transition state of an electrophilic aromatic substitution, the substituent has been assumed to adopt an extended conformation so that the distance of the pole from the ring is determined by the number of methylene groups in the carbon chain.[3] We now report two studies of how the substituent effect of the nitrogen pole depends on the conformation of the side-chain, the number of carbon atoms between the pole and the ring being kept constant. In this paper, the conformation of the side-chain is constrained by making it part of a cyclohexane ring: in the following paper, the constraint is applied by making the side-chain part of the bridge of an azacyclophane.

RESULTS

The nitration of a series of phenylcyclohexylammonium ions containing either protonated (–$^+$NH$_3$) or methylated (–$^+$NMe$_3$) nitrogen poles have been studied in aqueous sulphuric acid. As usual,[3] the reaction has been followed from the change in the u.v. spectrum. Stoicheiometric second-order rate coefficients (k_2) calculated from the equation Rate = k_2[ArH][HNO$_3$] are listed in Table 1 and plotted logarithmically in the Figure.

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[1] Part III, F. de Sarlo, G. Grynkiewicz, A. Ricci, and J. H. Ridd, *J. Chem. Soc.* (*B*), 1971, 719.

[2] F. R. Goss, C. K. Ingold, and I. S. Wilson, *J. Chem. Soc.*, 1926, 2440; F. R. Goss, W. Hanhart, and C. K. Ingold, *ibid.*, 1927, 250; C. K. Ingold and I. S. Wilson, *ibid.*, p. 810.

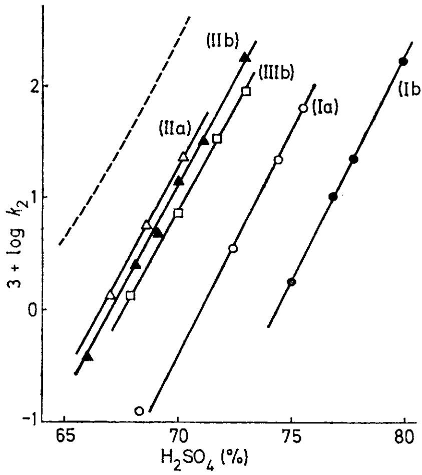
[3] T. A. Modro and J. H. Ridd, *J. Chem. Soc.* (*B*), 1968, 528.

In principle, the phenylcyclohexylammonium ions with protonated poles could undergo reaction through the neutral amines but the parallelism of the rate profiles with those for the methylated poles and with that for benzene (see Figure) shows that this reaction path is unimportant. This parallelism also permits the calculation of rates of nitration relative to benzene and these values, together with those for the related open chain derivatives, are in Table 2. All values are calculated with reference to the rate of nitration of benzene in 73·1% sulphuric acid at 25 °C as determined by Coombes, Moodie, and Schofield.[4] The results for the open-chain derivatives are based on the rate coefficients reported previously [1,3] but the relative rates for these substrates have been recalculated to refer to the above conditions.

TABLE 1

Stoicheiometric second-order rate coefficients (k_2/l mol^{-1} s^{-1}) for the nitration of phenylcyclohexylammonium ions in aqueous sulphuric acid at 25 °C

Substrate					
1-Ph·C_6H_{10}·$^+NH_3$	H_2SO_4 (%)	68·3	72·4	74·4	75·5
(Ia)	10^3k_2	0·126	3·55	21·9	63·1
1-Ph·C_6H_{10}·$^+NMe_3$	H_2SO_4 (%)	75·0	76·8	77·7	79·9
(Ib)	10^3k_2	1·78	10·2	22·4	166
trans-2-Ph·C_6H_{10}·$^+NH_3$	H_2SO_4 (%)	67·0	68·6	70·2	72·7
(IIa)	10^3k_2	1·35	5·62	22·9	151
trans-2-Ph·C_6H_{10}·$^+NMe_3$	H_2SO_4 (%)	66·0	68·1	69·1	70·0
(IIb)	10^3k_2	0·38	2·51	4·79	14·1
	H_2SO_4 (%)	71·1	72·9		
	10^3k_2	32·4	178		
cis-2-Ph·C_6H_{10}·$^+NH_3$	H_2SO_4 (%)	67·0	70·3	72·9	
(IIIa)	10^3k_2	1·70	26·3	224	
cis-2-Ph·C_6H_{10}·$^+NMe_3$	H_2SO_4 (%)	67·9	70·0	71·7	73·0
(IIIb)	10^3k_2	1·35	7·25	33·9	89·1



Plot of log k_2 for the nitration of phenylcyclohexylammonium ions in aqueous sulphuric acid at 25 °C. For key to numbering see Table 1 and structures in text. The points for *cis*-2-Ph·C_6H_{10}·$^+NH_3$ are omitted; these define the same line as that for *trans*-2-Ph·C_6H_{10}·$^+NH_3$. The broken line indicates the rate profile for benzene from ref. 4

The product compositions from these nitrations have been determined by oxidation to the corresponding benzoic acids followed by esterification and separation of the methyl esters by g.l.c. The results are listed in Table 3 for nitration in 80% sulphuric acid. Studies at other acidities have shown that the percentage of *ortho*-substitution in some of the protonated substrates decreases with acidity: we hope to investigate this in more detail later. The *meta* : *para* ratio is less sensitive to the acidity.

TABLE 2

Rate of nitration (relative to that of benzene) in 73·1% sulphuric acid at 25 °C

	Relative rate	
Substrate	R = H	R = Me
1-Ph·C_6H_{10}·$^+NR_3$	2·5 × 10^{-3}	8·16 × 10^{-5}
trans-2-Ph·C_6H_{10}·$^+NR_3$	7·27 × 10^{-2}	5·39 × 10^{-2}
cis-2-Ph·C_6H_{10}·$^+NR_3$	7·27 × 10^{-2}	2·70 × 10^{-2}
Ph·CH_2·$^+NR_3$	2·30 × 10^{-3}	4·28 × 10^{-5}
Ph·$(CH_2)_2$·$^+NR_3$	1·29 × 10^{-1}	1·29 × 10^{-1}

TABLE 3

Orientation of nitration in 80% sulphuric acid

	Orientation (%)		
Substrate	*o*	*m*	*p*
1-Ph·C_6H_{10}·$^+NH_3$		54	46
1-Ph·C_6H_{10}·$^+NMe_3$		73	27
trans-2-Ph·C_6H_{10}·$^+NH_3$	6	10	84
trans-2-Ph·C_6H_{10}·NMe_3	1	4	95
cis-2-Ph·C_6H_{10}·$^+NH_3$	21	12	67
cis-2-Ph·C_6H_{10}·$^+NMe_3$	1	5	94
Ph·CH_2·$^+NH_3$ [a]	21	45	34
Ph·CH_2·$^+NMe_3$		(85) [b]	
Ph·$(CH_2)_2$·$^+NH_3$ [c]	22	14	64
Ph·$(CH_2)_2$·$^+NMe_3$	6	16	78

[a] The *ortho*- and *para*-percentages for this ion were interchanged by mistake in the original publication[1] [b] For nitration in nitric acid: see ref. 2. [c] From ref. 1.

DISCUSSION

This work was carried out to obtain evidence on the relative importance of inductive and direct electrostatic interaction in the substituent effects of nitrogen poles. As in previous papers,[1,3] it is convenient to look first at the relative rates of *meta*-substitution to minimise the effect of electron-donation from the carbon chain. *meta*-Partial rate factors, calculated from the data in Tables 2 and 3, are listed in Table 4. This Table also shows the numbering used in the following discussion.

TABLE 4

meta-Partial rate factors for nitration in 73% sulphuric acid at 25 °C

	f_m	
Substrate	R = H (Series a)	R = Me (Series b)
1-Ph·C_6H_{10}·$^+NR_3$ (I)	3·5 × 10^{-3}	1·8 × 10^{-4}
trans-2-Ph·C_6H_{10}·$^+NR_3$ (II)	2·3 × 10^{-2}	6·6 × 10^{-3}
cis-2-Ph·C_6H_{10}·$^+NR_3$ (III)	2·6 × 10^{-2}	4·1 × 10^{-3}
Ph·CH_2·$^+NR_3$ (IV)	3·1 × 10^{-3}	1·1 × 10^{-4}
Ph·$(CH_2)_2$·$^+NR_3$ (V)	5·4 × 10^{-2}	6·2 × 10^{-2}

Consider first the comparison of the reactivity of the 1-phenylcyclohexylammonium ions (Ia, b) with the benzylammonium ions (IVa, b). These ions illustrate the effect of including the methylene group of the open ion in a cyclohexyl ring without change in the ring–pole

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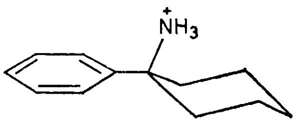
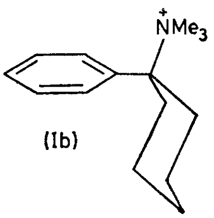
[4] R. G. Coombes, R. B. Moodie, and K. Schofield, *J. Chem. Soc.* (*B*), 1968, 800.

distance. From the conformational energies of monosubstituted cyclohexanes[5] the phenyl group should be equatorial in the protonated ion (Ia) but axial in the methylated ion (Ib); * however this conformational difference should not be of major importance in determining the reactivity at the *meta*-position.



(Ia)



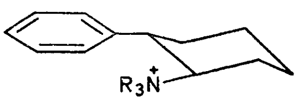
(Ib)

Comparison of the *meta*-partial rate factors for the protonated ions (Ia, IVa) (Table 4) shows that the presence of the cyclohexane ring has an insignificant effect on the reactivity at the *meta*-position. For the methylated ions (Ib, IVb), the cyclohexane derivative is the more reactive but the difference is less than a factor of two. The methylated poles are much more deactivating[6] and it is possible that the greater polarisability of the cyclohexyl ring is then more significant. The similarity of the partial rate factors in the protonated and methylated pairs of ions accords with the fact that the *meta*-partial rate factor for cyclohexylbenzene (2·5)[7] lies within the range of values reported for toluene.[8]

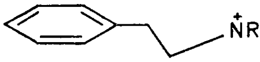
Now consider the reactivity at the *meta*-position of the *trans*-2-phenylcyclohexylammonium ions (IIa, b) and the 2-phenylethylammonium ions (Va, b). The structures (II) and (V) show that the inclusion of the carbon chain of the polar group as part of a cyclohexyl ring decreases the aromatic ring–pole distance. Hence, if the field effect of the pole is a significant factor, the relative reactivity of these ions in both the protonated and methylated series should be (V) > (II) > (I). The results in Table 4 show that this order is observed. This effect of the conformation of the carbon chain can also be seen from the ratios in Table 5 relating to an increase in the length of the carbon chain in the cyclohexyl and open-chain series. The interpretation in terms of the field effect assumes that the substituents occupy equatorial positions in the transition states for nitration of the *trans*-2-phenylcyclohexylammonium ions but this is supported by the similar reactivity of the *cis*-2-phenylcyclohexylammonium ions. With the *trans*-ions, the aromatic ring–pole distance could be increased by the adoption of the diaxial conformation but this is not possible with the *cis*-ions.

TABLE 5

Cyclohexyl series	Open-chain series
f_m^{II}/f_m^{I}	f_m^{V}/f_m^{IV}
6·6 (R = H)	17·4 (R = H)
36·7 (R = Me)	560 (R = Me)



(II) a; R = H, b; R = Me



(V) a; R = H, b; R = Me

A previous paper[3] has shown that the deactivating effect at the *meta*-position of the substituents $-[CH_2]_n-{}^+NMe_3$ in nitration can be related quantitatively to the effect of the poles on acid–base equilibria if the aromatic substituent effects are interpreted in terms of the electrostatic interaction in the transition state between the charge on the nitrogen pole and a unit charge at the centre of the ring. This unit charge is a crude model for the charge on the aromatic π-shell. The rate of *meta*-nitration of the benzene ring in phenylpyridinium ions and the 4-benzylpyridinium ion also accords with this model.[9] However, the present result suggests that this model is a marked oversimplification, at least when the ring–pole distance is short. From the conformational arguments outlined above and from the accepted bond lengths and bond angles, the distances from the nitrogen pole to the centre of the benzene ring are as follows for the ions listed in Table 4: (I) and (IV), 3·7 Å; (II) and (III), 3·9 Å; (V), 5·2 Å. On the basis of these distances, the above values of f_m^{II}/f_m^{I} should be much nearer to unity.

The simplest interpretation of the high values of f_m^{II}/f_m^{I} is in terms of the classical inductive effect operating through the carbon chain to the 1-position of the aromatic ring. However, for two reasons we feel that the use of these figures probably overestimates this inductive effect. First, the distances are based on an undistorted chair conformation of the cyclohexane ring and any distortion through steric interaction or the electrostatic repulsion of the positive groups in the transition state would increase the aromatic ring–pole distance and hence the electrostatic contribution to f_m^{II}/f_m^{I}. Secondly, the relative percentages of *para*-substitution in the nitration of the ions (II) and (I) suggests that the polarisability of the $2-{}^+NR_3-C_6H_{10}$ substituent is much greater than that of the $1-NR_3-C_6H_{10}$ substituent and this will itself increase the f_m^{II}/f_m^{I} ratio. Because of these complications a more detailed analysis of the relative importance of field and inductive effects is deferred to the following paper.

EXPERIMENTAL

Materials.—1-Phenylcyclohexylamine (Fluka) was distilled under vacuum from zinc powder before use. It was methylated to the *NN*-dimethyl derivative with formaldehyde and formic acid:[10] subsequently methylation to the

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* This argument assumes that the conformational energies of the $-CH_3$ and $-CMe_3$ groups are similar to those of the isoelectronic nitrogen poles ($-{}^+NH_3$, $-{}^+NMe_3$).

[5] J. A. Hinch, *Topics in Stereochemistry*, 1967, **1**, 199.

[6] For a discussion of the reasons for this difference see M. Brickman, J. H. P. Utley, and J. H. Ridd, *J. Chem. Soc.*, 1965, 6851.

[7] H. J. M. Dou, G. Vernin, and J. Metzger, *Compt. rend.*, 1968, **267**, 1515.

[8] J. H. Ridd, in 'Studies in Chemical Structure and Reactivity,' ed. J. H. Ridd, Methuen, London, 1965, ch. 7.

[9] F. De Sarlo and J. H. Ridd, *J. Chem. Soc.* (*B*), 1971, 712.

[10] R. T. Arnold and P. N. Richardson, *J. Amer. Chem. Soc.*, 1954, **76**, 3649.

quaternary iodide was carried out with methyl iodide in dry ether. The iodide (m.p. 160 °C) was dissolved in water and *trimethyl-1-phenylcyclohexylammonium perchlorate* was precipitated by the addition of saturated aqueous sodium perchlorate. The product, after recrystallisation from dry ethanol, had m.p. 153—154° (Found: C, 56·1; H, 7·5; N, 4·4. $C_{15}H_{24}ClNO_4$ requires C, 56·7; H, 7·6; N, 4·4%).

trans-2-Phenylcyclohexylamine was prepared from 2-chlorocyclohexanone by treatment with phenylmagnesium bromide to give 2-phenylcyclohexanone[11] followed by conversion into the oxime and reduction with sodium in ethanol. The product had m.p. 57—58 °C (lit.,[10] 59—60 °C). The amine was converted into the quaternary iodide as described above, m.p. 233—234 °C (lit.,[10] 233·5—235 °C). Treatment of an aqueous solution of the iodide with saturated aqueous sodium perchlorate gave *trimethyl-*trans*-2-phenylcyclohexylammonium perchlorate*, m.p. 203—204 °C (Found: C, 56·6; H, 7·7; N, 4·7%).

cis-2-Phenylcyclohexylamine was prepared by the reduction of *cis*-1-nitro-2-phenylcyclohexene by iron and acetic acid; this type of reaction appears to be stereospecific.[12] The product had b.p. 133 °C at 10 mmHg. The nitro-compound used as the starting material was prepared as described.[13] The amine was converted into the quaternary iodide and quaternary perchlorate as described above. Trimethyl-*cis*-2-phenylcyclohexylammonium iodide had m.p. 215—217 °C (lit.,[10] 215—217°). *Trimethyl-*cis*-2-phenylcyclohexylammonium perchlorate* had m.p. 120—122 °C (Found: C, 57·2; H, 7·6; N, 4·6%).

Kinetics.—Weighed quantities of the free base (or of the quaternary perchlorate) and of nitric acid (*d* 1·42) were added to separate volumes of sulphuric acid of the required concentration to give known concentrations of the reactants (*ca.* 5×10^{-3}M). Since the nitric acid used contained some water, a small amount of sulphuric acid (*d* 1·84) was added to the solution containing nitric acid so that the percentage of water remained unchanged. The solutions of the reactants were brought to 25 °C and mixed. Samples (2 ml) were extracted at suitable times by a calibrated pipette and quenched in distilled water to give a final volume of 50 ml. The optical density (D) of these solutions was then measured at *ca.* 270 nm in a 1 cm cell in a Unicam SP 500 spectrophotometer. The combined concentration of nitro-compounds (x) was calculated from the equation $x = (yD - \varepsilon_1 a)/(\varepsilon_2 - \varepsilon_1)$ where y is the dilution factor, a is the initial concentration of the aromatic substrate, ε_1 is the extinction coefficient of the aromatic substrate, and ε_2 is the effective extinction coefficient of the mixture of nitro-compounds formed. The wavelengths and extinction coefficients used are in Table 6. As usual with these nitrations in sulphuric acid, satisfactory second-order kinetics were obtained. Some kinetic runs were also carried out on the nitration of the benzyltrimethylammonium ion: these agreed well with the rate profile reported previously.

TABLE 6

Substrate	(Ia)	(Ib)	(IIa)	(IIb)	(IIIa)	(IIIb)
λ/nm	274	263	277	274	274	274
ε_1	25	335	26	43	40	22
ε_2	7500	7958	9060	9281	7900	9330

Products.—A slight excess of nitric acid was added to a solution of the aromatic substrate [0·5 g (amine) or 1·0 g (quaternary salt)] in sulphuric acid (5 ml) of the required concentration. After allowing sufficient time for nitration to go to completion, the mixture was diluted with water (to *ca.* 100 ml), brought to pH 9—10, and oxidised by the gradual addition of a slight excess of potassium permanganate (5%) at 90 °C. The solution was finally heated under reflux for 9 h and filtered. The oxides of manganese were washed and the combined filtrates were concentrated, acidified, and extracted several times with ethyl acetate and ether. The organic layer was dried (Na_2SO_4) and evaporated to give a mixture of nitrobenzoic acids. This mixture was suspended in dry ether and methylated with excess of nitromethane. After evaporation, the resulting methylnitrobenzoates were dissolved in ethyl acetate and analysed by g.l.c. on a Carbowax 20M column at 200 °C.

[2/214 *Received, 2nd February*, 1972]

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[11] M. S. Newman and M. D. Farbman, *J. Amer. Chem. Soc.*, 1944, **66**, 1550.

[12] *Cf.* N. Kornblum, W. D. Gurowitz, H. O. Larson, and D. E. Hardies, *J. Amer. Chem. Soc.*, 1960, **82**, 3099.

[13] H. E. Zimmerman and T. E. Nevins, *J. Amer. Chem. Soc.*, 1957, **79**, 6559.