Highly Selective Aromatic Chlorination. Part 3.[1] Kinetics and Mechanism of Chlorination of Electron-rich Aromatic Compounds by *N*-Chloroamines in Acidic Solution

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The highly selective chlorination of electron-rich aromatic compounds with *N*-chloroamines in trifluoroacetic acid (TFA) is first order in both the aromatic substrate and the chlorinating agent. Kinetic and competitive kinetic studies show that electron-donating substituents on the substrate and electron-withdrawing substituents on the *N*-chloroamine have a marked rate-enhancing effect. Two mechanisms that fit the experimentally observed kinetics and that account for the high selectivity for 4-chlorination in terms of an electronic effect are proposed, namely an arenium-ion mechanism and an electron-transfer chain reaction. Evidence from chemical trapping experiments and from other studies suggest that for the majority of the substrates the chlorination proceeds by the arenium ion mechanism. However, for substrates, such as 1,4-dimethoxybenzene, that are very susceptible to one-electron oxidation chlorination may proceed at least in part by the electron-transfer chain reaction.

In previous papers in this series[1,2] we have reported the remarkable selectivity of aromatic chlorination by acidic solutions of *N*-chlorodialkylamines and *N*-chlorotrialkylammonium salts. In particular, the *N*-chlorinated amines are efficient reagents for monochlorination of the 4-position of aromatic compounds that have a π-donor (+*M*) substituent. Thus phenols, phenol ethers, anilines, and related compounds with a vacant 4-position are rapidly chlorinated at room temperature. The related selectivity of chlorination of alkylbenzenes by *N*- chloroamines has also been reported very recently by Minisci and co-workers.[3]

From our studies it is clear that the selectivity arises from electronic effects of the substituents on the aromatic ring rather than from steric effects of a bulky attacking species. Furthermore, the dependence of the selectivity on a strongly acid reaction medium indicates that the active species are the positively charged protonated chloroamines rather than their free bases. The latter conclusion concurs with the limited kinetic studies carried out on these reactions in the 1950s.[4] It is also noteworthy that similar selectivities in aromatic chlorinations have been reported with the positively charged *S*-chlorodimethylsulphonium chloride.[5]

In this paper we describe our kinetic and competitive kinetic studies which have been designed to throw light on the influence of electronic effects of substituents on the rates of reaction. We also report on chemical trapping experiments to trap reactive intermediates. The results are used to propose a mechanism for these aromatic chlorinations.

Results

Kinetic Method.—2-Chloroanisole was chosen as the substrate since its reactions with *N*-chloroamines occur at a convenient rate for kinetic studies and do not readily proceed beyond monochlorination. The reactions of more reactive substrates such as anisole and phenol are too fast to be followed using the methods described below. The reactions were carried out with trifluoroacetic acid (TFA) as the solvent in a thermostatted waterbath at 25, 21, or 5 °C with a greater than eightfold excess of substrate over chloroamine. In all the kinetic studies, with the exception of a set of experiments with *N*-chloro-*N*-methylcyclohexylamine, the reaction rates were monitored titrimetrically. Aliquots of the reaction mixtures were added to excess of aqueous potassium iodide and the iodine liberated by the unchanged *N*-chloroamine [reaction (1)] was titrated against standard thiosulphate. The validity of the method was checked with standard solutions of *N*-chloroamines in TFA, which also served to show that the *N*-chloroamines are stable in TFA solution for much longer than the chlorination reaction times.

$$R_2\overset{+}{N}HCl + 2I^- \longrightarrow R_2NH + I_2 + Cl^- \qquad (1)$$

For *N*-chloro-*N*-methylcyclohexylamine the reaction was also followed by measuring the build-up of the product, 2,4-dichloroanisole, with time by g.c. This method was not as convenient or reliable as titrimetry and was not used to a greater extent.

Determination of the Order of Reaction in Substrate and N-*Chlorinated Amine.*—The titrimetric method gave good pseudo-first-order plots for ln[*N*-chloroamine] against time that were linear for at least 2 half-lives for the slowest reactions and >3 half-lives for the faster ones (see for example data for reaction of *N*-chloro-3-cyano-*N*-methylbenzylamine, Figure 1). These results show that the chlorinations are first order in *N*-chloroamine. This was also confirmed for the reaction of *N*-chloro-*N*-methylcyclohexylamine by following the formation of the product 2,4-dichloroanisole with time, which gave pseudo-first-order rate constants (k_{obs}) for a series of reactions with different initial *N*-chloroamine concentrations (Table 1). The mean value of these k_{obs} values, obtained by the g.c. method (5.77×10^{-5} s^{-1}), is close to that from the more precise titrimetric procedure (6.97×10^{-5} s^{-1}).

That the chlorinations are first order with respect to the aromatic compounds is apparent from the linear dependence of k_{obs} on the substrate concentration (Table 2). The calculated second-order rate constants for the reaction of 2-chloroanisole with *N*-chloro-*N*-methylcyclohexylamine are also included in Table 2.

Effect of N-*Chlorinated Amine Structure on the Rate of Chlorination.*—2-Chloroanisole has been chlorinated with a selection of *N*-chloroamines and the side spread of second-order rate constants (>10^6-fold) shows that the amine structure has a

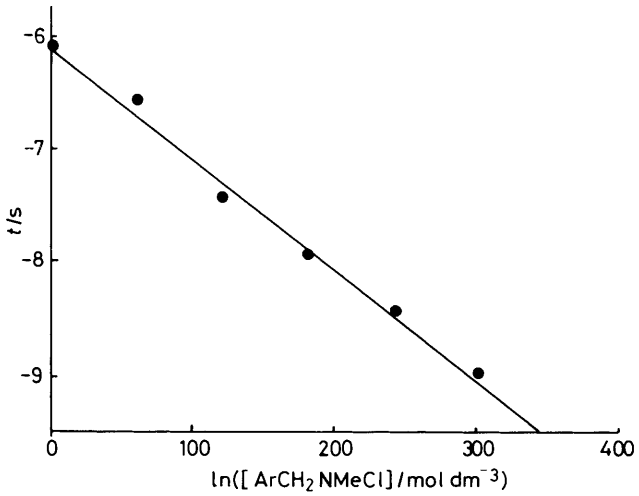


Figure 1. Pseudo-first-order plot of ln[*N*-chloroamine] against time for chlorination of 2-chloroanisole by *N*-chloro-3-cyano-*N*-methylbenzylamine in TFA at 25 °C.

Table 1. Pseudo-first-order rate constants (k_{obs}) and half-lives for the formation of 2,4-dichloroanisole in the chlorination of 2-chloroanisole by *N*-chloro-*N*-methylcyclohexylamine in TFA at 25 °C.[a]

Initial concentration of *N*-chloroamine/ 10^{-3} mol dm^{-3}	k_{obs}/ 10^{-5} s^{-1}	$t_{\frac{1}{2}}$/ 10^{3} s
2.33	5.36	1.30
3.84	5.93	1.17
5.18	5.98	1.16
5.72	5.97	1.16
5.96	6.22	1.12
7.36	5.17	1.34

[a] Initial concentration of 2-chloroanisole, 7.8×10^{-2} mol dm^{-3}; the reaction was followed by g.c. by measuring the build-up of 2,4-dichloroanisole with time.

Table 2. Dependence of the pseudo-first-order rate constants (k_{obs}) for the chlorination of 2-chloroanisole with *N*-chloro-*N*-methylcyclohexylamine, on substrate concentration at 25 °C.[a]

[2-Chloroanisole]$_0$/ 10^{-2} mol dm^{-3}	k_{obs}/ 10^{-5} s^{-1}	$k'_2 = k_{obs}$/[2-chloroanisole]/ 10^{-4} dm^3 mol^{-1} s^{-1}
1.53	1.32	8.63
3.10	2.66	8.58
4.70	4.23	9.00
6.25	5.33	8.53
7.80	6.97	8.94

[a] Initial concentration of *N*-chloro-*N*-methylcyclohexylamine, 1.7×10^{-3} mol dm^{-3}, the reaction was followed titrimetrically by measuring the disappearance of *N*-chloro-*N*-methylcyclohexylamine with time.

very marked effect on the rate of reaction (Table 3). The influence of electronic effects of substituents, free from the interfering steric effects, on the reactivity of *N*-chloroamines has been examined with 3- and 4-substituted *N*-chloro-*N*-methylbenzylamines (Table 4). A Hammett plot of $\log_{10}$ (second-order rate constant) *versus* σ (Figure 2) reveals the large dependence of the rate on the nature of the substituent (ρ = 2.65) and that electron-withdrawing groups enhance the rate of chlorination.

Relative Reactivities of Aromatic Substrates.—To obtain a measure of the reactivities of the substrates, phenol, anisole, and

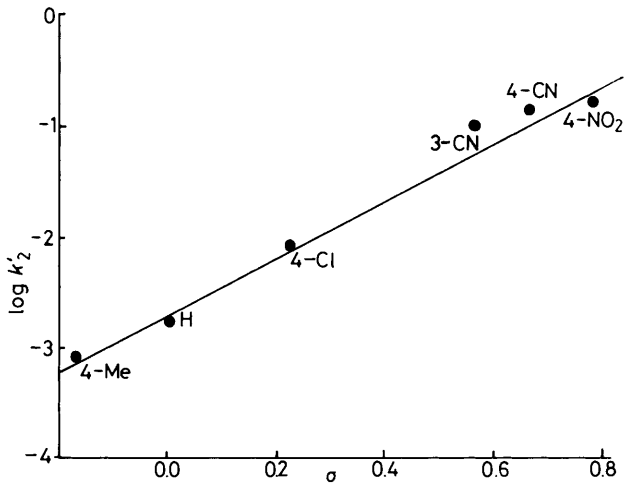


Figure 2. Hammett plot for the chlorination of 2-chloroanisole with substituted *N*-chloro-*N*-methylbenzylamines in TFA at 5 °C.

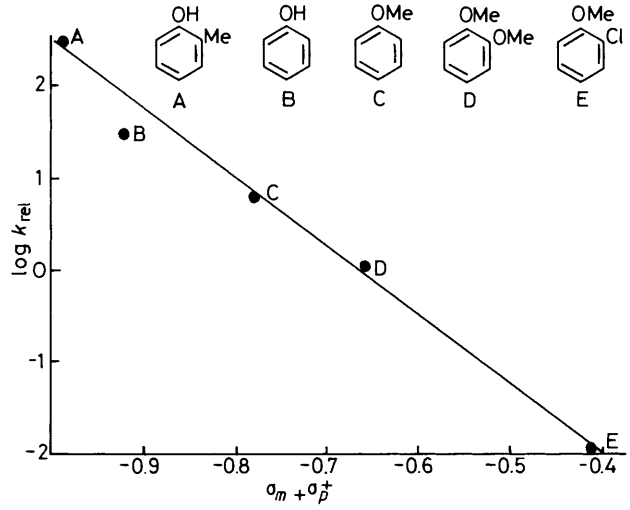


Figure 3. Plot of log (reactivity relative to 1,2-dimethoxybenzene) against $\sigma_m + \sigma_p^+$ for chlorination of electron-rich aromatic substrates by *N*-chloropiperidine in TFA at 21 °C.

three of their 2-substituted derivatives were chlorinated in pairs in competitive reactions using *N*-chloropiperidine and *N*-chlorotriethylammonium ion. The substrates were selected because each gives essentially one product (4-chlorination) and steric effects are minimised since none has a substituent in the 3- or 5-position. By using a large excess of the substrates over the chlorinating agent their relative reactivities could be obtained from the relative yields of the two 4-chlorinated products. Phenol, anisole, and 2-chloroanisole were chlorinated in direct competition with 1,2-dimethoxybenzene. However, because of analytical problems, this was not possible for 2-methylphenol and its reactivity relative to 1,2-dimethoxybenzene was obtained indirectly by competition with phenol and anisole. The reactivities of the substrates relative to 1,2-dimethoxybenzene (k_{rel}, Table 5) show that the electronic effects of substituents have a very pronounced effect on the rates of chlorination and that electron-donating groups enhance reactivity. The data give good linear Hammett plots of log k_{rel} against ($\sigma_m + \sigma_p^+$) with ρ = −7.4 (Figure 3) and −8.0 for *N*-chloropiperidine and *N*-chlorotriethylammonium ion respectively.

The relative reactivities of the three dimethoxybenzenes were

Table 3. Second-order rate constants for the chlorination of 2-chloroanisole in TFA at 25 °C.[a]

Chlorinating agent	k_{obs}/ 10^{-5} s^{-1}	k_2'/ 10^{-4} dm^3 mol^{-1} s^{-1}
N-Chloromorpholine	(9.54 ± 0.2) × 10^4	12.2 × 10^4
N-Chloro-*N*-methylbenzylamine	118 ± 16	150
N-Chloro-*N*-methylcyclohexylamine	6.57 ± 0.15	8.4
N-Chloroperhydroazocine	4.62 ± 0.07	5.9
N-Chloroperhydroazepine	2.94 ± 0.12	3.8
N-Chloropyrrolidine	2.09 ± 0.03	2.7
N-Chloro-2,2,5,6-tetramethylpiperidine	0.776 ± 0.005	0.99
N-Chloropiperidine	0.58 ± 0.05	0.74
N-Chloro-1-azoniabicyclo[2.2.2]octane	*ca.* 1.6 × 10^{-2}	0.02

[a] Initial concentrations; 2-chloroanisole, 7.8 × 10^{-2} mol dm^{-3} and *N*-chloroamine, *ca.* 3.5 × 10^{-3} mol dm^3; the reactions were followed titrimetrically by measuring the disappearance of *N*-chloroamine.

Table 4. Second-order rate constants for the chlorination of 2-chloroanisole in TFA at 5 °C.[a]

Chlorinating agent $XC_6H_4CH_2NMeCl$	k_{obs}/ s^{-1}	k_2'/ dm^3 mol^{-1} s^{-1}
X = 4-Me	(5.77 ± 0.5) × 10^{-5}	7.4 × 10^{-4}
H	(1.38 ± 0.07) × 10^{-4}	1.8 × 10^{-3}
4-Cl	(6.11 ± 0.7) × 10^{-4}	7.8 × 10^{-3}
3-CN	(7.6 ± 1.1) × 10^{-3}	9.8 × 10^{-2}
4-CN	(1.06 ± 0.12) ± 10^{-2}	1.4 × 10^{-1}
4-NO_2	(1.32 ± 0.06) × 10^{-2}	1.7 × 10^{-1}

[a] Initial concentration of 2-chloroanisole, 7.8 × 10^{-2} mol dm^{-3}; the reactions were followed titrimetrically by monitoring the disappearance of the *N*-chloroamine.

Table 5. Relative rates of chlorination of phenol, anisole, and some 2-substituted derivatives in TFA at 21 °C.

Substrate	Relative rate of chlorination[a] by *N*-chloropiperidine	Relative rate of chlorination[a] by *N*-chlorotriethylammonium ion
2-Methylphenol	253[b]	562[b]
Phenol	28	50
Anisole	6.2	5.2
1,2-Dimethoxybenzene	1.0	1.0
2-Chloroanisole	0.01	0.009

[a] Values ± 5%. [b] Calculated from reactivities relative to phenol and to anisole.

Table 6. Relative reactivities of isomeric dimethoxybenzenes towards chlorination by *N*-chloropiperidine in TFA at 21 °C.

Dimethoxybenzene	Relative reactivity
1,3	50 000
1,2	6.0
1,4	1.0

also measured (Table 6). For the competition between the 1,2- and 1,4-isomers the product distribution was monitored during the course of reaction. This revealed the ratio of the mono-chlorinated products and hence the relative reactivities of the substrates remained constant throughout the reaction. The reactivity of 1,3-dimethoxybenzene was so much greater than that of either of its isomers it was impractical to obtain the value by direct competition. Instead, it was measured indirectly utilising 2- and 3-methylphenol as competing substrates.

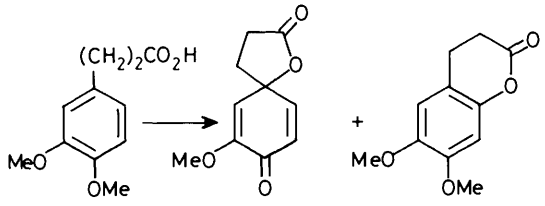
Trapping and Attempted Trapping of Reactive Intermediates.— The possibility that the chlorinations might involve reaction of the substrate radical cation with chloride ion was investigated by carrying out the chlorination of anisole with *N*-chloropiperidine in the presence of competitive nucleophiles [Reactions (2) and (3)].

$$ArH^{+\cdot} \xrightarrow{Cl^-} ArHCl^{\cdot} \xrightarrow[-H^+]{-e^-} ArCl \quad (2)$$

$$ArH^{+\cdot} \xrightarrow{HX} ArHX^{\cdot} \xrightarrow[-H^+]{-e^-} ArX \quad (3)$$

$$HX = HF, CH_3CO_2H, H_2O$$

A threefold excess of fluoride over oxidant, or using a 1:1 ratio of acetic acid or water to TFA as solvent gave an unchanged chloroanisole product distribution and no evidence of fluoro- or acetoxy-anisoles or methoxyphenols respectively. Similarly, reactions of anisole with *N*-chloromorpholine and *N*-chloro-*N*-methylbenzylamine in the presence of bromotrichloromethane gave chloro- but no bromo-anisoles (<0.1%). Attempts to trap aromatic radical cations in these chlorinations by intramolecular cyclisation were also unsuccessful. Thus the reactions of *N*-chlorotetramethylpiperidine with 3-(3,4-dimethoxyphenyl)propionic acid showed broadening of ^{1}H n.m.r. signals of the substrate (seen in earlier studies with other dimethoxybenzenes[1]) and gave chlorinated products rather than the cyclised products expected of the aromatic radical cation.[6] [Reaction (4)]. The possible involvement of aminium radicals in these chlorinations was examined with *N*-chloro-*N*-methylpentylamine and *N*-chloro-*N*-methyl-4-phenylbutylamine. The aminium radicals from these amines, particularly the phenylbutylamine, should undergo Hofmann–Löffler–Freytag cyclisation[7] in competition with the aromatic chlorination [Reaction (5)]. Anisole and five-substituted anisoles were used as substrates, however, only in the reaction of 1,4-dimethoxybenzene was a significant yield of the *N*-methylpyrrolidine detected (Table 7).



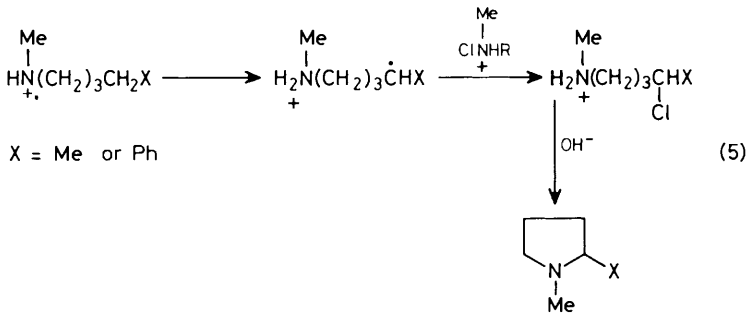
(4)

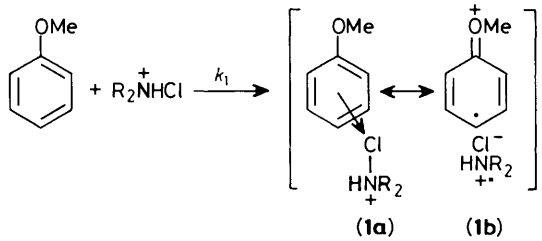
Discussion

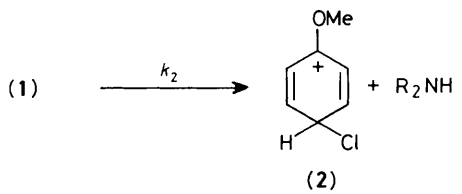
In the previous papers in this series we used product studies to investigate the highly selective chlorination of electron-rich

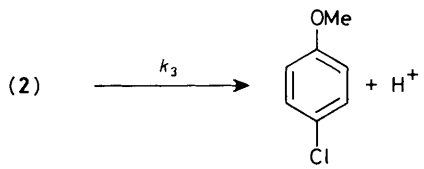
Table 7. The amino products following work-up of the reactions of *N*-chloro-*N*-methylpentylamine and *N*-chloro-*N*-methyl-4-phenylbutylamine with aromatic compounds in TFA.

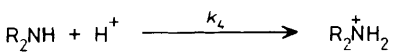
Substrate	*N*-chloroamine $X(CH_2)_4NMeCl$	Product distribution (%) $X(CH_2)_4NHMe$	$(CH_2)_3CHXNMe$
1,4-Dimethoxybenzene	X = Me	97	3
Anisole	Me	100	—
1,4-Dimethoxybenzene	Ph	77	23
2-Chloroanisole	Ph	100	—
4-Chloroanisole	Ph	100	trace
1,2-Dimethoxybenzene	Ph	100	trace
4-Methoxytoluene	Ph	100	—
Anisole	Ph	100	—



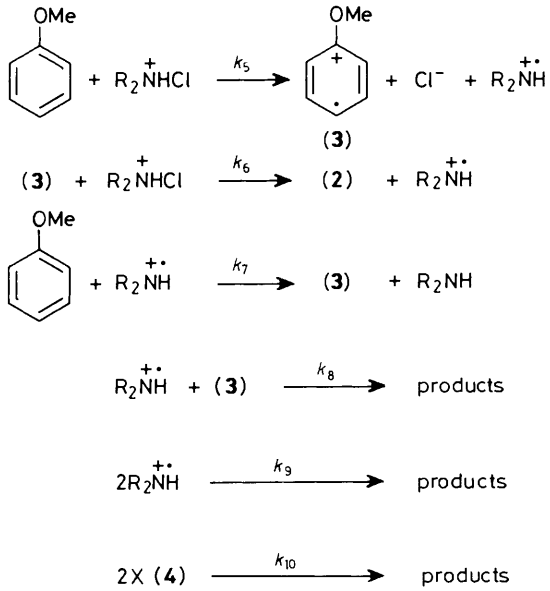








Scheme 1.



Scheme 2.

aromatic compounds with *N*-chlorinated amines in acid solution. This work implicates protonated *N*-chlorodialkylamines or *N*-chlorotrialkylammonium ions, depending on the *N*-chlorinated amine employed, as the active chlorinating agent rather than chlorine or a solvent derived species such as chlorine trifluoroacetate or protonated chlorine trifluorocetate.[1,2]

The results can be accounted for by two alternative mechanisms (Schemes 1 and 2, illustrated with anisole and a protonated *N*-chlorodialkylamine). The first is an arenium-ion mechanism involving Cl^+ transfer from the *N*-chloroammonium ion to the aromatic substrate. The high selectivity for 4-substitution would arise from the preferred arrangement of reactants in a charge-transfer complex. This is an electronic rather than a steric effect, in agreement with our previous observations that the high selectivity does not arise from the bulk of the attacking reagent.[1,2] Such an orientation of reactants might be expected in the charge-transfer complex since it allows a maximum separation of positive charges. This is illustrated in the resonance hybrid with complete electron transfer (**1b**). Donor–acceptor

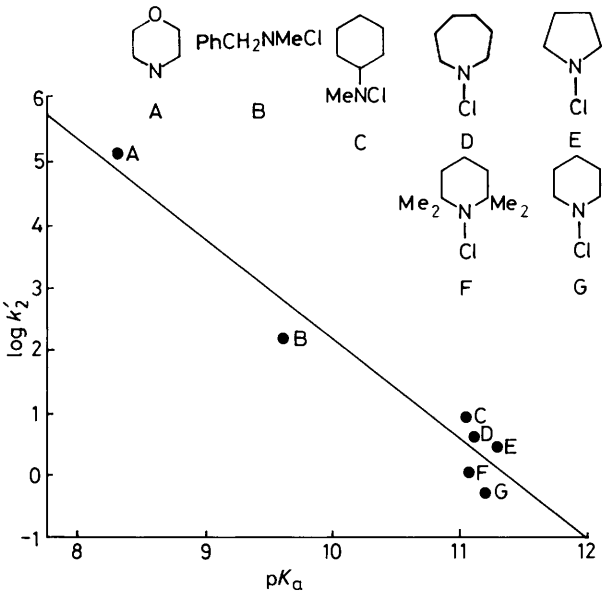
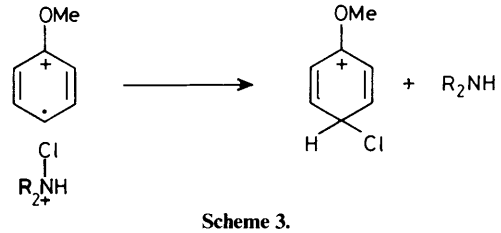


Figure 4. Plot of log (second-order rate constant for chlorination) against pK_a of parent amine for reaction of *N*-chloroamines with 2-chloroanisole in TFA at 25 °C.

complexes between aromatic compounds and halogens are well documented[8] although they do not normally lead to selective aromatic substitution. However, there is good evidence that the selectivity of chlorinations by other reagents can arise from highly organised complexes.[9] Presumably the donor–acceptor interactions of aromatic compounds with neutral halogens would not involve as large a charge separation and as a result, such strong directional effects as the positively charged *N*-chloroammonium ion in complex (**1**).

In Scheme 2 electron transfer in the charge-transfer complex initiates a chain reaction with aromatic radical cations and aminium radicals as chain carriers. The one-electron reduction of *N*-chloroammonium ions is well documented and the reactions of the resultant aminium radicals has been extensively investigated by Minisci and others. The high selectivity in these chlorinations would arise from chlorine-atom transfer between the aromatic radical cations and the *N*-chloroammonium ion. Repulsion of positive charges in this reaction might well lead to a marked selectivity for 4-substitution (Scheme 3). The radicals



Scheme 3.

formed in the electron–transfer chain reaction would also account for e.s.r signals and paramagnetic broadening of ^1H n.m.r. spectra in the reactions of 1,4-dimethoxybenzene[1] and naphthalene[11] and also for some of the products obtained from substrates with blocked 4-positions.[1]

The observed kinetic rate law, (Equation I) cannot be used to decide between the two alternative schemes, since, although it is consistent with the arenium-ion mechanism (Scheme 1), a steady-state treatment reveals that it will also be observed with Scheme 2 (Equation II) if the main termination step is the crossed reaction between $R_2\overset{+\bullet}{N}H$ and $Ar\overset{+\bullet}{H}$ ($k_8 \gg k_9$ or k_{10} gives Equation II). Only if the chain terminations (k_9) and (k_{10}) become significant will there be deviations from the first-order kinetics observed.

$$-d[R_2\overset{+}{N}HCl]/dt = k[ArH][R_2\overset{+}{N}HCl] \quad (I)$$

$$-d[R_2\overset{+}{N}HCl]/dt = \left[k_5 + \left(\frac{k_5k_6k_7}{k_8}\right)^{\frac{1}{2}}\right][ArH][R_2\overset{+}{N}HCl) \quad (II)$$

The influence of substituents on the rates of chlorination are large and Hammett correlations show that electron-donating groups on the aromatic substrate (ρ is large, negative, and correlates with σ^+) and electron-withdrawing groups on the *N*-chloroamine (ρ is positive and correlates with σ) favour reaction. The latter influence is also apparent, for both the aliphatic and benzylic *N*-chloroamines, from the linear correlation between $\log_{10}$(second-order rate constant for chlorination) by a given *N*-chloroamine and the pK_a of the parent amine (Figure 4). Clearly factors, such as electron-withdrawing groups, that increase the acidity of the protonated amine similarly increase the reactivity of the *N*-chloroammonium ion.

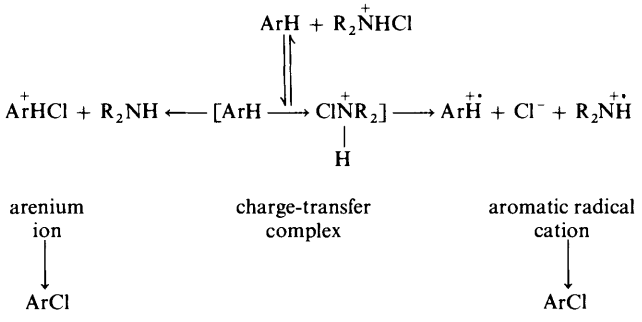
The size and direction of the electronic effects are consistent with the arenium-ion mechanism. This is well illustrated by a comparison of the ρ values for other arenium-ion substitutions with those found in this study (Table 8). However, since both the arenium-ion and electron-transfer mechanisms both rely on π-electron availability the electron-transfer chain reaction might be expected to show similar substituent effects. Indeed Sheldon and Kochi[17] point out that distinctions between these mechanisms cannot easily be made on the basis of substituent effects.

A closer analysis of structural effects on the reactivity of the *N*-chloroamines reveals the significantly lower reactivity of the six-membered ring *N*-chloropiperidine than the 5-, 7-, and 8-membered ring analogues (Table 3). Such trends have been noted before, although the differences in rates in this study are much smaller than reported previously.[18] Such rate-structure profiles occur in reactions where the hybridisation of a ring carbon or nitrogen changes from sp^3 to sp^2 and have been attributed to changes in torsional strain accompanying these changes in hybridisation. The electron-transfer chain reaction which involves the formation of an sp^2-hybridised nitrogen in the aminium radical could account for the attenuated trend in the cyclic *N*-chloroamine reactivities. Likewise for the arenium-ion mechanism the rate-determining transition state between the charge-transfer and σ complexes could have significant contribution from the radical cation structure (**1b**). These conclusions could also explain the low reactivity of *N*-chloro-1-azoniabicyclo[2.2.2]octane. This bridgehead *N*-chloroammonium ion would be expected to react more slowly in any process that leads to the formation of the strained bridgehead aminium radical.[18c]

It has been suggested[19] that in a reaction in which an aromatic compound donates one electron to an electrophilic reagent, 1,2- and 1,4-dimethoxybenzene should be more reactive than the 1,3-isomer. This conclusion is in agreement with the energies of the charge-transfer absorptions of the three compounds with the acceptor tetracyanoethene which predicts the order of reactivity 1,4- > 1,2- > 1,3-dimethoxybenzene.[20] By contrast, bromination of the three aromatics in acetic acid, considered to be a classical arenium-ion mechanism, gives the order of reactivity 1,3- > 1,2- > 1,4-dimethoxybenzene.[21] These observations suggest that the order of reactivity of these substrates might be a useful mechanistic probe to distinguish between the mechanisms in Schemes 1 and 2. Competitive chlorinations with *N*-chloropiperidine show that the order of reactivity is the same as for bromination in acetic acid, suggesting that the reactions proceed by an arenium-ion mechan-

Table 8. Hammett ρ values for reactions of aromatics compounds with electrophilic reagents.

Reaction	Reagents	ρ	Ref.
Nitration	HNO_3/Ac_2O	−6.0	12
Chlorosulphonation	SO_2Cl_2/CH_3NO_2	−7.2	13
Bromination	Br_2/HOAc	−12.1	14
Chlorination	Cl_2/CH_3NO_2	−13.8	15
Chlorination	Cl_2/HOAc	−10.0	15
Chlorination	*N*-chloropiperidine/TFA	−7.4	This study
Chlorination	*N*-chlorotriethylammonium ion/TFA	−8.0	This study
Electron transfer	Co(III) triacetate/HOAc	−2.4	16



Scheme 4.

ism. However, the validity of this conclusion can be questioned on the grounds that in a competitive reaction involving aromatic radical cations the results are likely to be complicated by crossed one-electron exchange between the aromatic substrates and the radical cations. Consequently, the product distribution will not necessarily reflect the ease of one-electron oxidation of the aromatics but would depend on the relative stabilities of the radical cations towards further reaction. Such complications have been reported previously for the one-electron oxidation of aromatics by peroxydisulphate.[22]

Trapping experiments provide more convincing evidence that the chlorinations normally proceed *via* an arenium-ion mechanism. Thus, all attempts to trap aromatic radical cations from the reactions of anisole with external nucleophiles (HF, CH_3CO_2H, and H_2O) were unsuccessful. Although the range of external nucleophiles that can be used in the reactions is limited by the acidity of the solvent and by the need to avoid nucleophile oxidation [Reaction (6)]. In the presence of a trap the aromatic radical cations, if present, would have been expected to be diverted, at least in part, to products other than chloroaromatics. Indeed, the solvent TFA should be sufficiently nucleophilic to trap aromatic radical cations,[23] however, aromatic trifluoroacetates were not detected.

$$Nu^- + R_2\overset{+}{N}HCl \longrightarrow Nu^{\cdot} + Cl^- + R_2\overset{+\cdot}{N}H \quad (6)$$

The intramolecular cyclisation of the 3-(3,4-dimethoxyphenyl) propionic acid radical cation has been achieved by one-electron oxidation of the parent acid by thallium(III) trifluoroacetate in TFA.[6] However, with the chlorinating systems chlorination of the dimethoxyphenylpropionic acid (and not cyclisation) occurs, confirming that at least for this substrate, the chlorinations do not involve aromatic radical cations.

Attempts to trap aromatic radical cations from the reaction of *N*-chloro-*N*-methylcyclohexylamine and *N*-chloromorpholine with anisole using bromotrichloromethane were also unsuccessful.

Further evidence against the electron-transfer chain reaction comes from the absence of aminated aromatic products. These products would be predicted from the work of Minisci and co-workers, which shows that electron-rich aromatics are rapidly aminated by dialkylaminium radicals.[24] The possible involvement of aminium radicals in these chlorinations was investigated further using *N*-chloro-*N*-methylpentylamine and *N*-chloro-*N*-methyl-4-phenylbutylamine. If these chlorinating agents generate their corresponding aminium radicals they should undergo the Hofmann–Löffler–Freytag reaction[7] to give, on basic work-up, the 2-substituted *N*-methylpyrrolidine [Reaction (5)] in competition with aromatic chlorination. With five electron-rich substrates (Table 7) only aromatic chlorination was observed; interestingly, however, with a sixth, 1,4-dimethoxybenzene, significant amounts of the pyrrolidines were obtained. As expected, higher pyrrolidine yields were obtained from *N*-chloro-*N*-methyl-4-phenylbutylamine where δ-hydrogen abstraction can occur more readily than from the *N*-chloropentylamine. These experiments suggest that for these six aromatic substrates aminium radicals are only formed in the reactions of 1,4-dimethoxybenzene, a substrate that is particularly susceptible to one-electron oxidations and which is blocked to 4-chlorination. For the reactions of the other aromatics, even the two structurally related substrates, 1,2-dimethoxybenzene and 4-methoxytoluene, aminium radicals are not present.

In conclusion, the evidence presented above suggests that these highly selective aromatic chlorinations normally take place by an arenium-ion mechanism (Scheme 1). However, with substrates that are particularly prone to one-electron oxidation (1,4-dimethoxybenzene and naphthalene[11]) part, or all, of the reaction may proceed by an electron-transfer mechanism such as Scheme 2 (Scheme 4). The high selectivity for 4-substitution probably arises from strong directional effects in the substrate-*N*-chloroammonium ion charge-transfer complex formed prior to chlorine-atom transfer to give the chlorocyclohexadienyl cation (σ-complex).

Experimental

Materials.—All materials were commercial reagent grade unless otherwise stated and were obtained from Aldrich Chemical Co. Ltd., BDH Ltd., Fisons Scientific Apparatus Ltd., or Lancaster Synthesis Ltd.

N-Chloro-2,2,6,6-tetramethylpiperidine, *N*-chloropyrrolidine, *N*-chloroperhydroazepine, and *N*-chloroperhydroazocine were prepared by the method of Spanswick and Ingold.[25] *N*-Chloro-2,2,6,6-tetramethylpiperidine had b.p. 96–98 °C at 20 mmHg (lit.,[26] 65 °C at 7 mmHg); δ(CCl_4) 1.2 (s, 12 H), and 1.6 (s, 6 H). *N*-Chloropyrrolidine had b.p. 46 °C at 42 mmHg (lit.[27] 29–30 °C at 20 mmHg); δ($CDCl_3$) 1.9 (m, 4 H) and 3.2 (m, 4 H). *N*-Chloroperhydroazepine had b.p. 85–87 °C at 46 mmHg; δ($CDCl_3$) 1.7 (s, 8 H) and 3.2 (s, 4 H). *N*-Chloroperhydroazocine had b.p. 85–87 °C at 24 mmHg; δ($CDCl_3$) 1.7 (s, 10 H) and 3.3 (s, 4 H). The *N*-chloro-*N*-methylbenzylamines were also prepared by the same method but owing to their thermal instability they were not distilled (^{1}H n.m.r. details in Table 9). *N*-Methylpentylamine and *N*-methyl-4-phenylbutylamine were

Table 9. ^{1}H N.m.r. absorptions of $CDCl_3$ solutions of *N*-chloro-*N*-methylbenzylamines.

$XC_6H_4CH_2NMeCl$	ArH	$ArCH_2N<$ (s, 2 H)	N(Cl)Me (s, 3 H)	ArMe (s, 3 H)
X = H	7.35 (s, 5 H)	4.0	2.9	—
4-Me	7.2 (s, 4 H)	4.0	2.9	2.35
4-Cl	7.35 (s, 4 H)	4.0	3.0	—
3-CN	7.3–7.8 (m, 4 H)	4.1	3.0	—
4-CN	7.4 (d, 2 H) 7.5 (d, 2 H)	4.05	3.0	—
4-NO_2	7.5 (d, 2 H) 8.2 (d, 2 H)	4.05	3.0	—

prepared from pentylamine and 4-phenylbutylamine, respectively, by conversion into their formamides and reduction with lithium aluminium hydride. The pentylamine had b.p. 117–119 °C at 760 mmHg (lit.,[28] 114 °C at 745 mmHg); *m/z* 101 (M^+, 9%), 70(1), 57(2), 44(100), and 43(7) and the phenylbutylamine had b.p. 130–140 °C at 46 mmHg, (97% pure by g.c. analysis); δ(CCl_4) 1.3–2.0 (m, 5 H), 2.3 (s, 3 H), 2.3–2.8 (m, 4 H), and 7.2 (s, 5H). *N*-Chloro-*N*-methylpentylamine was prepared as described above and had b.p. 56–57 °C at 43 mmHg. *N*-Chloro-4-phenylbutylamine was prepared from the secondary amine by the standard method and was used without further purification. The preparations of *N*-chloro-1-azoniabicyclo[2.2.2]octane and the other *N*-chloroamines used in this study have been reported previously.[2]

Methods.—The ^{1}H n.m.r. spectroscopic and g.c. procedures have been reported previously.[2] Mass spectra were recorded with an AEI MS 3076 spectrometer operating at 70 eV. Small scale preparative chromatography was performed on a Harrison Research Chromatotron Model 7924, fitted with a 25 cm rotor with a 2 mm coating of silica. The chromatotron was equipped with a Fluid Metering Inc. FM1 RP-G150 pump adapted to give a flow rate of 1–10 cm^3 min^{-1}.

Kinetic Studies.—(*a*) *Rates of chlorination of* 2-*chloroanisole by* N-*chloramines.* Solutions of the *N*-chloroamines in TFA were prepared by dissolving a measured quantity of the required *N*-chloroamine in ice-cold TFA before being brought to thermal equilibrium in a stoppered flask in a thermostatted water bath. To this solution was added a known amount of 2-chloroanisole. The time course of the reaction was followed by removing aliquots of the mixture at suitable time intervals and estimating the unchanged *N*-chloroamine by iodimetric titration (sodium thiosulphate and starch indicator).

The reaction of *N*-chloro-*N*-methylcyclohexylamine with 2-chloroanisole was also monitored by g.c. analysis. For these reactions 2,4,6-trichloroanisole, which had been shown not to be a product of the reaction, was added as the internal standard. Portions of the reaction mixture were withdrawn and analysed directly by g.c. to give the build-up of the product, 2,4-dichloroanisole, with time.

(*b*) *Competitive chlorinations of aromatic compounds.* The substrates were allowed to react in pairs in TFA solution in a thermostatted water bath (21 °C). TFA solutions of the substrate pairs and of *N*-chloropiperidine or *N*-chlorotriethylammonium ion were thermally equilibrated before a measured volume of the chlorinating-agent solution was added to the aromatic substrates. When the reaction was complete the mixture was added dropwise to ice-cooled water and the organic material was extracted into diethyl ether. The ether layer was dried ($MgSO_4$) and analysed by g.c.

The competitive reaction of 1,2- and 1,4-dimethoxybenzene was also followed with respect to time. For this purpose aliquots of the reaction mixture were removed at suitable time intervals and the ratio of the chlorinated product analysed directly by g.c.

Trapping Experiments.—(*a*) *Attempted trapping of aromatic radical cations with added nucleophiles.* Anisole was added to a solution of *N*-chloropiperidine and the nucleophile (NaF, AcOH, or H_2O) in TFA at room temperature. The progress of the reaction was followed by ^{1}H n.m.r. spectroscopy and the product mixtures were worked up, as described above, and analysed by g.c.

(*b*) *Attempted trapping of aromatic radical cations with bromotrichloromethane.* Anisole was added to a solution of the *N*-chloroamine in TFA containing 10% v/v bromotrichloromethane. Product analysis was by g.c.

(*c*) *Attempted intramolecular cyclisation of* 3-(3,4-*dimethoxyphenyl*)*propionic acid.* *N*-Chloro-2,2,6,6-tetramethylpiperidine was added to an equimolar quantity of 3-(3,4-dimethoxyphenyl)-propionic acid in TFA at room temperature. The progress of the reaction was monitored by ^{1}H n.m.r. spectroscopy. After 3 days the reaction was neutralised with sodium carbonate and extracted with diethyl ether. The ether-soluble components were separated by chromatography (Chromatotron) on silica gel eluting with 5% acetone in chloroform. The separated components were analysed by m.s.

(*d*) *Hofmann–Löffler–Freytag reaction to trap aminium radicals.* The aromatic compound was added to an equimolar amount of *N*-chloro-*N*-methylaminopentylamine or *N*-chloro-*N*-methyl-4-phenylbutylamine in TFA. After 18 h the mixture was added to aqueous potassium iodide before the addition of aqueous sodium thiosulphate. The mixture was then made strongly basic with aqueous sodium hydroxide and extracted into diethyl ether. The ether layer was analysed by g.c.

Acknowledgements

J. M. T. thanks the SERC for the award of a research studentship.

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Received 12*th December* 1988; *Paper* 8/04830D