Isotope Effects in Nucleophilic Substitution Reactions. I. The Mechanism of the Reaction of Phenylbenzyldimethylammonium Ion with Thiophenoxide Ion

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A kinetic study of the nucleophilic substitution reactions of a series of para-substituted phenylbenzyldimethylammonium nitrates with sodium thiophenoxide at 0 °C in N,N-dimethylformamide containing a large excess of sodium nitrate, has shown the reaction to be a secondorder process which is first-order in both the substrate and the nucleophile. A Hammett p value of +2.04 for different para-substitutents on the N-phenyl group of the quaternary ammonium salt and a large nitrogen kinetic isotope effect of 1.0200 ± 0.0007 have excluded any mechanism involving a carbonium ion intermediate but are in accord with an $S_N 2$ mechanism with a substantial amount of carbon-nitrogen bond rupture in the transition state.

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Une étude cinétique des réactions de substitution nucléophile d'une série de nitrates de p-Xphénylbenzyldiméthylammonium par le thiophénolate de sodium, à 0 °C dans la N.N-diméthylformamide contenant un grand excès de nitrate de sodium, a permis de démontrer que la réaction est du deuxième ordre soit du premier ordre dans chacun des réactifs. Sur la base (a) d'une valeur ρ de Hammett de +2.04 pour différents substituants en para du groupement phényle du sel d'ammonium quaternaire et (b) d'un grand (1.0200 \pm 0.0007) effet isotopique cinétique de l'azote, on peut exclure tout mécanisme impliquant un intermédiaire carbocationique; toutefois les résultats sont en accord avec un mécanisme S_N^2 impliquant une portion importante de rupture du lien carbone-azote dans l'état de transition.

[Traduit par le journal]

Introduction

Several authors (1-7) have studied the nucleophilic substitution reactions of quaternary ammonium ions

[1]
$$Nu^- + R'NR_3 \rightarrow NuR' + NR_3$$

 $Nu^- = Nucleophile$

and the reverse of this reaction (the Menschutkin reaction) in both protic (1-4) and dipolar aprotic solvents (4-7). The earliest reports, based on extensive kinetic studies using alcohols or water as a solvent, indicated that these reactions proceed by a simple $S_N 2$ mechanism, eq. 2.

[2]
$$Nu^- + R' \overset{+}{N} R_3 \rightarrow [\overset{\delta^-}{N} u \overset{-}{--} \overset{\delta^+}{N} R_3] \rightarrow NuR' + \overset{\cdots}{N} R_3$$

δ+

More recently, Leffek and co-workers (5–7) have studied these reactions in the dipolar aprotic solvents chloroform and acetone and have concluded on the basis of an extensive kinetic study (5) and large alpha secondary hydrogen-deuterium isotope effects (1.20 in acetone and 1.25 in chloroform (6)) that these reactions proceed by an "ionic internal nucleophilic substitution mechanism" (6, 7) involving triple ions of the type $[(R'NR_3)_2Nu^-]^+$.¹ The rate-determining step of the reaction involves ionization of the carbon-nitrogen bond to give a carbonium ion intermediate (R'^+) which reacts in a fast step with the nucleophile in the triple ion complex to give the products, eq. 3.

[3]

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$$3 \operatorname{R'NR_3 X} \xrightarrow{k_1} [(\operatorname{R'NR_3)_2 X}]^+ + [\operatorname{R'NR_3 X_2}]^-$$
$$[(\operatorname{R'NR_3)_2 X}]^+ \xrightarrow{\operatorname{slow}} [\operatorname{R'NR_3 R'NR_3 X}]^+ \xrightarrow{\operatorname{fast}} \operatorname{R'X} + \operatorname{NR_3} + \operatorname{R'NR_3}$$

Leffek's work which suggested that quaternary ammonium salts reacted by an S_N1 mechanism fits very nicely with a proposal by Sneen and Larsen (8, 9) which suggested that all nucleophilic substitution reactions proceed by the ionizing or carbonium ion mechanism illustrated in eq. 4. A quaternary ammonium ion has been ¹K. T. Leffek, private communication.

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used to illustrate how Sneen's proposal would apply to the reactions under investigation.

$$R'NR_{3} \stackrel{k_{1}}{\rightleftharpoons} R'^{+} + NR_{3}$$

$$k_{-1}$$

$$R'^{+} + Nu^{-} \rightarrow R' - Nu$$

If the k_1 step in eq. 4 is rate determining $(k_2 \gg k_{-1} [\dot{N}R_3])$ then first-order kinetics would be observed. This corresponds to the normal S_N mechanism. If, on the other hand, the k_2 step is rate-determining $(k_{-1} [NR_3] \gg$ k_2) then there is a pre-equilibrium followed by a slow bimolecular reaction and second-order kinetics would be observed. This mechanism, which has been referred to as an 'ion-pair $S_N 2$ ' (10) or an $S_N 2C^+$ (11) mechanism, often cannot be distinguished from the normal S_N2 mechanism even by a detailed kinetic analysis (10). Thus both Sneen's proposal which suggests that reactions involving a carbonium ion intermediate can be kinetically identical to normal S_N2 reactions, and Leffek's work imply that quaternary ammonium ions react only by a carbonium ion mechanism rather than by the S_N^2 mechanism proposed by earlier workers. This investigation, which was started with the object of establishing whether the nucleophilic substitution reactions of quaternary ammonium ions occur by an $S_N 1-S_N 2C^+$ or by an $S_N 2$ mechanism, was undertaken because it was not obvious why a reaction thought to proceed by an S_N2 mechanism in protic solvents should react by an S_N1 mechanism in dipolar aprotic solvents and because several workers (12) had cast doubt on Sneen's proposal that all nucleophilic substitution reactions proceed by a carbonium ion mechanism.

Results

Product Analysis

[4]

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The reactions of several *para*-substituted phenylbenzyldimethylammonium nitrates with sodium thiophenoxide were studied at 0 °C in N,N-dimethylformamide containing a large excess of an inert salt (sodium nitrate) to eliminate the salt effects which were observed at lower ionic strengths. The products of the reaction were identified from their spectra and from a comparison of their gas chromatographic retention times with those of authentic samples. A quantitative gas chromatographic analysis using



the internal standard technique (13), showed that the benzylphenyl sulfide was formed quantitatively. This result was confirmed when it was found that a theoretical yield of N.N-dimethylaniline could be recovered from a reaction taken to completion. This analysis was done using the micro-kjeldahl method (14) on the N,N-dimethylaniline recovered from a reaction taken to completion. Finally, the only possible side products (methylphenyl sulfide and benzylmethylphenyl amine produced by attack at an N-methyl carbon) were found in a gas chromatographic analysis to account for only 0.4% of the product. Thus there is, in essence, only one reaction occurring and the isotope effects and other constants are clearly those associated with the reaction shown in eq. 5.

Kinetics and Hammett p Value

The reactions of the different para-substituted phenylbenzyldimethylammonium salts were monitored by titrating the unreacted thiophenoxide ion with mercury(II) ion (15). The individual rate constants were obtained when the data was treated using the usual method for a second-order reaction that is first-order in each reactant. Good straight line plots (correlation coefficients of > 0.99) up to more than 90% of completion were obtained for each run. The rate constants given in Table 1 are the average of the values obtained from at least three separate kinetic runs where the concentration of the quaternary ammonium salt was approximately 0.025 M and where the concentration of the thiophenoxide ion ranged from 0.025 to 0.080 M.

The rate constants in Table 1 were used to

TABLE 1. Rate constants for the nucleophilic substitution[6]reaction of para-substituted phenylbenzyldimethylammo-
nium nitrates with thiophenoxide ions at $0 \,^{\circ}\mathrm{C}$

Substituent (Z) on the N-phenyl group	$\frac{k \times 10^2}{(1 \text{ mol}^{-1} \text{ s}^{-1})}$
	5.55
—H	1.73
CH ₃	0.917
OCH3	0.493

construct the Hammett plot shown in Fig. 1. The ρ value for substitution in the leaving group was found to be +2.04 with a correlation coefficient of 0.998. This ρ value indicates that there is a substantial reduction of the positive charge on the nitrogen atom bonded to the phenyl group in the transition state of the rate-determining step of the reaction.

Nitrogen Kinetic Isotope Effect

The nitrogen kinetic isotope effect for the reaction of phenylbenzyldimethylammonium nitrate and sodium thiophenoxide at 0 °C was calculated using eq. 6 (16).



FIG. 1. Correlation of log k/k_0 and the Hammett p constants for the reaction of a series of *para*-substituted phenylbenzyldimethylammonium nitrates with sodium thiophenoxide in DMF.

$$k^{14}/k^{15} = \frac{\ln(1-f)}{\ln\left(1-\frac{R_0}{R_f}\right)f}$$

where f is the mole fraction of quaternary ammonium salt that has reacted, R_0 is the ratio of the ¹⁴N/¹⁵N in the ammonium nitrogen of the starting material and R_f is the ratio of the 14 N/ 15 N in the nitrogen of the N,N-diméthylaniline produced when the reaction was taken to small extents of completion. Since there were two nitrogen atoms in the starting material, the ¹⁴N/¹⁵N ratio of the ammonium nitrogen atom had to be determined by analyzing the nitrogen gas obtained from the degradation of the N,Ndimethylaniline (17) that was produced in a reaction taken 100% to completion. The ¹⁴N/¹⁵N ratio in the product was obtained by analyzing the nitrogen gas from the N,N-dimethylaniline produced when the reaction was taken to various extents of reaction between 17 and 38% of completion. The results of these experiments are given in Table 2. The large nitrogen kinetic isotope effect, $k^{14}/k^{15} = 1.0200$ indicates that there is substantial carbon-nitrogen bond rupture in the transition state of the rate-determining step of this reaction.

Discussion

Product Analysis and Kinetic Studies

The product analysis study has shown that the nucleophilic substitution reaction of each of the *para*-substituted phenylbenzyldimethylammonium ions with thiophenoxide ion occurs only at the benzyl carbon to give a quantitative yield of benzylphenyl sulfide and the corresponding *para*-substituted *N*,*N*-dimethylaniline. This ensures that all the parameters reported in this paper are those for the nucleophilic substitution reaction shown in eq. 5.

This reaction can occur by way of either an $S_N 2$ mechanism, eq. 7, or by one of the several possible variations of the carbonium ion mechanism shown in Scheme 1.

The kinetic study showed that each of these reactions were second-order processes which were first-order in both the nucleophile and the substrate. While these results do not establish the mechanism they can be used to eliminate some of the mechanisms depicted in eq. 7 and Scheme 1.

Second-order kinetics are obviously consistent with the simple, one-step S_N^2 mechanism.

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Experiment number	Initial concentration of quaternary ammonium salt (M)	Initial concentration of thiophenoxide ion (M)	Extent of reaction* (%)	$\frac{k^{14}}{k^{15}}$
1	0.03835	0.06492	16.6	1.0200
2	0.02751	0.02953	16.6	1.0197
3	0.02501	0.07869	21.3	1.0191
4	0.02637	0.07021	21.7	1.0203
5	0.02464	0.05439	22.0	1.0200
6	0.01653	0.06618	37.8	1.0212
				1.0200 + 0.0007†

TABLE 2.	Nitrogen	n kinetic	isotope e	effect in	the nuc	leophili	c substitution	reaction	of
pheny	lbenzyldi	methyla	mmonium	n nitrate	with so	odium tl	hiophenoxide	at 0°C	

*Based on the yield of benzylphenyl sulfide and N,N-dimethylaniline. †The error limits are the standard deviation.



[7]

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They are not, however, consistent with several of the mechanisms described in Scheme 1. If the slow or rate-determining step of the reaction is any of the k_1 , the k_2 or the k_3 steps of Scheme 1, the rate will only depend on the concentration of the quaternary ammonium ion and first-order kinetics will be observed. The rate expressions for these three possible mechanisms are shown as No. 2, 3 and 4 of Table 3. It is perhaps worth noting that this conclusion holds true no matter how the products are formed *i.e.* by reaction 4, 5 or 6 or even by some combination of these three reactions. These mechanisms are examples of the S_N1 mechanism.

The second group of mechanisms that are described in Scheme 1 are the $S_N 2C^+$ mechanisms where the reaction between one of the carbonium ion intermediates and the thiophenoxide ion is the slow or rate-determining step of the reaction. Two possibilities exist within this framework. The first mechanism involves the formation of a free carbonium ion ($C_6H_5CH_2^+$) which reacts in the slow k_6 step with the thiophenoxide ion. Since the k_6 step is slow and since the $C_6H_5CH_2^+$ does not accumulate during the reaction, the free carbonium ion is formed reversibly and

$$k_{-3}$$
 $(CH_3)_2N \longrightarrow Z$ $\gg k_6[C_6H_5S^-].$

This requires the rate expression to have a term

 $k_{-3}\left[(CH_3)_2N-\sqrt{2}-Z\right]$

in the denominator (mechanism 5, Table 3) and means that the observed rate constant should decrease during the reaction in the same way, and for the same reason that the mass law effect is observed.

Since the second-order rate constants do not decrease during the reaction even though the concentration of the *para*-substituted N,N-dimethylaniline increases markedly, the nucleophilic substitution reaction cannot proceed to any substantial degree by way of the free carbonium ion.

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SCHEME 1. A is an intimate ion-nucleophile pair, B is a solvent separated ion-nucleophile pair, and C is the separate carbonium ion intermediate. The product may be formed via one or more of the k_4 , k_5 or k_6 steps. The counter ions have been omitted to simplify the diagram.

TABLE 3. Rate expressions for different mechanisms based on Scheme 1*

Type of mechanism	Rate-determining step	Rate expression [†]
1. S _№ 2	the only step	$k[R_4NO_3^-][NaSC_6H_5]$
2. S _N 1	k_1	$k_1[R_4NNO_3^-]$
3. S _N 1	k2‡	$\frac{k_1k_2[\mathbf{R}_4NNO_3^-]}{k_{-1}}$
4. S _N 1	k ₃ §	$\frac{k_1 k_2 k_3 [\mathbf{R}_4 \text{NNO}_3^-]}{k_{-1} k_{-2}}$
5. S _N 2C+	<i>k</i> ₆ §	$\frac{k_1 k_2 k_3 k_6 [\mathbf{R}_4 \mathbf{NNO}_3^-] [\mathbf{NaSC}_6 \mathbf{H}_5]}{k_{-1} k_{-2} k_{-3} [(\mathbf{CH}_3)_2 \mathbf{N} - \bigcirc -\mathbf{Z}]}$
6. S _N 2C+	k4	$\frac{k_1k_4[\mathbf{R}_4\mathbf{NNO}_3^-][\mathbf{NaSC}_6\mathbf{H}_5]}{k_{-1}}$
7. S _N 2C ⁺	k5‡	$\frac{k_1k_2k_5[\mathbf{R}_4NNO_3^-][NaSC_6H_5]}{k_{-1}k_{-2}}$
8. S _N 2C ⁺	$k_4 + k_5$	$\left[k_{4} + \frac{k_{5}k_{2}}{k_{-2}}\right] \frac{k_{1}[R_{4}NNO_{3}^{-}][NaSC_{6}H_{5}]}{k_{-1}}$

*R₄ $\dot{N}NO_3$ represents the phenylbenzyldimethylammonium nitrate and $\dot{N}a\bar{S}C_6H_5$ represents sodium thiophenoxide. The rate expression does not imply that the reactants are ion pairs. ‡Assumes that no product is formed via the k_4 step. \$Assumes that no products are formed by either the k_4 or k_5 steps.

The second set of mechanisms where the final step is rate-determining involve the formation of either the intimate or solvent separated carbonium ion complexes in pre-equilibrium steps which are followed by a slow reaction $(k_4$ for the intimate ion complex and k_5 for the solvent separated complex respectively) with the thiophenoxide ion. Both these mechanisms would lead to second-order kinetics (No. 6 and 7, Table 3) and are, therefore, consistent with the observed results. This would also be true for a process where both the intimate and solvent

Number	Reaction	Solvent	P	Reference 18	
1	$C_{6}H_{5}CH_{2}\dot{N}(CH_{3})_{2}I^{-} \rightarrow C_{6}H_{5}CH_{2}I + \ddot{N}(CH_{3})_{2}$	CHCl₃	+1.4		
2		70% water 30% ethanol	+3.43	19a	
3	Ż Ż Reaction 2	50% water 50% ethanol	+4.19	19 <i>a</i>	
4	Reaction 2	70% DMSO 30% water	+3.87	20	
5	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	90% acetone 10% water	-3.30	196	
separated io	n complexes exist and react with the dest	royed (mechanisms	2–4, Table	4) hav	

TABLE 4. Hammett p values for reactions producing or destroying quaternary ammonium salts

separated ion complexes exist and react with the nucleophile in a slow step (mechanism 8, Table 3).

Thus, the kinetic investigation has eliminated several mechanisms and has indicated that these reactions are either $S_N 2$ or $S_N 2C^+$ processes involving an intimate and/or a solvent separated carbonium ion complex.

Hammett p Value

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The Hammett plot shown in Fig. 1 indicated that the ρ value found by changing the *para*-substituent on the phenyl ring of the leaving group (eq. 5) was +2.04. The sign of the ρ value indicates that the positive charge on the quaternary ammonium nitrogen has decreased in the transition state of this reaction (18). An estimate of the extent to which the positive charge has been reduced and thus the amount of carbon-nitrogen bond rupture that has occurred in the transition state, can be obtained by comparing the observed ρ value with those found in similar reactions of other quaternary ammonium salts. Some relevant reactions and their ρ values are given in Table 4.

Burns and Leffek (18) found a ρ value of +1.4 for the reactions of *para*-substituted phenylbenzyldimethylammonium ions with iodide ion in chloroform and suggested that there was only a small degree of carbon-nitrogen bond rupture in the transition state. Other workers (19, 20) who have studied equilibrium reactions where the positive charge is completely

destroyed (mechanisms 2-4, Table 4) have found large ρ values ranging from +3.4 - +4.2.² Since the observed ρ value of +2.04 is approximately half way between the value reported by Burns and Leffek and the extreme values observed for the equilibrium reactions, it would seem that there is quite a substantial reduction in the positive charge on nitrogen and thus considerable (but not nearly complete) carbonnitrogen bond rupture in the transition state of this reaction.

The magnitude of the ρ value can also be used to give some indication of the mechanism of the reaction. The S_N2C⁺ mechanism requires that the carbon-nitrogen bond is broken in a rapid pre-equilibrium step and that the product is formed in a rate-determining reaction between one of the carbonium ion complexes and the nucleophile. If the reaction proceeds by this mechanism then the ρ value should be that observed for an equilibrium reaction of the type shown in Table 4 *i.e.* a ρ value of greater than +3.4.² The much smaller value of +2.04 is obviously not consistent with the S_N2C⁺ mechanism.

The smaller ρ value is however, in the range

²The ρ value should be at least as large for an equilibrium involving quaternary ammonium salts since hydrogens on the ammonium nitrogen hydrogen bond to solvent and lower the ρ value. Equilibrium ρ values range from +2.8 - +3.5 for anilinium ions (19, 20) and from +3.4 - +4.2 for N,N-dimethylanilinium ions where hydrogen bonding to solvent is greatly reduced (20).

expected for an $S_N 2$ mechanism. The ρ value for the formation of a quaternary ammonium salt from methyl iodide and para-substituted N,Ndimethylanilines (reaction 5, Table 4) is large and negative ($\rho = -3.30$) indicating that the nitrogen atom has attained almost a full positive charge and that the carbon-nitrogen bond formation is almost complete in the transition state of this $S_N 2$ reaction. The principle of microscopic reversibility requires that the transition state for the reverse reaction, the decomposition of the quaternary ammonium salt in an S_N^2 reaction, have an early transition state with a fairly small amount of carbon-nitrogen bond rupture. As a result, a reasonably small positive ρ value should be observed. The observed ρ value of +2.04 is obviously consistent with an S_N^2 mechanism.

Thus the ρ value suggests that the nucleophilic substitution reactions of *para*-substituted phenylbenzyldimethylammonium ions with thiophenoxide ion proceed by way of an S_N2 mechanism with considerable, but not nearly complete carbon-nitrogen bond rupture in the transition state.

Nitrogen Kinetic Isotope Effect

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The above conclusions have been confirmed by the large nitrogen kinetic isotope effect $(k^{14}/k^{15} = 1.0200 \pm 0.0007)$ observed for this reaction. In an S_N2C⁺ reaction the carbonnitrogen bond is broken in a pre-equilibrium step and the nitrogen isotope effect should be very small, probably only a few tenths of one percent.³ For an S_N2 process on the other hand, the carbon-nitrogen bond is broken in the transition state of the rate-determining step and a normal nitrogen kinetic isotope effect of 1-3% $(k^{14}/k^{15} = 1.01-1.03)$ should be observed.

The nitrogen kinetic isotope effect of 1.0200 observed for this reaction is approximately half of the theoretical maximum nitrogen isotope effect of 1.03-1.04 at 0 °C (21) and clearly illustrates that the carbon-nitrogen bond is broken in the rate-determining step of the reaction. Since the kinetics have established that the carbon-sulfur bond is formed in the rate-deter-

mining step, both the bond changes must occur in the same step and thus the nucleophilic substitution reactions of quaternary ammonium ions in dipolar aprotic solvents do, indeed, proceed by way of an $S_N 2$ mechanism.

It is worth noting that a test for an $S_N 2C^+$ mechanism, based on the leaving group isotope effect (22), fails in this case. Graczyk and Taylor have shown that the value of a leaving group heavy atom isotope effect will vary in an $S_N 2C^2$ process when the concentration of the attacking nucleophile is changed. This occurs because the ionization (k_1) step (eq. 4) becomes more ratedetermining as the concentration of the attacking nucleophile is increased and k_2 [Nu⁻] becomes greater than k_{-1} [NR₃]. This shift in the ratedetermining step requires that the observed heavy atom isotope effect (significant only when the carbon-leaving group bond is broken in the rate-determining step) increase with increasing concentration of the attacking nucleophile. This trend is not even suggested by the individual results shown in Table 2, even though the relative concentrations of thiophenoxide ion (attacking nucleophile) have been varied over a larger range than those of Graczyk and Taylor, i.e. from very small values (reaction 2 where $[C_6H_5S^-]/R_4NNO_3^-] = 1.18$) to large values (reaction 3 where $[C_6H_5S^-]/[R_4NO_3^-] =$ 3.15).

The magnitude of the nitrogen kinetic isotope effect has been used to give an accurate measure of the relative amount of carbon-nitrogen bond rupture in the transition states of a series of closely related compounds (23). This comparison cannot be made with any certainty in this case because the isotope effect measured in this study is the first value that has been determined for a nucleophilic substitution reaction of a quaternary ammonium salt. Some estimate of the degree of carbon-nitrogen bond rupture can be obtained however, from a comparison with the nitrogen isotope effects for concerted 1,2-elimination reactions of quaternary ammonium salts where a $C-N^+$ bond is broken in the transition state. Typical values for these reactions range from $k^{14}/k^{15} = 1.009 - 1.0186$ at 60 °C (23) and the reactions with an isotope effect of ≥ 1.014 are thought to have substantial carbon-nitrogen bond rupture in the transition state.

⁴This effect would be observed only if k_{-1} [NR₃] and k_{-2} [Nu⁻] are the same order of magnitude.

³A simple calculation (19c) of the isotope effect expected for a pre-equilibrium C—N bond rupture has shown that the isotope effect, based on the observed frequencies of the stretching vibrations of the quaternary ammonium salt and the N,N-dimethylaniline, is very small or inverse. The bending modes do not appear to modify the value of the isotope effect to any significant degree.

The nitrogen isotope effect in the substitution reaction under investigation would be roughly equivalent to an isotope effect of 1.016-1.017at 60 °C (14). Since this value is near the largest values observed for elimination reactions and in fact, is approximately half of the theoretical maximum isotope effect, it would appear that there must be substantial weakening of the carbon-nitrogen bond in the transition state of this reaction. Finally, it is worth noting that the magnitude of the Hammett ρ value and the nitrogen isotope effect both indicate that this reaction is one where there is substantial carbonnitrogen bond rupture in the transition state.

Selectivity of the Reaction

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The mechanism of these reactions has been confirmed in yet another way. The benzhydryldimethylphenylammonium ion was prepared and treated under the normal reaction conditions. If a carbonium ion intermediate were produced during the reaction, then this compound would form a very stable carbonium ion and react very much faster than the benzyl compounds reported in this paper. In fact, the benzhydryl compound did not react and it is safe to conclude that the benzhydryl carbonium ion did not form. It is then obvious that the less stable benzyl carbonium ion would not form and one must again conclude that the phenylbenzyldimethylammonium ions react by an S_N2 mechanism. The benzhydryl compound probably fails to react because the benzhydryl carbon is too sterically crowded to allow the nucleophile to attack in an $S_N 2$ reaction.

Finally, one unusual feature of the reactions of the phenylbenzyldimethylammonium ions is the high selectivity, *i.e.* the benzyl carbon is approximately 500 times more reactive than the methyl carbon. This difference in reactivity, which is more characteristic of carbonium ion processes (benzyl:methyl greater than 400:1) than of S_N^2 reactions (benzyl:methyl $\simeq 4:1$) (24), is thought to be caused by the poor leaving groups in these reactions. This large difference in reactivity has been observed in reactions of other quaternary ammonium salts (1-3, 25) and thus would seem to be normal for S_N^2 reactions with poor leaving groups. This suggests that a large selectivity cannot be used as an indication of a carbonium ion mechanism.

In conclusion, these results clearly illustrate (1) that Sneen's proposals concerning nucleo-

philic substitution reactions are incorrect and that while many reactions do proceed by the $S_N 1-S_N 2C^+$ mechanism (22, 26) that some reactions do, indeed, react by way of an $S_N 2$ mechanism, and (2) that the nucleophilic substitution reactions of quaternary ammonium salts in dipolar aprotic solvents and probably also in protic solvents as the early results indicated (1-3), react by an $S_N 2$ mechanism. Finally the reasonably large Hammett ρ value and nitrogen kinetic isotope effect both suggest there is substantial carbon-nitrogen bond rupture in the transition state of these reactions.

Experimental

Materials

The quaternary ammonium bromides were prepared by stirring benzyl bromide with a 10% excess of the appropriate para-substituted N,N-dimethylaniline in benzene at room temperature for 24 h. The solid bromides were recovered by filtration, dissolved in water, and treated with silver oxide for 3 h (14). The solution was filtered and the filtrate neutralized with nitric acid (1). The water was then removed under reduced pressure to give the quaternary ammonium nitrates which were purified by recrystallization. All the products except the p-methoxyphenylbenzyldimethylammonium nitrate which was recrystallized from acetone and ether, were recrystallized from isopropanol-ether mixtures. The yields of the purified products based on the benzyl bromide and the melting points of each product are: p-methoxyphenylbenzyldimethylammonium nitrate (40%, 95.5-96.0 °C), p-methylphenylbenzyldimethylammonium nitrate (59%, 138–139 °C), p-chlorophenylbenzyldimethylammonium nitrate (55%, 127–128 °C), and phenylbenzyldimethylammonium nitrate (70%, 157-158 °C). All of the reactants with the exception of the *p*-methoxy- and *p*-chloro-N,N-dimethylanilines were commercially available.

The p-methoxy-N,N-dimethylaniline was prepared from p-anisidine using the method described by Leffek (18). The p-chloro-N,N-dimethylaniline was prepared from p-chloroaniline using the method described by Chambers (27). Freshly distilled p-chloroaniline (63 g, 0.49 mol) were mixed with 230 g (0.68 mol) of polyphosphoric acid and 48 g (1.5 mol) of methanol at room temperature. After the mixture had been heated at 190-200 °C for 24 h, it was cooled and made basic by adding a 40% NaOH solution. The product was then extracted with ether. The remaining alkaline solution was mixed with 128 g NaOH and steam distilled. The additional product in the distillate was extracted with ether. The combined ether layers were dried, the ether removed under reduced pressure, and the product distilled under reduced pressure to give 48 g (63%) of p-chloro-N,Ndimethylaniline. The melting point of the product was 33-34 °C; lit. (18) m.p. 32-33 °C.

The benzhydryldimethylphenylammonium bromide was prepared by refluxing 9.45 g (0.038 mol) of benzhydryl bromide with 6.90 g (0.057 mol) of N,N-dimethylaniline in 20 ml of anhydrous benzene for 24 h. The benzene was removed under reduced pressure and the solid

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recrystallized from acetone and water to give 5.5 g (39%) of benzhydryldimethylphenylammonium bromide of m.p. 134.5–135.0 °C. The benzhydryl bromide required for this synthesis was obtained by bubbling HBr through a solution of 10.0 g (0.054 mol) of benzhydrol in 25 ml of anhydrous benzene for 2 h, removing the benzene under reduced pressure, and recrystallizing the solid from ligroin (b.p. 30–60 °C) (28). The yield of benzhydryl bromide was 9.45 g (71%) and the m.p. was 39–39.5 °C; lit. (28) m.p. 42–44 °C.

The solvent, Fisher reagent grade N,N-dimethylformamide, was further purified before use. After the solvent had been dried for at least 24 h over solid NaOH, several grams of sodium thiophenoxide were added and the solvent was distilled at a reduced pressure under a nitrogen atmosphere.

The sodium thiophenoxide was prepared by mixing a 10% excess of freshly distilled benzene thiol with a sodium ethoxide solution prepared from anhydrous ethanol. The ethanol was removed under reduced pressure and the solid was quickly transferred to a glove bag filled with nitrogen. The product was washed several times with ether and then transferred to a vacuum desiccator where it was stored under vacuum until it was required.

Product Identification and Analysis

All the para-substituted N,N-dimethylanilines were available or had been prepared during the synthesis of the quaternary ammonium salts. The other products were prepared as follows. The benzylphenyl sulfide was formed when 9.3 g (0.05 mol) of benzyl bromide were refluxed for 2 h with a sodium thiophenoxide solution prepared from 5.7 g (0.04 mol) of benzene thiol and 30 ml of a 2.25 N solution of sodium ethoxide in ethanol (29). The product was recovered by filtration of the solid that formed when the reaction mixture was poured into a large excess of water. Recrystallization from ethanol gave 6.2 g (72%) of benzylphenyl sulfide, m.p. 42 °C; lit. (29) m.p. 40-41 °C. Methylphenyl sulfide was produced in the same way by refluxing 30 g (0.21 mol) of methyl iodide with 100 ml of a 2.25 N solution of sodium thiophenoxide in ethanol. The product, a liquid, was separated from the aqueous layer, dried and distilled under reduced pressure (b.p. 60-62 °C at 8 Torr; lit. (30) b.p. 58-60 °C at 6 Torr). The yield was 22.5 g (86%).

The amine impurity, benzylmethylphenyl amine was prepared using the procedure described by Grillot and co-workers (31, 32). Equimolar amounts (0.1 mol) of benzene thiol (10 g) N-methylaniline (10.7 g) and a 35-40% solution of formaldehyde (8 ml) were dissolved in 20 ml ethanol and refluxed for 9 h. After the mixture had cooled, the bottom layer was removed and extracted with ether. The combined ether layers were dried and then the ether was removed under reduced pressure and the product distilled (b.p. 159 °C at 1 Torr, lit. (31) m.p. 36-38 °C) to give 32 g (70%) of N-methyl-N-phenylaminomethyl sulfide. This product was mixed with THF and added slowly to the Grignard reagent prepared by reacting 25.2 g (0.16 mol) bromobenzene with 4 g (0.17 mol) magnesium in THF. The mixture was refluxed for 1 h after the addition was complete, and then poured onto a mixture of 350 g crushed ice, 20 g NH₄Cl and 200 ml of water. The product was extracted with ether. The ether layers were washed with a 10% solution of NaOH and then the amine was extracted with 2 N HCl.

The aqueous extracts were made basic and the amine was extracted into ether. After drying over KOH the ether was removed under reduced pressure and the product distilled to give 27.6 g (70%) of benzylmethylaniline with a b.p. 120 °C at 1 Torr, lit. (32) b.p. 162–3 °C at 8 Torr.

The products of the reaction were recovered quantitatively from reaction mixtures in the following manner. The reaction mixture was poured into 1400 ml of pH 12water (the pH was adjusted using NaOH) and the products were extracted with 100, 75, 70 and 70 ml of ether. The last traces of DMF were removed by extracting the combined ether layers three times with 50 ml of pH 12water.

The products were identified in two ways. One method involved concentrating the ether layer to a volume of a few ml on a rotary evaporator and examining the concentrate by gas chromatography. The analysis was done using a flow rate of 50 ml/min and a 15 ft, $\frac{1}{4}$ in. column of 10% Carbowax 20 M on Chromosorb P at 168 °C until the dimethylaniline and methylphenyl sulfide had been eluted, and then at 235 °C where the benzylphenyl sulfide and benzylmethylphenyl amine were eluted. The products had retention times identical to those of authentic samples. An analysis based on the area under each peak indicated that at least 99.6% of the product was formed by reaction at the benzyl carbon.

The major products were also identified by comparing their infrared and n.m.r. spectra with those of authentic samples. The products were first separated by extracting the ether solution once with 70 ml and three times with 40 ml of 2.5% H₂SO₄. Evaporation of the ether gave the sulfide product which was dissolved in a few ml of spectrograde CCl₄. The acid layers were combined, made basic by adding solid NaOH and extracted with three 50 ml portions of ether. Evaporation of the ether gave the amine product which was dissolved in a few ml of spectrograde CCl₄. These solutions were examined by n.m.r. and i.r. spectroscopy. The spectra were identical to those of authentic samples of benzylphenyl sulfide and the *para*-substituted *N*,*N*-dimethylanilines.

The extent of reaction and yield of each product were obtained from the quantitative analysis of both the benzylphenyl sulfide and the N,N-dimethylaniline. The analyses were carried out on the ether solution containing the sulfide and the sulfuric acid solution containing the dimethylaniline. The analysis of the benzylphenyl sulfide involved concentrating the ether solution to approximately 5 ml on the rotary evaporator and adding it to approximately 45 mg (accurately weighed) of the internal standard, diphenyl ether. The solution was diluted to 10 ml and analyzed using the internal standard technique (13) on a 15 ft, $\frac{1}{4}$ in. column of 10% SE-30 on Chromosorb P at 150 °C and a flow rate of 110 ml/min.

The first step in the analysis of the N,N-dimethylaniline was removing the water in the sulfuric acid solution under reduced pressure. The concentrate was then mixed with 100 mg of red mercuric oxide, 2.5 g of potassium sulfate and 2 ml of concentrated H_2SO_4 and heated for approximately 6 h (2 h after the solution had become clear and colorless) in a kjeldahl digestion apparatus.

The ammonium sulfate solution from the kjeldahl

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digestion was placed in a kjeldahl-type distillation apparatus, made basic with an excess of 40% aqueous sodium hydroxide solution, and the ammonia distilled into 50 ml of 0.01 N sulphuric acid. Back titration with 0.01 N NaOH gave the amount of ammonia and thus the amount of the N,N-dimethylaniline that had been produced in the reaction.

Quantitative yields of benzylphenyl sulfide and the N,N-dimethylanilines were obtained for reactions taken 100% to completion. The extent of reaction in runs stopped part way to completion was obtained by averaging the results of the benzylphenyl sulfide and the N,N-dimethylaniline analyses.

Kinetic Measurements

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The rates of the reactions were measured at 0 °C in an ice-distilled water bath. The following preparations for a kinetic run were performed in a glove bag under a nitrogen atmosphere. Thirty ml of DMF cooled to 0 °C, were pipetted into a 50 ml volumetric flask containing 2.40 g of NaNO₃ and sufficient quaternary ammonium salt to prepare 50 ml of a 0.025 *M* solution of the quaternary ammonium salt. An amount of sodium thiophenoxide such that 20 ml of the solution would contain sufficient thiophenoxide ion to prepare 50 ml of a solution between 0.030 and 0.075 *M* in thiophenoxide ion, was weighed into a tared 25 ml volumetric flask. Finally, approximately 30 ml of cold DMF were placed in a ground-glass stoppered flask.

After all the containers had been temperature equilibrated, 25 ml of DMF were added under a stream of nitrogen, to the 25 ml volumetric containing the sodium thiophenoxide. When the salt had dissolved, 20 ml of this solution was poured under a stream of nitrogen into the 50 ml volumetric flask containing the quaternary ammonium salt. This flask was fitted with a serum cap and the reaction was followed by titrating the unreacted thiophenoxide ion contained in a 2.5 ml sample with a standard solution of Hg²⁺ ion (15).

Nitrogen Kinetic Isotope Effect

The nitrogen isotope effect was determined by comparing the ${}^{14}N/{}^{15}N$ ratios of the nitrogen in the N,Ndimethylaniline formed after small extents of reaction, between 17 and 38% of completion, with this ratio in the ammonium nitrogen in the starting material. The latter was obtained by measuring this ratio of the nitrogen in the N,N-dimethylaniline from a reaction taken to completion (16).

The N,N-dimethylaniline was recovered from the reaction mixture and decomposed in a kjeldahl digestion to ammonium sulfate using the procedure described in the section titled product identification and analysis. Finally, the ammonium ions were oxidized to nitrogen gas for mass spectrometric analysis (17). The magnitudes of the isotope effects shown in Table 2 do not vary either directly or indirectly with the extent of reaction. This indicates that the samples are not contaminated with traces of nitrogen containing impurities since impurities of this type would contaminate the samples of varying $1^{4}N/1^{5}N$ ratio with some nitrogen of constant isotopic ratio and thus would alter the observed effect in a way that would be related to the extent of reaction.

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