164. *Mechanism of Substitution at a Saturated Carbon Atom.   Part
LX.*   Nucleophilic Substitutions of the "Missing" Charge Type.*

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Two S_N2 substitutions of Type 4 (neutral reagent, positive substrate)
are described for the first time, and are shown to have the predicted kinetic
characteristics.   They are the reactions of trimethylamine with the tri-
methylsulphonium ion and with the dimethyldiphenylammonium ion.

WHEN collecting nucleophilic substitutions from the literature, and defining them as a class
in 1935, Hughes and Ingold [1] qualified their dominating generic analogy by dividing them
into four electrostatic types, predicting different kinetic characteristics for these types,
particularly as to the effect of the polarity of the medium on rate.   However, Type 4,
which refers to a neutral substituting agent acting on a cationic substrate, could not be
illustrated from the literature, or from any experiments that they had done up to that

* Part LIX, *J.*, 1957, 1279.
[1] Hughes and Ingold, *J.*, 1935, 244.

time; and so its existence and kinetic properties remained a prediction, as they have done more or less ever since. No one seems to have observed the postulated reactions in isolation, even qualitatively, though they have been plausibly assumed as steps in more complex processes.

The first example of Type 4 on which we now report is the very reaction which Hughes and Ingold said should be observable, *viz.*, the reaction of a trialkylamine with a trialkyl-sulphonium ion, specifically the reaction:

$$Me_3N + MeSMe_2^+ \longrightarrow Me_3NMe^+ + SMe_2$$
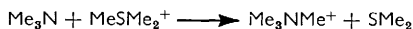
When trimethylamine acts on trimethylsulphonium nitrate, the nitrate anion having been chosen as a weak enough nucleophile not to compete with the amine, the reaction formulated goes to completion in each of the four solvents in which we have investigated it, *viz.*, water, methanol, ethanol, and nitromethane. This was shown, first by isolating the products, and then kinetically.

The reaction follows the second-order law closely, as shown by the typical run recorded in Table 1, and by the collection of rate constants of different runs assembled in Table 2. The reaction is clearly of first order in each reagent, and therefore must have the bimolecular mechanism S_N2.

As will be seen from Table 2, a 25-fold increase in the concentration of trimethylamine values makes no difference to the second-order rate constant, but a 15-fold increase in the concentration of trimethylsulphonium nitrate decreases the constant by 7%. This indicates a weak negative salt-effect, just as we should expect from a bimolecular reaction in which the ionic charge is of the same magnitude in the initial and the transition state but is spread over more atoms in the transition state.

TABLE 1. *Integrated second-order rate constants ($\bar{k}_2$ in sec.$^{-1}$ mole^{-1} l.) of reaction of trimethylamine with trimethylsulphonium nitrate in ethanol at 60·13°.*

{Initially, [Me$_3$N] = 0·2559M, [Me$_3$SNO$_3$] = 0·0929M. Samples of 6·47 ml. at 0° added to 20·36 ml. of 0·1031N-HCl and titrated with 0·0326N-Ba(OH)$_2$.}

t (min.)	Titre (ml.)	Reaction (%)	$10^4\bar{k}_2$	t (min.)	Titre (ml.)	Reaction (%)	$10^4\bar{k}_2$
0	11·58	0·00	—	430	24·23	80·5	3·06
25	13·30	10·95	3·07	551	25·24	87·0	3·07
53	14·88	21·0	3·02	676	25·90	91·2	3·06
80	16·24	29·7	3·03	∞	27·29	100	—
121	17·96	40·6	3·05			Mean	3·05
165	19·47	50·2	3·08		Corrected for thermal expansion		3·27
249	21·48	63·0	3·02				

TABLE 2. *Dependence of second-order rate constants (k_2 in sec.$^{-1}$ mole^{-1} l.) of reaction of trimethylamine with trimethylsulphonium nitrate in ethanol at 60·13° on initial concentrations of reagents.*

	Series A: [Me$_3$N]$_0$ varied			Series B: [Me$_3$SNO$_3$]$_0$ varied	
[Me$_3$N]$_0$	[Me$_3$SNO$_3$]$_0$	10^4k_2	[Me$_3$N]$_0$	[Me$_3$SNO$_3$]$_0$	10^4k_2
0·2559	0·0929	3·27	0·0953	0·1472	3·26
0·1479	0·0933	3·18	0·9968	0·0646	3·30
0·0711	0·0977	3·23	0·1012	0·0382	3·35
0·0403	0·1005	3·20	0·1000	0·0190	3·48
0·0199	0·0996	3·19	0·1004	0·0097	3·52
0·0101	0·0975	3·25			

The steadiness of the rate constant with wide variation in the concentration of trimethylamine shows that the conceivably competing reaction of self-decomposition of trimethylsulphonium nitrate, to give methyl nitrate which then rapidly methylated the trimethylamine, is unimportant. At the higher temperature, 101·6°, the rate of self-decomposition of trimethylsulphonium nitrate was measured both in ethanol and in methanol. In ethanol it had a rate 1/3000th of that of a reaction of the sulphonium salt with trimethylamine, initially in concentration 0·1266M, at the same temperature. In

methanol its rate was 1/4000th of that of a reaction in that solvent of the sulphonium salt with trimethylamine, initially in concentration 0·1136M, at that temperature. We see, then, why the kinetic equation of the S_N2 mechanism is so accurately obeyed.

For the same reason for which an S_N2 reaction of the present electrostatic type should have a weak negative salt effect, it should be moderately retarded as we pass from less to more polar solvents. This is illustrated for four pure solvents in Table 3.

TABLE 3. *Comparison of the rates of reaction of trimethylamine with trimethylsulphonium nitrate in different solvents all at 44·6°.*

Solvent	Water	Methanol	Ethanol	Nitromethane
$10^6 k_2$	6·53	41·3	66·7	775
Rel. rate	1	6	10	119

We can make a further prediction. The reduced rates in the more polar solvents are ascribed essentially to the greater negative energy of solvation of the smaller ion of the initial state than of the larger ion of the transition state, the difference increasing with increasing polarity of the solvent, so increasing the activation energy, which we assume to be measured with sufficient approximation by the quantity E in the Arrhenius equation $\ln k_2 = \ln B - E/RT$. But, furthermore, the rise of activation energy towards more polar solvents must be, not merely enough, but more than enough to account for the rate reduction; for it must overcome the predicted, kinetically countervailing, effect of solvation on the entropy of activation. The solvation shell is more ordered around the smaller ion of the initial state than around the larger ion that is the transition state, and the relative gain in the statistical probability of the latter from its reduced solvation must increase as solvation in general strengthens. Thus an increase in solvent polarity will lead to a rise in the entropy of activation, which we assume to be measured with sufficient approximation

TABLE 4. *Effect of temperature on the rate of reaction of trimethylamine with trimethylsulphonium nitrate in various solvents.*

Solvent	Temp.	$10^4 k_2$	Solvent	Temp.	$10^4 k_2$
Water	44·57°	0·0653	Ethanol	24·47°	0·0777
	60·46	0·368		44·60	0·667
	75·02	1·59		60·13	3·18
	101·60	17·0		75·02	12·1
Methanol	44·60	0·413		101·60	96·3
	60·46	2·12	Nitromethane	24·43	1·18
	75·02	8·23		34·81	3·15
	101·60	75·2		44·57	7·75
				60·46	31·3

TABLE 5. *Arrhenius parameters of the reaction of trimethylamine with trimethyl-sulphonium nitrate in various solvents.*

(B is in sec.$^{-1}$ mole^{-1} l. E is in kcal./mole. The formal standard deviations in E were about 0·1 kcal./mole.)

Solvent	Water	Methanol	Ethanol	Nitromethane
$10^{10} B$	4·90	3·05	0·944	0·190
E	23·07	21·61	20·55	17·99

by $\ln B$ of the above equation. To sum up: as the polarity of the solvent increases, B should rise; but E should rise so steeply that the rate itself falls.

In Table 4 our rate constants for various temperatures in the solvents mentioned are collected. They give good Arrhenius plots, from which the parameters shown in Table 5 are calculated, which illustrate the points just made.

As a second example of a nucleophilic substitution of Type 4, we examined the reaction between trimethylamine and dimethyldiphenylammonium nitrate:

$$Me_3N + MeNMePh_2^+ \longrightarrow Me_3NMe^+ + NMePh_2$$
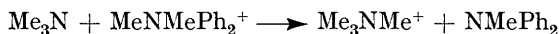
It was shown, first preparatively and later kinetically, that the reaction goes quantitatively in the direction represented. It pursued a second-order course in ethanol, as shown

by the illustrative run in Table 6. The substantial invariance of the second-order constants with changes in the initial concentration of either reagent, shown in Table 7, establishes that the reaction is of first order in each reagent, and hence must be an S_N2 substitution.

TABLE 6. *Integrated second-order rate constants ($\bar{k}_2$ in sec.$^{-1}$ mole^{-1} l.) of reaction of trimethylamine with dimethyldiphenylammonium nitrate in ethanol at 60·46°.*

{Initially, $[Me_3N] = 0.1492M$, $[Me_2NPh_2 \cdot NO_3] = 0.0822M$. Samples of 6·47 ml. at 0° added to 10·18 ml. of 0·1152N-HCl and titrated with 0·03223N-Ba(OH)$_2$.}

t (min.)	Titre (ml.)	Reaction (%)	$10^4\bar{k}_2$	t (min.)	Titre (ml.)	Reaction (%)	$10^4\bar{k}_2$
0	6·42	0	—	95	16·24	59·5	13·3
10	8·20	10·83	13·2	115	17·20	65·3	13·3
20	9·73	20·05	13·3	140	18·20	72·0	13·4
30	10·97	27·6	13·1	190	19·60	79·9	13·4
45	12·70	38·1	13·5	∞	22·91	100	—
60	13·97	45·6	13·3			Mean	13·3
75	15·07	52·5	13·3		Corrected for thermal expansion		14·2

TABLE 7. *Dependence of second-order rate constants (k_2 in sec.$^{-1}$ mole^{-1} l.) of reaction of trimethylamine with dimethyldiphenylammonium nitrate in ethanol at 60·46° on initial concentrations of reactants.*

$[Me_3N]_0$	0·1492	0·1496	0·0751
$[Me_2Ph_2N \cdot NO_3]_0$	0·0822	0·0416	0·0240
10^4k_2	14·2	13·9	14·5

EXPERIMENTAL

Preparations.—Trimethylsulphonium iodide, prepared from dimethyl sulphide and methyl iodide in ethanol (Found: I, 62·1. Calc. for C_3H_9SI: 62·2%), was converted with aqueous silver nitrate into the sulphonium nitrate, which, after being dried in a vacuum over phosphoric oxide, was crystallised from acetone–ethanol. It had m. p. 134—134·5° in sealed tubes (Found: NO_3, 44·8. Calc. for $C_3H_9O_3NS$: NO_3 44·6%). Quantities suitable for subsequent experiments were placed in a number of weighed tubes attached to a vacuum line which included a phosphoric oxide chamber, and, after thorough drying of their contents, the tubes were sealed, reweighed, and preserved until required, when they were broken under the solvents to be used.

Dimethyldiphenylammonium sulphate was prepared in a crude form by heating N-methyl-diphenylamine with dimethyl sulphate without a solvent at 140—150° for 2 hr., and extracting the salt with the minimum amount of water. From this solution, the iodide was precipitated by the addition of saturated aqueous potassium iodide, and was washed with, and crystallised several times from, ethanol. It had m. p. 158° (Found: C, 51·6; H, 4·5; I, 38·9. Calc. for $C_{14}H_{16}NI$: C, 51·7; H, 5·0; I, 39·0%). It was now converted by means of aqueous silver nitrate into the *nitrate*, which after being well dried in a vacuum over phosphoric oxide crystallised from acetone–ethanol–ether. It has m. p. 190° (decomp.) (Found: C, 64·7; H, 6·1; N, 10·7. $C_{14}H_{16}O_3N_2$ requires C, 64·6; H, 6·2; N, 10·8%).

Kinetics.—Sealed tubes were used, which were loaded at 0° with either 6·47 or 11·79 ml. of the reaction mixtures, heated in the thermostat, and, at known times, withdrawn, chilled in solid carbon dioxide and ethanol, broken under hydrochloric acid, and titrated with barium hydroxide (mixed indicator of Bromocresol Green and Methyl Red). The first tube withdrawn marked the time-zero, and infinite-time readings were obtained by heating tubes for a long period and if necessary to a higher temperature than that of the experiment. The concentrations of the reagents in the solutions as originally made up were only approximately known, but, when the trimethylamine was in excess, these zero- and infinite-time readings gave the concentrations of both reagents at the time-zero. When the sulphonium or ammonium nitrate was in excess, the nitrate ion was determined gravimetrically by nitron reagent, and the trimethylamine by titration, in the original solutions, and then, when the latter determination was repeated at the time-zero, the concentrations of both reagents were known at that time. Concentrations were always calculated as at 0°. Second-order rate constants were computed from the formula $\bar{k}_2 = \{2\cdot303/t(a-x)\} \log \{b(a-x)/a(b-x)\}$ and were corrected for expansion of the solvents from 0° to the reaction temperature.

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