Aromatic Nucleophilic Substitution.   Specific Salt Effects on Rate Constants with Benzyltrimethylammonium Methoxide in Methanol

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The reaction rate constants for the reaction of benzyltrimethylammonium methoxide (BTAM) and activated aromatic halides have been determined. The reactions are second order, but the rate constants increase with increasing concentration of BTAM. This rate increase is attributed to a specific salt effect in which benzyltrimethylammonium ion associates with the nitro group of activated aryl halide. London forces are the probable cause of this association.

The effect of added salts on the reaction of activated aryl halides and nucleophiles has been previously reported.[2] The rate constants for the reaction of 2,4-dinitrochlorobenzene with $LiOCH_3$, $NaOCH_3$, and $KOCH_3$ were found to change with changing concentrations of $M^+OCH_3^-$. The rate constant increased with increasing concentration of $KOCH_3$, but decreased with increasing concentration of $NaOCH_3$ or $LiOCH_3$ in the solvents methanol and 50% v/v benzene–methanol. For LiOH, NaOH, and KOH (in dioxane–water solvent) the rate constants decreased with increasing concentration. However, with tetrabutylammonium hydroxide as a nucleophile, the rate constants increased with increasing concentration of the nucleophile.

The decreases in rate constants can be readily understood on the basis of ion pairing, in which the ion pair ($M^+OCH_3^-$) is less reactive than the free methoxide ion.[2a] The increases in rate constant were less readily explained, for it seems unlikely that the ion pair should be more nucleophilic than free methoxide ion. The increases were tentatively attributed to a special salt effect, the association of the K^+ ion with the nitro group. It was argued that this rate-increasing effect opposed the rate-decreasing (ion-pairing) effect to give the net rate increase that was observed. The much larger rate increases observed with the tetrabutylammonium hydroxide reagent seem to involve a special salt effect. Experiments with a related nucleophile, benzyltrimethylammonium methoxide, should shed additional light on such special salt effects.

Results

The rate constants for the reaction of benzyltrimethylammonium methoxide and five activated aryl halides were determined graphically and then checked by a least-squares computer program. The least-squares constants are those reported. For 2,4-dinitrochlorobenzene, the reaction was found to be first order in the nucleophile and first order in the aryl halide. The other reactions followed second-order

kinetic plots and their order was not investigated further. Products were isolated from the reaction mixtures; their purity and identity showed that the reactions are uncomplicated replacements of the aryl halide. (Details are given in Experimental Section.) In Table I the reaction rate constants for benzyltrimethylammonium methoxide are compared with those of $NaOCH_3$ as a nucleophile.

TABLE I

COMPARISON OF RATE CONSTANTS FOR THE REACTION OF SODIUM METHOXIDE AND BENZYLTRIMETHYLAMMONIUM METHOXIDE WITH THE SAME ARYL HALIDE[a]

Substance	NaOCH₃ Temp, °C	k_2, l./mol sec	Benzyltrimethyl-ammonium methoxide Temp, °C	k_2, l./mol sec
2,4-Dinitrochloro-benzene[b]	24.90	2.68×10^{-2}	26.70	3.30×10^{-2}
2,4-Dinitrobromo-benzene[c]	25.0	1.95×10^{-2}	26.70	2.21×10^{-2}
2,4-Dinitroiodo-benzene[c]	25.0	5.76×10^{-3}	26.70	7.07×10^{-3}
2,6-Dinitrochloro-benzene[d]	26.35	9.06×10^{-4}	26.70	9.06×10^{-4}
4-Cl-3,5-Dinitro-benzamide[e]	0	1.19×10^{-2}	0.06	1.24×10^{-2}

[a] Concentrations of $NaOCH_3$ are not known in every case. The change k_2 with changing concentration of $NaOCH_3$ is small for 2,4-dinitrochlorobenzene.[2] [b] Reference 2. [c] A. L. Beckwith, J. Miller, and G. D. Leahy, *J. Chem. Soc.*, 3552 (1952). [d] J. Miller, *ibid.*, 1475 (1953). [e] J. Miller, *J. Amer. Chem. Soc.*, 77, 180 (1955).

There is general agreement between the rate constants with $M^+OCH_3^-$ and $R_4N^+OCH_3^-$.

From Figure 1, the salt effect is an increase in the rate constant for every aryl halide. The nature of the halogen displaced seems to have a slight effect on the rate constant. The per cent change in rate constant as the concentration of benzyltrimethyl ammonium methoxide concentration is changed from 0.01 to 0.08 *M* is given in Table II. For the methoxy dechlorination the per cent change is slightly greater than that for the displacement of bromine or iodine. This occurs for both methoxide and hydroxide as a nucleophile. However, the similarity in rate constant change for all substrates is more striking than these slight

(1) Support of this research by Grant GP-4603 from the National Science Foundation is gratefully acknowledged.

(2) (a) J. D. Reinheimer, J. T. Gerig, and J. C. Cochran, *J. Amer. Chem. Soc.*, **83**, 2873 (1961); (b) J. D. Reinheimer, W. F. Kieffer, S. W. Frey, J. C. Cochran, and E. W. Barr, Jr., *ibid.*, **81**, 164 (1959); (c) J. D. Reinheimer and W. Hostetler, *Ohio J. Sci.*, **64**, 275 (1964).
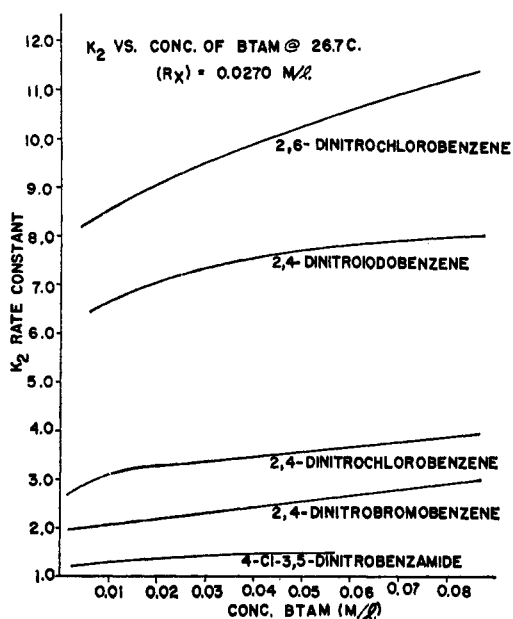
Figure 1.—Rate constant *vs.* BTAM concentration. The rate constant is plotted as *A* in *A* $\times$ 10^{-x} to facilitate comparison.

TABLE II

RATE CONSTANT CHANGE WITH CHANGE OF CONCENTRATION
OF $R^+OCH_3^-$ IN METHANOL AT 26.7°

Substance	k_2, l./mol sec [BTAM] = 0.010	k_2, l./mol sec [BTAM] = 0.080	% change
2,4-Dinitrochlorobenzene	3.05×10^{-2}	3.90×10^{-2}	28
2,6-Dinitrochlorobenzene	8.5×10^{-4}	11.2×10^{-4}	30
4-Cl-3,5-Dinitrobenzamide	1.32×10^{-1}	1.72×10^{-4}	30
2,4-Dinitroiodobenzene	6.5×10^{-3}	8.0×10^{-3}	22
2,4-Dinitrobromobenzene	2.05×10^{-2}	2.55×10^{-2}	24
	$[Bu_4N^+OH^-]$ = 0.018	$[Bu_4N^+OH^-]$ = 0.0850	
2,4-Dinitrochlorobenzene[a]	1.10×10^{-3}	1.61×10^{-3}	45
2,4-Dinitrobromobenzene[a]	7.51×10^{-4}	1.03×10^{-3}	37

[a] Temperature = 25.0°; solvent is 48.8% dioxane in water.[2c]

differences; the amount of data which supports these differences is not large. Table III summarizes all of the rate data.

The thermodynamic functions for the reaction of BTAM are displayed in Table IV. The activation energies are comparable with those for the reaction of $NaOCH_3$ with the same compounds except for that of 2,6-dinitrobenzamide. Miller obtained a ΔE_A of 19.77 kcal/mol for the reaction of 2,6-dinitrochlorobenzene and $NaOCH_3$, while our results were 17.70 kcal/mol (ref *d* of Table I) for BTAM reagent. The compounds which have two *o*-nitro groups have a somewhat more negative entropy of activation.

Discussion

In Table I, the general agreement of the rate constants for the nucleophiles sodium methoxide and benzyltrimethylammonium methoxide is presented. The rate constants for the larger cation are somewhat larger, but not appreciably so. This agreement indicates that the free methoxide ion is the most

TABLE III

| Substance (concn, *M*)	Temp, °C	Concn of R_4N^+ $^-OCH_3$, *M*	Rate constant k_2, l./mol sec
2,4-Dinitrochlorobenzene (0.0270)	26.7	0.0042	2.85×10^{-2}
		0.0067	2.96
		0.0105	3.15; 3.09; 3.05
		0.0209	3.21
		0.0248	3.30
		0.0335	3.36
		0.0418	3.51; 3.46
		0.0496	3.59
		0.0836	3.92
		0.1115	4.13
		0.1673	4.68; 4.74
	49.5	0.0104	24.1; 25.2
		0.00836	24.7
	0.06	0.0104	0.177; 0.179
		0.0416	0.202
2,4-Dinitrochlorobenzene (0.0135)	26.7	0.0335	3.32
		0.0335	3.37
	0.06	0.0104	0.174; 0.175
2,4-Dinitrobromobenzene	26.7	0.0042	2.04×10^{-2}
		0.0084	2.12
		0.0105	2.09
		0.0167	2.17
		0.0209	2.21
		0.0418	2.37
		0.0836	2.59
		0.1115	2.78
		0.1673	2.97; 3.05
2,4-Dinitrobromobenzene (0.0270)	49.5	0.0104	17.6; 17.6
		0.00836	17.6
	0.06	0.0104	0.116; 0.112
2,6-Dinitrochlorobenzene (0.0270)	26.7	0.0105	8.58×10^{-4}
		0.0209	9.06
		0.0418	9.92
		0.0836	11.2
		0.1064	10.8
		0.1673	14.1
	0.06	0.0826	0.608; 0.616
	49.5	0.0832	100.4; 101.4; 97.6
4-Chloro-3,5-dinitrobenzamide (0.0270)	26.7	0.0059	1.26×10^{-1}
		0.0074	1.28
		0.0099	1.35
		0.0124	1.36
		0.0248	1.41
		0.0496	1.49
	0.06	0.0247	$0.124; 0.124 \times 10^{-2}$
2,4-Dinitroiodobenzene (0.0270)	26.7	0.0084	6.51×10^{-3}
		0.0167	6.87
		0.0209	7.07
		0.0418	7.57
		0.0836	7.99
		0.1115	8.42
	49.5	0.0084	63.6
		0.0104	64.8; 64.8
	0.06	0.0104	0.316; 0.312

important nucleophilic species. Attack by the bulky ion pair of $R_4N^+OCH_3^-$ should be less favored sterically than that by the smaller ion pair, $Na^+OCH_3^-$. The steric effect should cause smaller rate constants for $R_4N^+OCH_3^-$, which is not the case.

If the above argument is correct, the observed rate increases should be due to special salt effects or to normal salt effects in which a negatively charged ion is attacking a negative ion. The second possibility, though a remote one, would explain rate increases with hydroxide ions.

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TABLE IV

THERMODYNAMIC FUNCTIONS FOR THE REACTIONS OF BENZYLTRIMETHYLAMMONIUM METHOXIDE
AND ACTIVATED ARYL HALIDES AT 26.7°

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Aryl halide	BTAM concn, M	ΔEA, kcal	ΔH^*, kcal	ΔF^*, kcal	ΔS^*, eu
2,4-Dinitrochlorobenzene	0.0104	17.45	16.85	+19.62	−9.2
2,4-Dinitrobromobenzene	0.0104	17.74	17.14	+19.86	−9.1
2,4-Dinitroiodobenzene	0.0104	18.80	18.20	+20.52	−7.7
2,6-Dinitrochlorobenzene	0.0832	18.30	17.70	+21.60	−13.0
4-Chloro-3,5-dinitrobenzamide	0.0247	14.80	14.20	+18.72	−15.0

The accepted mechanism, the intermediate complex mechanism, is given in eq 1.[3] If the second step of

$$(1)$$
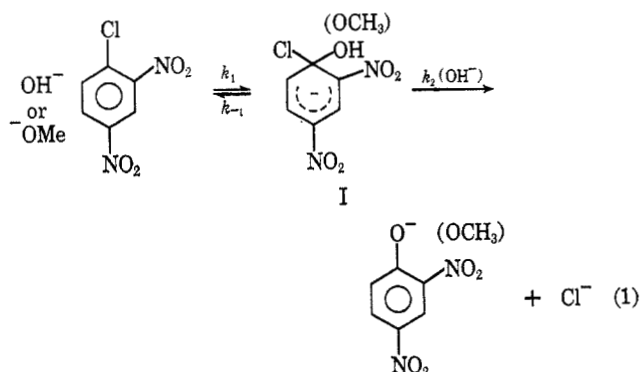
eq 1 requires assistance by OH⁻ for its completion, increasing salt concentration would be rate increasing, for a negative ion is attacking a negatively charged II. No special hypotheses about salt must be invoked.[4] Base catalysis by hydroxide ion is similar to the base catalysis in the reaction of piperidine with activated aromatic compounds.[5] *Several* arguments against this hypothesis may be advanced. (1) The rate expression should be second order in hydroxide with base catalysis. This order is not observed; it is first order to high per cent completion. (2) For hydroxide nucleophiles, LiOH, NaOH, and KOH, the rates decreased with increasing [OH⁻]. Catalysis by hydroxide would be much smaller than that observed in other reactions. The most reasonable conclusion would be that base catalysis by hydroxide does not exist. (3) The experimental rate-increasing effects of $R_4N^+OCH_3^-$ and $R_4N^+OH^-$ are similar. Since there is no proton in the intermediate complex II when methoxide is the nucleophile, base catalysis cannot be invoked. The rate increases must have the same fundamental cause; this cannot be base catalysis.

Since normal salt effect theories are not applicable, these results must be explained on the basis of a special salt effect. Bunton[6] has obtained results similar to those of Hostetler and Reinheimer, and Bunton has designated his salt effects as "special salt effects." The special salt effects may be due to the association of the R_4N^+ with the NO_2 group or with the π complex of the benzene ring.

Hyne[7] has suggested the association of the nitro group with R_4N^+. He has presented nmr evidence that

(3) J. F. Bunnett, *Quart. Rev.* (London), **12**, 1 (1958).

(4) A referee has called this hypothesis a "straw man that is set up for later burning at the stake." While this hypothesis is a remote possibility, it would seem reasonable to exhaust all conventional theories before invoking new concepts.

(5) J. F. Bunnett and C. Bernesconi, *J. Amer. Chem. Soc.*, **87**, 5209 (1965).

(6) C. A. Bunton, S. J. Farber, and E. J. Fendler, *J. Org. Chem.*, **33**, 29 (1968).

(7) (a) J. B. Hyne and A. R. Fabris, *Can. J. Chem.*, **46**, 73 (1968); (b) J. B. Hyne, *J. Amer. Chem. Soc.*, **85**, 305 (1963).

the *meta* and *para* protons of nitrobenzene are deshielded owing to a specific interaction between tetrabutylammonium bromide and the nitrobenzene. He argues that the Br⁻ interacts with the ring and the R_4N^+ with the nitro group. The ring thus achieves a slightly greater positive charge (δ+) and the nitro group a negative charge (δ−). If one applies this concept to the benzyltrimethylammonium methoxide, the methoxide ion would be attracted to the slightly positive benzene ring and then rapidly migrate to the halogen-carrying carbon. The slightly greater positive charge on the ring would aid the nucleophilic attack.

One problem with this explanation is the position of the nitro group in some of these substrates. Hyne[7] reports that the downfield shift is small for the *ortho* hydrogens and larger for the *meta* and *para*. In compounds with two nitro groups, the group *para* to the halogen being displaced could associate with the tetraalkylammonium group. However, the salt effects on 2,6-dinitrochlorobenzene and 4-Cl-3,5-dinitrobenzamide are the same; these compounds have two *ortho* nitro groups and no *para* nitro groups. The wrong end of the molecule is achieving a positive charge. This difficulty may be surmounted by assuming that an initial association of the methoxide ion with the benzene ring as a complex with the somewhat denuded π electrons occurs. The nucleophile then moves in such a way as to form the σ-bonded intermediate II. If the essential step were the initial formation of the σ complex, the slight distance differences to form the σ-bonded intermediate would not matter.

A second problem is the attraction by the π-electron system for the negatively charged methoxide ion. One generally expects the system to be electron donating, rather than electron attracting.

Dispersion forces may be an important factor. Since the RN_4^+ is large and polarizable and the K⁺ is of low polarizability, a difference in rates may be explained on this basis. In the transition state leading to II, the delocalization of the charge *via* London forces would tend to reduce the energy of this transition state and hence favor the reaction. These forces may operate through the association of the RN_4^+ with the nitro group, or with the π-electron system of the activated halide. Grunwald and Price[8] have suggested that dispersion forces between the acid species and the solvent may be decisive in relative acid strengths. In particular, picric acid with its highly polarizable anion is a stronger acid in solvents of higher polarizability. Grunwald and Price found that delocalization of electrons in the picrate ion, that is, resonance between the phenoxide oxygen and the nitro group, enhanced the effect of the dispersion forces. When Li⁺ salts

(8) E. Grunwald and E. Price, *ibid.*, **86**, 4517 (1964).

are added to the solutions of picric acid and acetic acid, the extra dispersion energy of the picrate ion is largely lost. Grunwald and Price argue that this loss is the result of the formation of ion pairs with lithium ion, and these ion pairs are "poor centers of dispersion." To summarize, delocalization favors increased dispersion forces, while localization minimizes the dispersion forces.

The dispersion forces argument may be summarized as illustrated in complex III. The complex III will

III
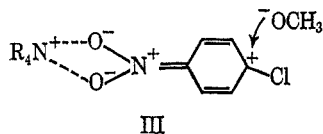
enhance the attack of OCH_3^-, since the C_1 will carry a greater charge due to the delocalization through R_4N^+. If the transition state is one in which $(C \cdots OCH_3)$ bond making has progressed farther than indicated by III, the delocalization of the negative charge (supplied by $^-OCH_3$) is also favored by the polarizability of R_4H^+.

If RN_4^+ interacts with the π-electron system, a similar argument applies.

IV
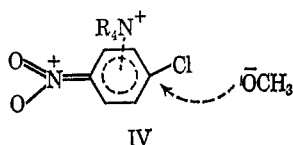
The authors[9] favor the dispersion forces as a cause of the enhanced rates. Their preference for association with the nitro group is based on the somewhat greater delocalization for this point of association compared with the π-electron system.

Experimental Section

Kinetic Procedure.—The dinitrohalo compound was weighed into a volumetric flask and dissolved in dry methanol. The flask was placed in the constant-temperature bath; after equilibrium temperature was attained, the solution was diluted to volume. The BTAM solution was prepared in a similar manner. A known volume was pipeted into a volumetric flask at room temperature (25°). This flask was placed in the constant-temperature bath and the solution was diluted to the mark. Samples (50 ml) were pipeted into two flasks. The reaction was started by mixing the contents of these flasks by means of a bent connecting tube. Samples (10.0 ml) were pipeted at timed intervals into a stopping solution of acetic acid, and the halide evolved was determined by a potentiometric titration with $AgNO_3$.

Since the volume[10] of the volumetric flask changes very slightly for a 25° temperature change, no corrections for solvent expansion are needed with the above technique. Rate constants were obtained from a linear least-squares program.

Isolation of Products of Kinetic Runs.—A sample from kinetic experiments of 2,4-dinitrochlorobenzene with BTAM was allowed to stand for several days. The reaction mixture was acidified and the methanol was removed in a flash evaporator. The product was shown to be pure by thin layer chromatography and the melting point observed, 83–84° is in reasonable agreement with the literature value[11] of 88° for 2,4-dinitroanisols. A similar procedure was used with 4-chloro-3,5-dinitrobenzamide. No odor of NH_3 was observed at the end of the experiment, and the melting point of the product was again reasonable, 160–162°. The literature values[12] were 165° for the 4-methoxy-3,5-dinitrobenzamide and 181° for the 4-methoxy-3,5-dinitrobenzoic acid.

Purification of Starting Materials.—These were commercial products which were recrystallized to constant melting point. 2,6-Dinitrochlorobenzene was recrystallized twice from methanol, mp 86–87.5° (lit.[13] mp 87–88°). 4-Chloro-3,5-dinitrobenzamide was recrystallized from methanol, mp 184–186.5° (lit.[14] mp 186°). The halodinitrobenzenes were purified as reported previously.[2c]

The benzyltrimethylammonium methoxide was prepared from a commercial sample purchased from the Miles Chemical Co. of Elkhart, Ind. After considerable time was spent in preliminary experiments, the following method of purifying the BTAM was adopted. Part of the methanol was removed from the 40% BTAM solution in a flash evaporator at low temperature for 10 min. A steam bath was used intermittently to warm the flask. Anhydrous ether was then added until the solution became cloudy, and the flask was cooled in a Dry Ice–ether mixture. The BTAM precipitated and was removed by filtration. The white solid was dissolved in anhydrous methanol and the process was repeated. The final step was to remove Cl^- and OH^- that had been carried along by an ion-exchange process. A macroreticular resin, IRA-900, was put on the methoxide cycle by means of $NaOCH_3$ in methanol. The process was very slow; several weeks were required to remove Cl^- from the resin. At first, magnetic stirring and a 1 N $NaOCH_3$ solution were used, but the resin was broken into a fine powder. A laboratory shaker was then used to convert the resin (partially 90%) into the methoxide cycle. The $NaOCH_3$ was changed each day until the Cl^- concentration was low; then the resin was placed in a column; and the last of the Cl^- was removed in the normal manner. The recrystallized BTAM solution was passed through the column to remove the remaining chloride and hydroxide. The BTAM was stored in a glass flask with a siphon. Nitrogen was used to push the BTAM from this storage flask.

(9) The authors are indebted to a referee for the suggestion of dispersion forces.

(10) Kolthoff and Sandell, "Textbook of Inorganic Analysis," The Macmillan Co., New York, N. Y., 1952, p 505. The cubical coefficient of expansion for Pyrex was used in this calculation.

$$V_{50°} = V_{25°} + 9.6 \times 10^{-6} \times 100.00 \text{ ml} \times 25° = V_{25°} + 0.024 = 100 + 0.024 = 100.02 \text{ ml}$$

(11) N. A. Lange, "Handbook of Chemistry," 9th ed, Handbook Publishers, Inc., Sandusky, Ohio, 1956, p 522.

(12) F. K. Beilstein, "Handbuch der organischen Chemie," Vol. 10, 4th ed, Edwards Brothers, Inc., Ann Arbor, Mich., p 184; Vol. 10, 2nd supplement, p 108.

(13) N. A. Lange, Handbook of Chemistry, 9th ed, Handbook Publishers, Inc., Sandusky, Ohio, 1956, p 457.

(14) J. Miller, *J. Amer. Chem. Soc.*, **77**, 180 (1955).