Electrolyte Effects on Bimolecular Nucleophilic Displacements[1]

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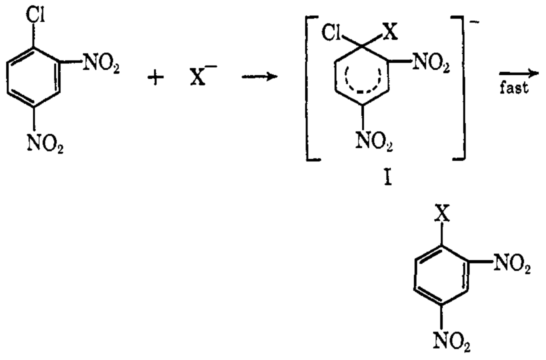
Abstract: Specific kinetic salt effects have been observed for reactions between 2,4-dinitrochlorobenzene and hydroxide or thiophenoxide ion or aniline in water or in aqueous ethanol or aqueous *t*-butyl alcohol, and between *n*-pentyl bromide and thiosulfate ion in aqueous ethanol. Measurements of the activity coefficients of 2,4-dinitrochlorobenzene and aniline in aqueous salt solutions show that these specific salt effects can be separated into initial and transition-state effects, that cations of low charge density stabilize the transition state for the ion–molecule reaction, and both anions and cations of low charge density stabilize it for the reaction between aniline and 2,4-dinitrochlorobenzene. Ion atmosphere effects appear to be relatively unimportant.

Reinheimer and his coworkers observed large kinetic salt effects upon the reactions between hydroxide or alkoxide ion and 2,4-dinitrochlorobenzene.[2,3] The Debye–Hückel relationship predicts no salt effect for such reactions, but the salt concentration used in these experiments was much too high for application of this relationship. Many of the experiments were done in solvents of low polarity, and it was noted that electrolytes could affect the reaction rate by changing the equilibrium between an ion-paired metal alkoxide and the reactive free alkoxide ion.[2,4,5] Reinheimer and his coworkers could not account for all the kinetic salt effects in these terms, *e.g.*, the observation that the salt effect *increased* with increasing solvent polarity, and they noted that interactions between the metal cation and the nitro groups could also be important.[2]

The reaction between nucleophiles and 2,4-dinitrochlorobenzene involves slow addition to give a tetrahedral intermediate which decomposes very rapidly to products,[6] and we were interested in finding whether there would be similar salt effects on a simple SN2 reaction involving an anionic nucleophile and an alkyl halide, and whether the specific salt effects on both types of displacement would disappear in polar solvents. We had observed fairly large electrolyte effects for the attack of hydroxide ion upon *p*-nitrophenyl diphenyl phosphate in water,[7] and there are cation effects for ester saponifications in hydroxylic solvents.[8] It therefore seemed probable that specific salt effects upon nucleophilic substitution by lyate ions might be general.

All these displacements by lyate ions were carried out at electrolyte concentrations which were higher than those for which the Debye–Hückel equation can be applied, but the qualitative extension of this treatment predicts that the salt effects upon anion–molecule reactions should be small and negative.[9]

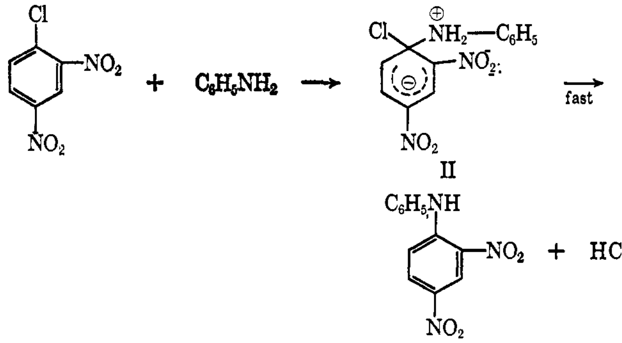
We used the reaction between *n*-pentyl bromide and sodium thiosulfate in aqueous ethanol as an example of an SN2 reaction[10] in order to see whether these specific salt effects disappeared for such a simple system, and that of hydroxide or thiophenoxide ion with 2,4-dinitrochlorobenzene in water or aqueous ethanol or *t*-butyl alcohol as examples of addition of a nucleophilic anion. We also examined the reaction between aniline and 2,4-dinitrochlorobenzene as an example of addition of an uncharged nucleophile.



X = OH, SC_6H_5

The second-order reaction between amines and 2,4-dinitrochlorobenzene has been studied very extensively; the rate-limiting step is known to be nucleophilic addition, and elimination of the proton and the chloride ion is fast.[6]

According to simple electrostatic theory the reaction should be subject to a positive salt effect, because two



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[1] This work was supported by the National Science Foundation. This support is gratefully acknowledged.

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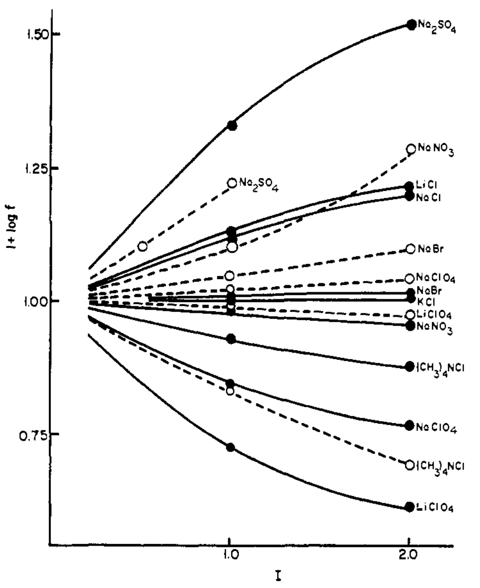

Figure 1. Variation of activity coefficients with ionic strength in water at 25.0°: solid line and solid points, 2,4-dinitrochlorobenzene; broken line and open points, aniline.

neutral molecules give a highly polar transition state,[9] and we were interested in finding whether the specific salt effects which had been observed for anionic substitutions would also appear here.

There are many reactions for which part of the specific kinetic salt effect is caused by changes in the activity coefficients of the initial state which can complicate attempts to relate electrolyte effects to mechanism.[11-14]

Most of the earlier work had been on spontaneous or acid-catalyzed hydrolyses, and we were curious to see whether similar initial state effects were important in nonsolvolytic nucleophilic displacements. Water is a convenient solvent for experiments in which one attempts to differentiate between electrolyte effects upon the initial and transition states, and we used it where possible in our work.

Experimental Section

Materials. *n*-Pentyl bromide (MCB) was redistilled, bp 128.5–129.5° (lit.[15] bp 129°). 2,4-Dinitrochlorobenzene was recrystallized from ethanol, mp 52–52.5° (lit.[16] mp 52°). Aniline (BA) was distilled, bp 183–184° (lit.[17] bp 184°). Thiophenol was redistilled under reduced pressure immediately before the samples were made up. The salts were reagent grade materials, dried before use, or were prepared *in situ* by neutralization of the acid with the base. The neutrality of all the aqueous salt solutions was checked before use.

Kinetics. The reaction between *n*-pentyl bromide and sodium thiosulfate was followed by the method of Hammett and his coworkers, using sodium acetate as buffer.[10] Portions of the reaction mixture were added to water and then were titrated against standard iodine solution using starch as indicator. In making up the aqueous ethanolic reaction solution we allowed for the water of crystallization of sodium thiosulfate. The composition of one of the aqueous ethanolic solvents was that used earlier by Hammett and his coworkers.[10]

The concentrations of reactants were equal and the second-order rate constants, k_2, were calculated graphically by plotting $1/C$ against time (where C is the reactant concentration).

The reaction between 2,4-dinitrochlorobenzene and lyate ion was followed spectrophotometrically using a Gilford spectrophotometer and determining the absorbance at 3580 Å. The concentration of 2,4-dinitrochlorobenzene was *ca.* $10^{-4}M$ and much smaller than that of the lyate ion, the first-order rate constants, k_ψ, with respect to the chlorobenzene were calculated using the integrated first-order rate equation, and $k_2 = k_\psi/C_{\mathrm{O\bar{H}}}$.

The reaction between aniline and 2,4-dinitrochlorobenzene in water was followed spectrophotometrically at 3650 Å, using a Gilford spectrophotometer. The aniline concentration was 0.055 M and that of 2,4-dinitrochlorobenzene was *ca.* 10^{-5} M. The values of the first-order rate constants, k_ψ, were determined in the usual way, and divided by the aniline concentration to give k_2. Because of the low solubility of 2,4-dinitrophenylaniline in water, we could not study this reaction in all the salt solutions which were used for the other reactions.

The reaction between thiophenoxide ion and 2,4-dinitrochlorobenzene in ethanol–water 25:75 w/w was followed spectrophotometrically at 3700 Å, in solutions containing 5×10^{-3} M sodium hydroxide, 5×10^{-4} M sodium thiophenoxide, and 5×10^{-6} M 2,4-dinitrochlorobenzene. Freshly prepared solutions were used in these experiments, and it was found that doubling the thiophenoxide ion concentration did not affect the second-order rate constant. Duplicate kinetic runs agreed within 3%, and the units of the second-order rate constants are in $\sec^{-1}$ mol^{-1} l.

Determination of Activity Coefficients. The solubility of 2,4-dinitrochlorobenzene in aqueous salt solution was determined at 25.0°. Tubes containing solid 2,4-dinitrochlorobenzene in the aqueous electrolytes were shaken periodically, and after several days the solid was filtered off. One portion (1 ml) of the solution was made up to 25 ml with 0.015 M sodium borate and the absorbance measured at 3580 Å to determine the amount of 2,4-dinitrophenol which had been formed by hydrolysis. This amount was always very small. Another 1-cc portion of the filtered solution was made up to 25 ml with 0.6 M NaOH to hydrolyze the 2,4-dinitrochlorobenzene completely, then 1 cc of this solution was made up to 25 cc with 0.015 M sodium borate and the amount of 2,4-dinitrophenol determined from the absorbance at 3580 Å.

The activity coefficients of aniline were known for several salts in water,[18] but where necessary we measured them by partitioning aniline between water and *n*-hexane (Spectrograde) and determining the aniline concentrations spectrophotometrically following the general procedure of Long and Bergen.[18] All the activity coefficients are referred to water at 25° as the standard state.

Results

Activity Coefficients. The activity coefficients of aniline and 2,4-dinitrochlorobenzene in water at 25° show the expected pattern of "salting-in" and "salting-out" effects (Figure 1), where $\log f_s$ is plotted against ionic strength. Ions of high charge density, *e.g.*, lithium or sulfate, "salt-out" the solute, whereas ions of low charge density, *e.g.*, tetramethylammonium or perchlorate, "salt-in."[19]

Salt effects upon the activity coefficient of 2,4-dinitrochlorobenzene are often larger than those upon aniline (Figure 1). The Setchenhow equation breaks for some of the salts at high ionic strength, particularly for those salts which "salt-in" or "salt-out" the solutes strongly.

Kinetics. Hydrolysis of 2,4-Dinitrochlorobenzene. We use the superscripts 0 and s to denote reactions in the absence and presence of salts. The reaction between 2,4-dinitrochlorobenzene and hydroxide ion is close to second order in water (Table I), as in other

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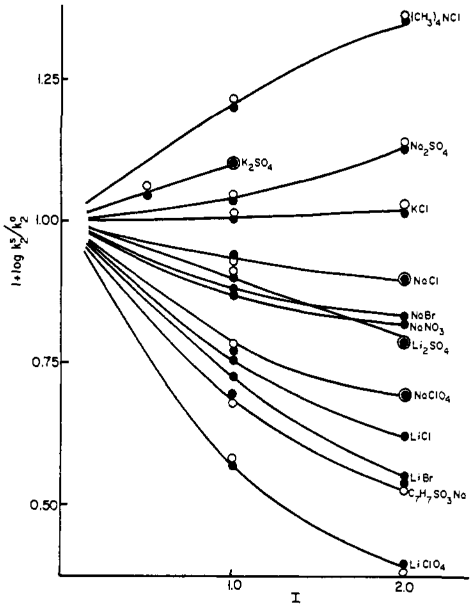

Figure 2. Salt effects upon the reaction of 2,4-dinitrochlorobenzene with hydroxide ion in water: ○, at 25.0°; ●, at 45.0°.

solvents,[6] and for the low concentrations of hydroxide ion which were used the second-order rate constants are only slightly dependent upon the nature of the cation.[2,3] However, added electrolytes have large specific effects in water at 25 and 45°, and in aqueous ethanol and *t*-butyl alcohol, and plots of log k_2 against ionic strength curve slightly (Figures 2, 3, and 4). There is no very obvious pattern to the salt order, but for cations the rates decrease in the sequence $(CH_3)_4N^+ > K^+ > Na^+ > Li^+$, and for anions in the sequence $SO_4^{2-} > Cl^- > Br^- \sim NO_3^- > ClO_4 > p\text{-}CH_3C_6H_4SO_3^-$.

Table I. Reaction of 2,4-Dinitrochlorobenzene with Hydroxide Ion[a]

	C_{OH^-}, *M* 0.05	C_{OH^-}, *M* 0.10
	10^4k_2 l. mol^{-1} sec^{-1}	
LiOH	13.5	12.4
NaOH	13.5	12.7
NaOH	1.42[b]	
NaOH	27.6[c]	
NaOH	3.94[d]	
NaOH	3.27[e]	
KOH	13.5	12.8
$(CH_3)_4NOH$	13.5	13.3

[a] In water at 45.0°. [b] In water at 25.0°. [c] In ethanol-water 25:75 w/w at 45.0°. [d] In ethanol-water 25:75 w/w at 25.0°. [e] In *t*-butyl alcohol-water 18:82 w/w at 25.0°.

The kinetic salt effects in water do not change in going from 25 to 45° (Figure 2), and the activation parameters for the reaction in water in the absence of salts are $\Delta H^* = 21.5$ kcal mol^{-1}, $\Delta S^* = -5.5$ eu. The temperature effect is similar to those found for similar aromatic nucleophilic substitutions.

It is highly unlikely that ion-pairing effects are important in water and aqueous ethanol or *t*-butyl alcohol although there is evidence for them in less polar solvents.[2,4,5]

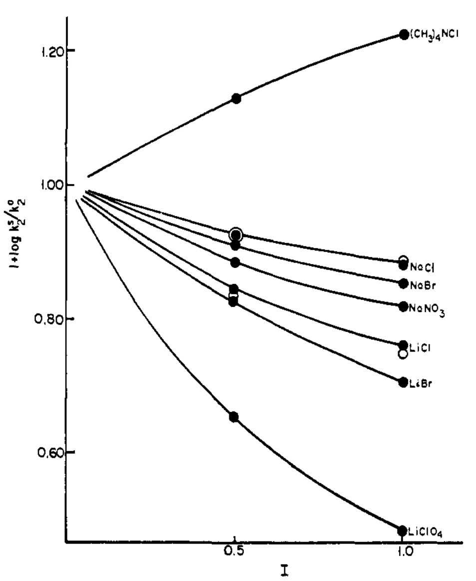

Figure 3. Salt effects upon the reaction of 2,4-dinitrochlorobenzene and lyate ion in ethanol-water 25:75 w/w: ○, at 25.0°; ●, at 45.0°.

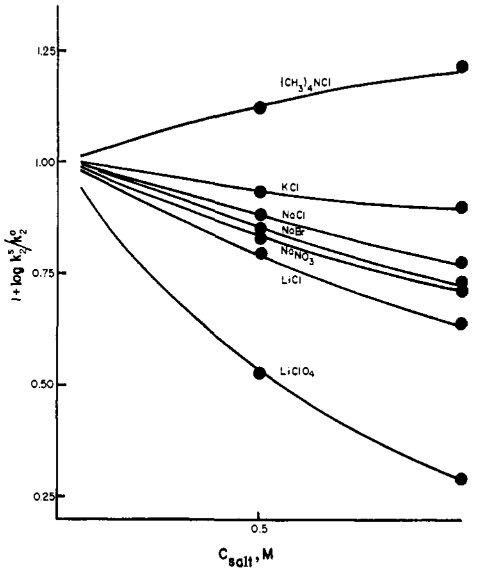

Figure 4. Salt effects upon the reaction of 2,4-dinitrochlorobenzene with hydroxide ion in *t*-butyl alcohol-water 18:82 w/w at 25.0°.

The second-order rate constants in the absence of salts increase as the solvent becomes less polar (Table I and ref 2). These results are in accord with the predictions of the qualitative Hughes-Ingold solvent theory,[9] but we should note that in changing from water to aqueous ethanol or methanol the lyate ion is changing from the hydroxide ion to a more nucleophilic alkoxide ion,[20] and we should also be decreasing the deactivation of the lyate ions by hydrogen bonding.[21] Both these effects should increase the rate.

Reaction between 2,4-Dinitrochlorobenzene and Thiophenoxide Ion. In agreement with other results we find that the thiophenoxide ion in aqueous ethanol is much more reactive than the lyate ion toward 2,4-dinitrochlorobenzene.[22] In ethanol-water 25:75 w/w at 25.0° with 5×10^{-4} *M* sodium thiophenoxide k_2 =

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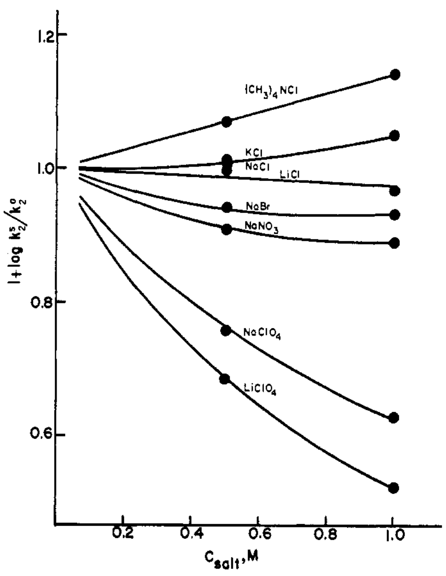

Figure 5. Salt effects upon the reaction of 2,4-dinitrochlorobenzene with thiophenoxide ion in ethanol-water 25:75 w/w at 25.0°.

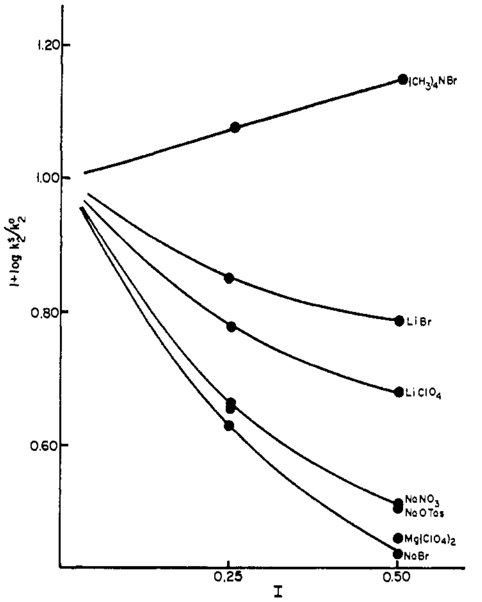

Figure 6. Salt effects upon the reaction of *n*-pentyl bromide with sodium thiosulfate in ethanol-water 55:45 w/w at 25.0°.

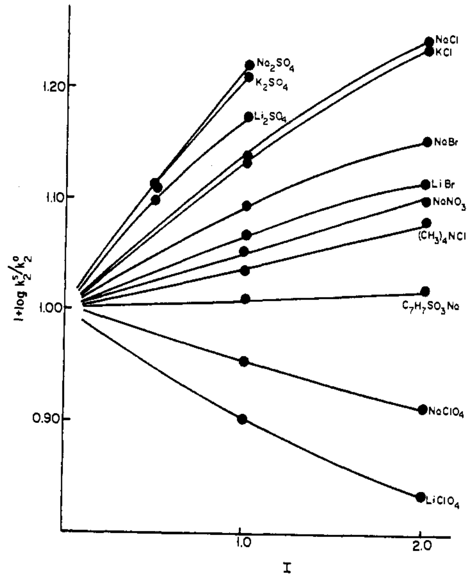

Figure 7. Salt effects upon the reaction of 2,4-dinitrochlorobenzene with aniline in water at 85.0°.

81.8 l. mol^{-1} sec^{-1}, and with 10^{-3} *M* sodium thiophenoxide k_2 = 82.8 l. mol^{-1} sec^{-1}; for the corresponding lyate ion reaction k_2 = 3.94 × 10^{-4} l. mol^{-1} sec^{-1} (Table I).

The kinetic salt effects upon this reaction are shown in Figure 5. The salt order is $(CH_3)_4NCl > KCl \sim NaCl > LiCl > NaBr > NaNO_3 > NaClO_4 > LiClO_4$, and is very similar to those observed for the reactions of lyate ions with 2,4-dinitrochlorobenzene in water or aqueous ethanol.

Reaction between *n*-Pentyl Bromide and Sodium Thiosulfate. The salt effects upon this S$_N$2 reaction, at a saturated carbon atom, are specific, and plots of log k_2 against ionic strength are curved (Figure 4 and Table II). Again it is unlikely that ion pairing is important in these polar solvents, and the qualitative effects are similar in both ethanol-water 44:56 and ethanol-water 55:45 w/w. The salt effect seems to depend upon the cation rather than the anion, as is shown in Figure 6 and Table II where the salts are arranged in the order of decreasing values of k_2. The rate decreases in the sequence $(CH_3)_4N^+ > Li^+ > Cs^+ \sim Na^+ > K^+ > Mg^{2+}$. The solvent effect upon k_2 in the absence of added salts is small, with k_2 increasing slightly with increasing water content of the solvent (Table II), in the opposite direction to that predicted by qualitative solvent theory.[9]

Table II. Second-Order Rate Constants for Reaction of *n*-Pentyl Bromide with Sodium Thiosulfate[a]

	C_{salt}, *M*		
	0.10	0.25	0.50
	10^4k_2, l. mol^{-1} sec^{-1}		
$(CH_3)_4NBr$	5.68		6.98
$(CH_3)_4NCl$	5.47	6.03	6.92
No salt[b,c]			
LiCl	4.07	3.70	3.06
$LiClO_4$	4.15	3.51	2.79
LiBr	4.06	3.50	2.92
NaOAc		2.94	2.09
$NaNO_3$	3.86	2.81	1.91
NaOTos	3.62	2.74	1.84
CsCl	3.59	2.72	2.13
NaBr	3.54	2.71	1.83
NaCl	3.58	2.68	1.83[d]
KCl	3.39	2.41	1.68
$Mg(ClO_4)_2$	2.40	1.86[e]	

[a] At 25.0° with 0.02 *M* reagents and 0.02 *M* NaOAc in ethanol-water 44:56 w/w. [b] In the absence of added salt 10^4k_2 = 4.81 l. mol^{-1} sec^{-1}. [c] In ethanol-water 55:45 w/w in the absence of salt 10^4k_2 = 4.53 l. mol^{-1} sec^{-1}. [d] With 0.05 *M* reagents and 1.0 *M* NaCl 10^4k_2 = 0.73 l. mol^{-1} sec^{-1}. [e] In ethanol-water 55:45 w/w 10^4k_2 = 1.31 l. mol^{-1} sec^{-1}.

Reaction between Aniline and 2,4-Dinitrochlorobenzene. The specific salt effects for this reaction in water at 85.0° are shown in Figure 7. In the absence of added salt, k_2 = 5.96 × 10^{-3} l. mol^{-1} sec^{-1}.

Plots of log k_2 against ionic strength curve slightly, and there are some obvious patterns in the salt order, *e.g.*, for cations the rate decreases in the sequence Na$^+$

$> K^+ > Li^+ > (CH_3)_4N^+$, and for anions in the sequence $SO_4^{2-} > Cl^- > Br^- > NO_3^- > ClO_4^-$. The anion, but not the cation, sequence is similar to that found for reaction with hydroxide ion.

Alkali metal halides also increase the rate of reaction of ammonia with 2,4-dinitrohalobenzenes in methanol (except for the fluorobenzene).[23]

Discussion

Kinetic Salt Effects. Although our reactions were carried out in water, or highly aqueous solvents, where ion pairing should be unimportant, we found both positive and negative effects, whereas simple electrostatic theory predicts small negative effects for the anion–molecule reactions and larger positive effects for the molecule–molecule reactions.[9] The salt effect upon the reaction between methoxide ion and the 4-bromo-3-nitro-N,N,N-trimethylanilium cation qualitatively fits the predictions of the Debye–Hückel relation,[24] but not enough salts were examined to decide whether the salt effect was independent of the nature of the electrolyte.

The large salt effects upon the SN2 reaction between thiosulfate ion and *n*-pentyl bromide show that specific interactions between cations and substituent groups, such as nitro, are not always responsible for these salt effects in polar hydroxylic solvents, and the similarity of the salt effects upon the reactions of lyate and thiophenoxide ions with 2,4-dinitrochlorobenzene in various solvents illustrates the generality of these phenomena.

Electrolyte Effects upon the Initial State of the Ion–Molecule Reactions. Our results on the salt effects upon the activity coefficients of 2,4-dinitrochlorobenzene and aniline (Figure 1), together with the rate measurements (Figures 2 and 7), show that initial state effects are in part causing the specific kinetic salt effects.

For the reaction between hydroxide ion and 2,4-dinitrochlorobenzene the Brønsted–Bjerrum rate equation gives

$$k_2^s/f_{\mathrm{ArCl}} = k_2^0 f_{\mathrm{O\bar{H}}}/f_{\mathrm{X}}^* \qquad (1)$$

The values of the activity coefficient, f_{ArCl}, of 2,4-dinitrochlorobenzene in aqueous salt solutions (Figure 1) show that the specificities of the salts do not arise solely from this factor, although the rate enhancement by sulfate ions is largely caused by an increase in the activity coefficient of 2,4-dinitrochlorobenzene. Using the second-order rate constant, k_2, and the values of f_{ArCl} we can calculate $f_{\mathrm{O\bar{H}}}/f_{\mathrm{X}}^*$ using eq 1 and taking k_2^0 as the second-order rate constant in the absence of salt.

The values of f_{ArCl} and $f_{\mathrm{O\bar{H}}}/f_{\mathrm{X}}^*$ (Table III) show that salts can have specific effects upon both the activity coefficient of the chlorobenzene and the ratio of the activity coefficients of the hydroxide ion and the anionic transition state. For example, all the alkali metal halides increase f_{ArCl}, *i.e.*, destabilize the substrate, but they also destabilize the transition state more than the hydroxide ion, *i.e.*, they decrease $f_{\mathrm{O\bar{H}}}/f_{\mathrm{X}}^*$, and their net effect is to decrease the rate. On the other hand sodium perchlorate decreases f_{ArCl}, *i.e.*, stabilizes the substrate; it is similar to the alkali metal halides in its effect upon $f_{\mathrm{O\bar{H}}}/f_{\mathrm{X}}^*$, and its over-all effect is to decrease the rate markedly. Sodium sulfate increases the rate slightly, but only because it increases f_{ArCl} very much, *i.e.*, it strongly destabilizes the substrate, and this effect overcomes its effect upon $f_{\mathrm{O\bar{H}}}/f_{\mathrm{X}}^*$, which is very similar to that of lithium chloride. Tetramethylammonium chloride behaves quite differently to the other salts—it decreases f_{ArCl} slightly, *i.e.*, it stabilizes the substrate, but this rate-retarding effect is much more than offset by the large increase of $f_{\mathrm{O\bar{H}}}/f_{\mathrm{X}}^*$, which shows that the major effect of tetramethylammonium chloride is to stabilize the large anionic transition state, relative to the small hydroxide ion.

Table III. Relation between Kinetic Salt Effect and Activity Coefficient of 2,4-Dinitrochlorobenzene[a]

Salt	Ionic strength 1.0 $f_{\mathrm{O\bar{H}}}/f_{\mathrm{X}}^*$	Ionic strength 2.0 $f_{\mathrm{O\bar{H}}}/f_{\mathrm{X}}^*$
LiCl	0.42	0.26[b]
NaCl	0.66	0.51
KCl	0.97	0.95
$(CH_3)_4NCl$	1.87	3.00
NaBr	0.67	0.57[b]
$LiClO_4$	0.72	0.58
$NaClO_4$	0.86	0.84
$NaNO_3$	0.75	0.72[b]
Na_2SO_4	0.53	0.41

[a] Calculated using values of k_2 at 25.0° in water and with k_0 determined in the absence of salts. [b] Using rate constants at 45.0°.

The results in Figure 1 and Table III show that f_{ArCl} is affected by both anions and cations, as would be expected from all that is known about the solubility of polar nonelectrolytes in aqueous salt solutions, because both anions and cations of low charge density tend to "salt-in" organic solutes relative to the effects of ions of high charge density.[19] On the other hand it is the bulky tetramethylammonium cation which is very effective at increasing $f_{\mathrm{O\bar{H}}}/f_{\mathrm{X}}^*$; the ions of high charge density, *e.g.*, Li^+ and SO_4^{2-}, decrease it.

These results show that one must be cautious in explaining kinetic salt effects in the absence of information on the activity coefficient of the substrate, even in highly polar solvents, and especially at relatively high salt concentrations.

We did not attempt to separate the various parts of the activity coefficient term for the reactions in aqueous alcohol, but the salt effects upon the reaction between lyate ions and 2,4-dinitrochlorobenzene are similar in both water and aqueous alcohol, and therefore probably have common origins, as appears to be the case for the reaction between thiosulfate ion and *n*-pentyl bromide.

Initial and Transition-State Effects upon the Molecule–Molecule Reaction. For the reaction between aniline and 2,4-dinitrochlorobenzene the Brønsted–Bjerrum rate equation is

$$k_2^s = k_2^0 f_{\mathrm{ArCl}} f_{\mathrm{PhNH_2}}/f_{\mathrm{X}}^* \qquad (2)$$

and here we can determine the effect of added salts upon the stability of the transition state, provided that we make the reasonable assumption that the difference in temperature between the two sets of measurements will be relatively unimportant. The values of $1/f_{\mathrm{X}}^*$ given in Table IV show that changes in the activity coefficients of the reagents are very important. In particular sodium chloride and sulfate enhance the rate by destabilizing the initial state more than the transition state, and

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for several salts, *e.g.*, potassium chloride and sodium nitrate and bromide, f_X^* is almost independent of the electrolyte concentration and only initial state effects are important.[25] Only with tetramethylammonium chloride and the perchlorates is there marked stabilization of the transition state, which more than offsets the effects of the salt upon the initial state.

Table IV. Specific Salt Effect upon the Transition State of the Reaction of Aniline with 2,4-Dinitrochlorobenzene[a]

	Ionic strength	
	1.0	2.0
Salt	$1/f_X^*$	
NaCl	0.77[b]	0.60[b]
KCl	1.00[b]	0.94[b]
$(CH_3)_4NCl$	1.82	3.22
NaBr	0.98	0.96
$NaNO_3$	0.95	0.88
$LiClO_4$	1.54	1.72
$NaClO_4$	1.24	1.26
Na_2SO_4	0.49	

[a] In water at 85.0°, using activity coefficients measured at 25.0°. [b] Calculated using Setschenow constants of 0.136 for NaCl and 0.115 for KCl.[18]

Although the reaction between 2,4-dinitrochlorobenzene and aniline formally leads to a transition state whose structure will be similar to that of the intermediate (II) which has considerable polar character, the salt effect cannot be explained in terms of a stabilization of the transition state by the electrostatic effect of ions acting by virtue of their point charges.

Relation between Kinetic Salt Effect and Mechanism. The relations between salt effect and mechanism cannot be explained in terms of simple electrostatic theories which treat ions as point charges, and for reactions involving ionic nucleophiles formation of a weakly nucleophilic ion pair is important in solvents of low polarity.[2,4,26] However, for reactions in polar hydroxylic solvents such as water the charge densities of the ions seem to be the dominant factor in determining the direction of the specific salt effect.

The effects upon the initial state of the reaction can in principle be determined experimentally,[19] and with this information in hand we can usefully consider reactions in terms of their charge type as well as mechanism.[9]

For the bimolecular anion–molecule reactions discussed here the results show that the relative stabilities of the small nucleophilic anion and the bulky anionic transition state are very dependent upon the cation of the salt, *e.g.*, the small alkali metal cations decrease $f_{\overline{OH}}/f_X^*$ for the reaction between hydroxide ion and 2,4-dinitrochlorobenzene, but tetramethylammonium cations have the opposite effect (Table III). We assume also that the positive salt effect of tetrabutylammonium ions upon the reaction between 2,4-dinitrochlorobenzene and hydroxide ion is caused by relative stabilization of the transition state,[2b] and that this is also true for the effect of tetramethylammonium ions upon the reactions of thiophenoxide ion.

The mean ion activity coefficients of the alkali metal hydroxides increase with decreasing charge density of the cation, but the over-all effects are small, and could arise from changes in the activity coefficient of the cation, rather than the anion, particularly because hydration of the cation depends very markedly upon its charge density.[27] In addition the empirical parameters which are used in the calculation of individual ion activity coefficients by the extended Debye–Hückel equation are very similar for Na^+, K^+, Rb^+, Cs^+, and $(CH_3)_4N^+$, and the *calculated* individual ion activity coefficient of hydroxide ion is therefore little dependent upon the nature of the univalent cation.[28] Therefore, the available evidence makes it improbable that these kinetic salt effects can be explained simply in terms of changes in the activity coefficient of the nucleophilic anion.

We observe very different results for acid-catalyzed hydrolyses, where the salt effects depend upon both the mechanism and the structure of the substrate.[7,11,14] Although the effects of salts and acids upon the initial state have not generally been determined the results seem to be clear.[14] For A1 reactions of uncharged esters and related compounds ions of low charge density "salt-in" the substrate and hence tend to retard the reaction, but this effect is more than offset by the ability of anions of low charge density to "salt-in," *i.e.*, stabilize, the carbonium ion like transition state relative to the proton.

On the other hand these low charge density anions do not stabilize the transition states for A2 reactions in which the positive charge is located on acidic –OH groups, as in $A_{Ac}2$ hydrolyses of carboxylic esters and anhydrides.[14,29] Salt and acid orders similar to those found for A2 reactions are observed for A1 hydrolyses in which the transition-state structure is close to that of the conjugate acid, as in hydrolyses of acetals.[30]

For reactions which involve the attack of one molecule upon another the position is less clear, although for the reaction between aniline and 2,4-dinitrochlorobenzene we find that both anions and cations of low charge density, *e.g.*, $(CH_3)_4N^+$ and ClO_4^-, stabilize the transition state, whereas ions of high charge density, *e.g.*, SO_4^{2-}, destabilize it but may assist the reaction because they destabilize the initial state even more.

Although we can separate the electrolyte effects upon initial and transition states only in water the similarity of the kinetic salt effects upon the reactions of lyate and thiophenoxide ion and 2,4-dinitrochlorobenzene in water and aqueous ethanol or *t*-butyl alcohol (Figures 2 and 3 and Table II) and the similarity of these effects and those for the reaction between thiosulfate ion and *n*-pentyl bromide in aqueous ethanol suggests (i) that for anion–molecule reactions the transition state is stabilized, relative to the nucleophilic anion, by cations of low charge density; (ii) that for molecule–molecule reactions both anions and cations of low charge density stabilize the transition state; and (iii) that ions of high charge density destabilize the transition state, but nonetheless may speed the reaction by strongly destabilizing the initial state.

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(25) We assume that the rate enhancements of the reaction between ammonia and 2,4-dinitrohalobenzenes in methanol by halide ions are also due to initial state effects,[23] although activity coefficient data are not available in this system.

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The solvent properties of water depend to a marked degree upon its structure, which is sensitive to added solutes, and the salt orders which we observe in these kinetic studies are qualitatively similar to that found for perturbations of the water structure,[31a] as judged, for example, by infrared spectroscopy.[31b] Added ions of high charge density orient the water molecule around themselves, but with decreasing charge density they merely break up the existing structure. For reaction between hydroxide ion and 2,4-dinitrochlorobenzene the increase of $f_{\overline{\mathrm{OH}}}/f_{\mathrm{X}}^*$ for the alkali metal cations (Table III) follows the increasing "structure-breaking" properties of these ions.[31] However, we note that some bulky tetraalkylammonium ions actually promote water–water hydrogen bonding by forming clathrate-like hydrates.[32]

The hydroxide ion is a "structure maker" in that it orients water molecules about itself; these water molecules should become arranged differently when the hydroxide ion is incorporated into the transition state, and a "structure-breaking" ion might be expected to assist this process. In much the same way we could assume that the increase of $1/f_{\mathrm{X}}^*$ with addition of tetramethylammonium or perchlorate ions (Table IV) is related to the ability of these ions to break up the water structure and so make it easier for the water molecules to hydrogen bond to the forming ammonium ion center in the transition state (II). Although superficially attractive these arguments have a number of weaknesses at least for the ion–molecule reactions. (i) The kinetic salt order is very similar for the three anion–molecule reactions considered here, and does not seem to be related to the effects of the nucleophilic anions upon the water structure. For example, the hydroxide and thiophenoxide ions should be very different in respect to their effects upon the water structure, but the kinetic salt orders for their reactions with 2,4-dinitrochlorobenzene are very similar (Figures 2–5), and these salt orders are similar to those observed for the reaction between thiosulfate ion and *n*-pentyl bromide (Figure 6). (ii) The kinetic cation order seems to be qualitatively similar for a variety of nucleophilic substitutions involving various substrates.[7,8] (iii) The salt orders are not particularly sensitive to the nature of the organic cosolvent, whereas if effects upon the water structure were all important we would expect to find very different kinetic salt orders for reactions carried out in water, aqueous ethanol, and aqueous *t*-butyl alcohol. Many organic solvents which do not interact strongly with water nonetheless enhance water–water hydrogen bonding as shown by changes in nmr chemical shifts,[33] by encouraging water-shell formation.[34] This enhancement of the water structure is particularly large for 5–7 mol % *t*-butyl alcohol.[33] However, we find similar kinetic salt orders in water, ethanol–water 25:75 w/w, and *t*-butyl alcohol water 18:82 w/w (5.1 mol %), although in aqueous ethanol the structure of the water should have been disrupted by the organic solvent, and with *t*-butyl alcohol it should have been enhanced.[33] Moreover the kinetic solvent effects for the reaction between hydroxide ion and 2,4-dinitrochlorobenzene, in the absence of salt, are not related in any obvious way to the effects of the organic cosolvents upon the water structure because addition of both ethanol and *t*-butyl alcohol to water increases the rate of reaction of lyate ion with 2,4-dinitrochlorobenzene (Table I).

For these reasons it does not seem possible to explain all these kinetic salt effects in terms of the indirect effects of the salts upon the free energies of the reactants and transition states, by virtue of changes in the water structure.

Although both the kinetic salt effects and the ionic effects upon water structure depend upon the size and charge density of the ions, it is not possible to account for all the kinetic salt effects in terms of the indirect effects of the ions, and therefore we must consider the possibility of direct interactions between the electrolyte and the reactants and transition states. The individual variations in the kinetic salt orders which we observe for these various reactions in different solvents suggest that several different factors contribute to these salt effects. Direct interactions between polar organic molecules and ions of low charge density have been demonstrated, even in solvents which contain enough water to hydrate the ions; *e.g.*, Grunwald and his coworkers have shown that dioxane can solvate large cations even in aqueous dioxane,[35] and there is a great deal of kinetic and stereochemical evidence for the solvation of carbonium ions by polar organic solvents.[36,37] Therefore it is not unreasonable that a cation of low charge density, such as tetraalkylammonium, should be "solvated" by a large anionic transition state which would have a structure close to the intermediate (I), or that a large dipolar transition state of structure similar to II should "solvate" an ion of low charge density.

However one chooses to interpret these results, they demonstrate the hazards of attempting mechanistic explanations of kinetic salt effects outside the range of concentrations at which the simple electrostatic theory can be applied.

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