Tetrahedron Letters No. 9, pp. 24-30, 1960. Pergamon Press Ltd. Printed in Great Britain.

ION PAIRS, NUCLEOPHILICITY AND SALT EFFECTS IN BIMOLECULAR NUCLEOPHILIC SUBSTITUTION[1]

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(Received 28 March 1960)

Second order rate constants for S_N2 reactions of lithium halides with alkyl halides and toluenesulfonates[3] in acetone correspond to an apparent nucleophilicity order, $I^- > Br^- > Cl^-$, in agreement with the one usually quoted.[4] It has been clear for some time, however, that the second order rate constants obtained under the usual kinetic conditions are far from actual rate constants for reaction of the organic substrates with dissociated halide ions. In this Communication we point out that the nucleophilicity order of the halides in acetone is actually $Cl^- > Br^- > I^-$, the exact reverse of that usually quoted.[4]

For bimolecular nucleophilic substitution reactions involving neutral

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[1] Research supported by the National Science Foundation.

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[3] J. S. Gall, I.D.R. Stevens and S. Smith, unpublished work.

[4] e.g., (a) A. Streitwieser, Jr., Chem. Reviews 56, 571 (1956); (b) C. G. Swain and C. B. Scott, J. Am. Chem. Soc. 75, 141 (1953); (c) J. O. Edwards, ibid. 76, 1540 (1954), 78, 1819 (1956); (d) J. Hine, Physical Organic Chemistry. McGraw-Hill Book Co., New York, N. Y., 1956, p. 138; (e) E. S. Gould, Mechanism and Structure in Organic Chemistry . Henry Holt and Co., New York, N. Y., 1959, p. 258.

substrates and anionic nucleophiles in acetone, second order rate constants tend to decrease with increasing concentration of the nucleophilic reagent. The University College, London, School has consistently ascribed this behavior to salt effects on the rate constant for the reaction.[5] The observation that the addition of lithium perchlorate decreases the second order rate constant in the reaction of lithium chloride with alkyl iodides[5c] was regarded as support for this interpretation. Moreover, in the reactions of lithium chloride[5c] and lithium bromide[5f] with alkyl iodides the rate constants were observed to decrease within a run. This was attributed to a negative salt effect due to a change in electrolyte composition during the reaction. This effect was associated with the negative salt effect order,[5f] $LiI > LiBr > LiCl > LiF$.

The observations of Ingold and coworkers[5] are more satisfactorily accounted for by taking account of ion association of the nucleophilic reagent and considering the relative reactivities of the dissociated anion,[6,7,8] ion pair,[6,7,8] ion triplet,[9] etc. Acree[6] very early ascribed

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[5] (a) P.B.D. de la Mare, J. Chem. Soc. 3169 (1955); (b) E. D. Hughes, C. K. Ingold and J.D.H. Mackie, ibid. 3173 (1955); (c) E. D. Hughes, C. K. Ingold and J.D.H. Mackie, ibid. 3177 (1955); (d) P.B.D. de la Mare, ibid. 3180 (1955); (e) L. Fowden, E. D. Hughes and C. K. Ingold, ibid. 3187 (1955); (f) L. Fowden, E. D. Hughes and C. K. Ingold, ibid. 3193 (1955); (g) P.B.D. de la Mare, ibid. 3196 (1955); (h) P.B.D. de la Mare, L. Fowden, E. D. Hughes, C. K. Ingold and J.D.H. Mackie, ibid. 3200 (1955); (i) Y. Pocker, ibid. 3939 (1959).

[6] S. F. Acree, Am. Chem. J. **48**, 353 (1912).

[7] A. Brändström, Arkiv Kemi. **11**, 567 (1957).

[8] (a) C. C. Evans and S. Sugden, J. Chem. Soc. 270 (1949); (b) C. C. Evans and S. Sugden, J. Chim. Phys. **45**, 147 (1948).

[9] R. D. Heyding and C. A. Winkler, Can. J. Chem. **29**, 790 (1951).

downward trends in second order rate constants with increasing salt concentration to incomplete dissociation of the salt and the much greater reactivity of the dissociated anion compared to the ion pair. While the second order rate constant for the exchange reaction of lithium radio-bromide with n-butyl bromide in acetone at 25° varies by a factor of 3.6 over a 400 fold range of salt concentrations, Evans and Sugden[8] have shown that a steady value is obtained on the assumption that only dissociated bromide ion is reactive. Similar analyses have been employed by Swart and leRoux,[10] Olson,[11] Winkler,[9] Moelwyn-Hughes[12] and Lichtin.[13] In all of these cases, the reactivity of the dissociated ion was found to be much larger than that of the ion pair, although the exact contribution of the latter to the reaction rate is difficult to assess in some instances.

Since dissociated ions appear to be more reactive than ion pairs, the rate depression by lithium perchlorate observed by Ingold[5c] is to be ascribed to common ion repression of the dissociation of the lithium chloride rather than to a salt effect on the second order rate constant. Further, Ingold's[5f] empirical negative salt effect order is simply the order of decreasing ion pair dissociation constants in acetone (Table I), or in other words, the order of decreasing ability to repress the dissociation of the

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[10] (a) E. R. Swart and L. J. leRoux, J. Chem. Soc. 2110 (1956); (b) L. J. leRoux and E. R. Swart, ibid. 1475 (1955).

[11] A. R. Olson, L. D. Frashier and F. J. Spieth, J. Phys. Chem. **55**, 860 (1951).

[12] (a) E. A. Moelwyn-Hughes, Trans. Faraday Soc. **45**, 167 (1949); (b) Farhat-Aziz and E. A. Moelwyn-Hughes, J. Chem. Soc. 2635 (1959).

[13] N. N. Lichtin and K. N. Rao, Abstracts, Division of Physical Chem. of the Am. Chem. Soc., Chicago, Illinois, Sept. 7-12 (1958) p. 12S.

nucleophilic salt. This interpretation is supported by observations in these Laboratories on the effects of added common ion and non-common ion salts in bimolecular nucleophilic substitutions in acetone solvent. For example, the rate of reaction of isobutyl p-toluenesulfonate with 0.04 M lithium chloride in acetone at 50° is decreased by a factor of three when 0.02 M lithium perchlorate is added, but it is increased by a factor of two by added 0.02 M tetrabutylammonium perchlorate.

The importance of ion association in controlling apparent nucleophilicity becomes evident when reactivities of lithium and tetrabutylammonium halides are compared. For example, in the reaction of n-butyl p-bromobenzenesulfonate with 0.04 M halide salts in acetone at 25°, the reactivity pattern is the following:

$$\begin{array}{ccccc} \text{LiI, 6.2} & > & \text{LiBr, 5.7} & > & \text{LiCl, 1.0} \\ \vee & & \wedge & & \wedge \\ (\text{n-Bu})_4\text{NI, 3.7} & < & (\text{n-Bu})_4\text{NBr, 18} & < & (\text{n-Bu})_4\text{NCl, 68} \end{array}$$

With lithium halides the order, $I^- > Br^- > Cl^-$, is observed, while the reverse order obtains for the tetrabutylammonium salts. This reversal arises because tetra-n-butylammonium chloride reacts 68 times as fast as lithium chloride, while lithium iodide reacts more rapidly than tetra-n-butylammonium iodide by a factor of 1.7. Similar results have been obtained with isobutyl p-toluenesulfonate in acetone at 50.0°:

$$\begin{array}{ccccc} \text{LiI, 10} & > & \text{LiBr, 5.8} & > & \text{LiCl, 1.0} \\ \vee & & \wedge & & \wedge \\ (\text{n-Bu})_4\text{NI, 4.3} & < & (\text{n-Bu})_4\text{NBr, 18} & < & (\text{n-Bu})_4\text{NCl, 65} \end{array}$$

The present data suggest that the nucleophilicity order of anions in acetone is actually $Cl^- > Br^- > I^-$, the one observed with the more dissociated tetrabutylammonium salts, and that the reactivity pattern of the lithium halides is governed largely by the extreme variation in the ion pair dissociation constants of the salts in acetone rather than by the inherent nucleophilicities of the anions.

While some contribution to the reaction rate in acetone may be made by species other than the dissociated halide ions, approximate second order rate constants, k_2, for reaction by way of dissociated anions may be estimated by dividing the apparent second order rate constant, k_2', by the degree of dissociation of the salt, α. The results of this treatment for n-butyl p-toluenesulfonate are summarized in Table I, the α values being obtained with the aid of measured values of the ion pair dissociation constants, K, and Debye-Hückel limiting law activity coefficients.

As is clear from Table I, the lithium and tetrabutylammonium salts lead to nearly the same k_2 values for the dissociated halide ions. These give the rate sequence, Cl^-, 18 > Br^-, 4 > I^-, 1.0. The $Cl^- > Br^-$ rate sequence has also been observed with benzyl and 1-phenyl-2-propyl p-toluenesulfonates.[3] The $Cl^- > Br^- > I^-$ order is also obtained with alkyl bromides as the substrates when the data of Ingold and coworkers[5b,d,e] are corrected for ion pairing. For example, with isopropyl bromide,[5b,d,e] the rate sequence becomes Cl^-, 11 > Br^-, 5 > I^-, 1.0 in acetone at 25°.

In general, the anion order in acetone is the reverse of that observed in water.[4] For example, for the reaction of methyl iodide with halide salts in water[10,14] at 25° the anion rate sequence is I^-, 160 > Br^-, 14 > Cl^-, 1.0. With methyl bromide in water[14] at 25°, the rate sequence is I^-, 140 > Cl^-, 1. Obviously, the change from water to acetone causes a reversal in

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[14] (a) E. A. Moelwyn-Hughes, J. Chem. Soc. 779 (1938); (b) R. H. Bathgate and E. A. Moelwyn-Hughes, ibid. 2642 (1959).

TABLE 1. Summary of Rate Constants for the Reaction of n-Butyl p-bromobenzenesulfonate with 0.04 M Salts in Acetone at 25.0°

Salt	10^4K	$10^3k_2'$	10^3k_2	Ave. 10^3k_2
		Rate Constants, l. mole^{-1} sec.$^{-1}$		
$(n\text{-}Bu)_4NCl$	22.8[15]	33.5	58	55
LiCl	0.027[16]	0.493	51	
$(n\text{-}Bu)_4NBr$	32.9[17]	9.09	13	13
LiBr	5.22[8]	2.81	12	
$(n\text{-}Bu)_4NI$	64.8[17]	1.68	2.0	3
LiI	69[16]	2.97	3.6	

the nucleophilicity order of the halides. The importance of the solvent is emphasized by the very large increases in rate associated with the solvent change from water to acetone. Even without recourse to specific solvation effects,[18] one could anticipate on electrostatic grounds[19] that solvent sensitivity of the halide ion reactions would increase in the order of decreasing anion size, namely, $I^- < Br^- < Cl^-$. This in turn makes a reversal in nucleophilicity order of the halides a perfectly logical result of a

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[15] M. J. McDowell and C. A. Kraus, J. Am. Chem. Soc. **73**, 3293 (1951).

[16] L. G. Savedoff, unpublished work.

[17] M. B. Reynolds and C. A. Kraus, J. Am. Chem. Soc. **70**, 1709 (1948).

[18] e.g., (a) E.A.S. Cavell, J. Chem. Soc. 4217 (1958); (b) J. A. Leary and M. Kahn, J. Am. Chem. Soc. **81**, 4173 (1959).

[19] e.g., (a) K. J. Laidler and H. Eyring, Ann. N. Y. Acad. Sci. **39**, 303 (1940); (b) A. A. Frost and R. G. Pearson, Kinetics and Mechanism. John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 135-138.

sufficiently large solvent change. The change from water to acetone increases k_2 by ca. 10^4 in the iodide ion-methyl iodide reaction.[20] However, the same solvent change is increasing k_2 for the chloride ion reactions by ca. 10^7.

The need to consider ion association in assessing nucleophilicity has a bearing on Bunnett's scrutiny of the dependence of relative nucleophilicities of the halide ions on the nature of the substrate (RCl, RBr, RI).[21] He employed the rate constants of Ingold and coworkers,[5] and these were variously affected by ion association, common ion repression and the method of calculation. For example, the rate constant for the reaction of lithium chloride (0.032 M) with alkyl iodides was considerably depressed by the presence of 0.11 M lithium perchlorate;[5c] however, when alkyl bromides were studied no lithium perchlorate was added.[5d] In the reaction of lithium bromide with alkyl iodides[5f] the rate constant was calculated by a procedure which gives a value which is inevitably too low. In addition, different salt concentrations were employed with the different alkyl halides. These factors influence the derived rate comparisons.

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[20] E. R. Swart and L. J. leRoux, J. Chem. Soc. 406 (1957).

[21] J. F. Bunnett, J. Am. Chem. Soc. **79**, 5969 (1957).