

are held in rigid proximity to each other by the molecular framework, in contrast to the open-chain cases, where the ends must first be brought together to achieve the transition state for a concerted process. The contrast between the two cases is manifested in the entropies of activation, those for the open-chain Cope rearrangement being large and negative<sup>10</sup> and that of the I → II reaction being small and positive.<sup>2a</sup> The

entropy changes and qualitative pressure effects are about what might be expected for the two kinds of reaction on any grounds and have no bearing on the question of whether the I → II rearrangement uses the same energy surface as the Diels-Alder retrogression of I to cyclopentadiene and hydroxycyclopentadiene.

(10) E. G. Foster, A. C. Cope and F. Daniels, *J. Am. Chem. Soc.*, **69**, 1893 (1947).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, JOHN CARROLL UNIVERSITY, CLEVELAND 18, OHIO]

## Determination of Dissociation Constants of Ion Pairs from Kinetic Data of Bimolecular Nucleophilic Substitutions. I. The Importance of Solvation and Ion Pairing on the Nucleophilic Reactivity of the Halide Anions

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The dissociation constants for the ion pairs of lithium chloride, bromide, and iodide in DMF at 0° have been determined from the variation, with concentration of the halides, of the second-order rate constants derived from their reaction with methyl toluenesulfonate in DMF at 0°. The rate of reaction of the halide anions is visibly in the order I<sup>-</sup> < Br<sup>-</sup> < Cl<sup>-</sup>. The significance of this order compared to the reverse order which is normally reported is discussed.

The nucleophilicities of the halide ions are of considerable interest because the usual order of reactivity [I<sup>-</sup> > Cl<sup>-</sup>] is opposite to that predicted by the generalization—the more basic a nucleophile the greater its nucleophilicity. Further, the ease with which iodide ion in acetone replaces chloride from an alkyl chloride is inconsistent with the easy displacement of iodide from an alkyl iodide compared to the sluggish displacement of chloride from an alkyl chloride by a common nucleophile. These irregularities have been ascribed by various authors to: (1) polarizability,<sup>2-5</sup> (2) solvation,<sup>3,6</sup> and (3) ion pairing.<sup>7</sup>

In the present report an effort to evaluate the importance of the above has been made by studying the rates of reaction of methyl *p*-toluenesulfonate (methyl tosylate) with lithium chloride, bromide, and iodide in dimethylformamide (DMF). Moreover, a method for determining the dissociation constant of ion pairs from kinetic data alone is described.

### Results

In DMF, the relative rates of reaction of the lithium halides (at 0.04 *M*) with methyl tosylate are visibly in the order Cl<sup>-</sup>, 7.8 > Br<sup>-</sup>, 3.2 > I<sup>-</sup>, 1.0. (After correction for ion pairing, the relative rates are Cl<sup>-</sup>, 9.1 > Br<sup>-</sup>, 3.4 > I<sup>-</sup>, 1.0.) This, of course, is directly opposite that observed with sodium halides in aqueous dioxane reacting with ethyl tosylate<sup>8</sup> where the order is Cl<sup>-</sup>, 0.14 < Br<sup>-</sup>, 0.32 < I<sup>-</sup>, 1.0; and likewise opposite to that observed with lithium halides reacting with *n*-butyl *p*-bromobenzenesulfonate in anhydrous acetone<sup>7</sup> where the order is Cl<sup>-</sup>, 0.16 < Br<sup>-</sup>, 0.92 < I<sup>-</sup>, 1.0. In addition, it was found that the presence of 9.1% by volume of water in the DMF (5 *M* H<sub>2</sub>O) caused a 24-fold reduction in the observed rate for displace-

ment by chloride ion but only a twofold retardation of the iodide. This retardation does not arise from the hydrolysis of the methyl halides since methyl iodide (1.6 *M*) in 20% H<sub>2</sub>O–80% DMF was only 0.35% hydrolyzed after 1 hr. at 0°. Consequently, with but 9% water in DMF the usual order of reactivity is restored, for, now, iodide is twice as reactive as chloride.

It was also found that *n*-butyl iodide is converted nearly quantitatively (99%) to *n*-butyl chloride by lithium chloride in anhydrous DMF after but 1 hr. and with but a 16% excess of lithium chloride.

As anticipated, the rate constants for the bimolecular reaction of halide anions with methyl tosylate in DMF are dependent on initial concentration of lithium halide. This was ascribed to ion pairing, and from the degree of variation of rate constants with initial concentration of the halide, the dissociation constants of the lithium halides in DMF at 0° were computed to be: LiCl, *K* = 0.180; LiBr, *K* = 0.385; and LiI, *K* = 1.80.

**Method.**—An examination of Table I and Fig. 1 clearly shows that, in DMF, not only is chloride ion a

TABLE I  
OBSERVED AND SPECIFIC RATE CONSTANTS OF THE METHYL  
TOSYLATE-LITHIUM HALIDE REACTION AT VARIOUS  
CONCENTRATIONS OF HALIDE IN DMF AT 0°

	[C], mole l. <sup>-1</sup>	10 <sup>3</sup> × <i>k</i> <sub>obsd</sub> ± <i>s</i> , <sup>a</sup> l. mole <sup>-1</sup> sec. <sup>-1</sup>	<i>K</i>	α <sup>b</sup>	<i>k</i> <sub>2</sub> × 10 <sup>2</sup> , l. mole <sup>-1</sup> sec. <sup>-1</sup>
LiCl	0.03933	4.54 ± 0.04	0.180	0.845	5.38
	.0985	3.84 ± .01	.180	.713	5.33
	.1940	3.23 ± .09	.180	.605	5.36
	.3911	2.61 ± .02	.180	.486	5.37
LiCl + 5.0 <i>M</i> H <sub>2</sub> O	.3678	0.116 ± .003			
LiBr	.03947	1.84 ± .02	0.385	0.914	2.00
	.2167	1.43 ± .03	.385	.714	2.00
LiI	.03818	0.581 ± .017	1.80	.979	0.593
	.3880	0.500 ± .007	1.80	.846	0.591
LiI + 5.0 <i>M</i> H <sub>2</sub> O	.1764	.276 ± .007			

<sup>a</sup> Standard deviation,  $s = \sqrt{\sum[d^2]/(N - 1)}$  where  $d$  = deviation from mean value and  $N$  = number of determinations.  
<sup>b</sup> Degree of dissociation, *i.e.*, ratio of "free" ion to total concentration.

better nucleophile than bromide, which is better than iodide, but also that the observed rate constants de-

(1) Based on the M.S. Thesis of J. Douglas Hutchison, John Carroll University, August, 1963.

(2) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 140.

(3) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p. 260.

(4) F. G. Bordwell, "Organic Chemistry," The Macmillan Co., New York, N. Y., 1963, p. 208.

(5) J. E. Leffer and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p. 250.

(6) H. R. McCleary and L. P. Hammett, *J. Am. Chem. Soc.*, **63**, 2254 (1941).

(7) S. Winstein, L. G. Savedoff, S. Smith, I. D. R. Stevens, and J. S. Gall, *Tetrahedron Letters*, **9**, 24 (1960).

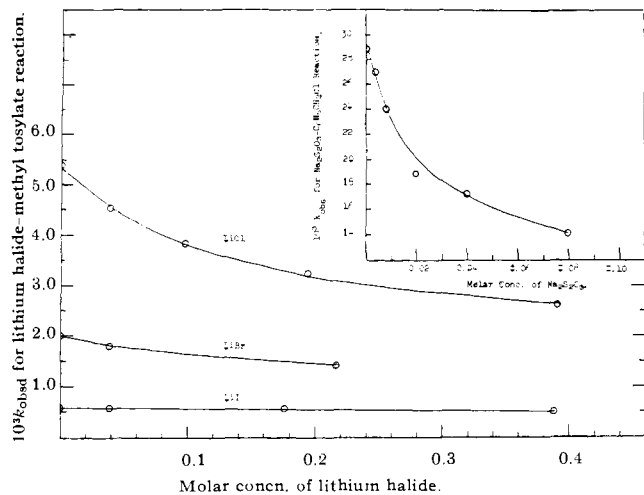


Fig. 1.—Dependency of second-order rate constants on concentration of nucleophilic reagent.

crease with increasing initial concentration of halide in a smooth and orderly manner. Winstein, *et al.*,<sup>7</sup> has argued well that this variation is best attributed to association of salts to ion pairs and is not a salt, or ionic strength, effect. Moreover, this smooth and orderly variation in rate constant with concentration permits an evaluation of dissociation constants of ion pairs from these data alone.

The method is relatively simple and is based on a few reasonable assumptions. It is first assumed that the reaction of methyl tosylate with halide ions in DMF is a simple bimolecular reaction<sup>8</sup> and ought to be first order in halide ion and first order in methyl tosylate.<sup>10</sup>

$$\text{rate} = k_2[X^-][\text{MeTos}] \quad (1)$$

However, where association exists, the halide ion concentration is not the total salt concentration. Since titration of halide does not distinguish between free ion and ion pair, the measured rate constant is one based on total salt concentration,  $[C]$ , and is not  $k_2$ ; *i.e.*

$$\text{rate} = k_{\text{obsd}}[C][\text{MeTos}] \quad (2)$$

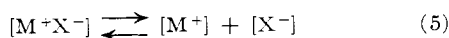
But since the rates are one and the same

$$k_{\text{obsd}}[C][\text{MeTos}] = k_2[X^-][\text{MeTos}] \quad (3)$$

and

$$k_{\text{obsd}}[C]/[X^-] = k_2 = k_{\text{obsd}}/\alpha \quad (4)$$

It is further assumed that the ion pairs will exhibit simple mass law equilibrium.



and

$$K = [M^+][X^-]/[M^+X^-] \quad (6)$$

(8) That methyl tosylate would react in a unimolecular manner is unlikely considering the instability of methyl carbonium ions. Although there is a possibility that DMF could react with methyl tosylate to produce a reactive intermediate, the methyl tosylate was never added to DMF alone but rather was the last reagent to be added in the initiation of the reaction. Further, the rate constant for the solvolysis of methyl iodide by DMF at 25° is small<sup>9</sup>:  $k_1 = 2.8 \times 10^{-7}$  sec.<sup>-1</sup>. The rate constant for the solvolysis of methyl tosylate at 0° would certainly be smaller and any contribution from the solvolysis reaction to the rate of displacement by halide would be negligible. To remove all doubt, the rate constant for the solvolysis of methyl tosylate in the presence of 0.115 M NaClO<sub>4</sub> was measured:  $k_1 = 2.3 \times 10^{-7}$  sec.<sup>-1</sup>. The maximum possible contribution to the rate of the slowest reaction is 1%.

(9) A. J. Parker, *J. Chem. Soc.*, 1328 (1961).

(10) Winstein has shown with the similar assumption for the reaction of halide with butyl *p*-bromobenzenesulfonate in acetone that the corrected rate constant,  $k_2$ , is the same for lithium and tetrabutylammonium salts, even though the ion pair dissociation constants are widely different for the two cations.

and initially where  $[M^+] = [X^-]$

$$[X^-] = \frac{-K + \sqrt{K^2 + 4K[C]}}{2} \quad (7)$$

Therefore

$$\frac{k_{\text{obsd}1}[C]_1}{[X^-]_1} = \frac{k_{\text{obsd}2}[C]_2}{[X^-]_2} = k_2 = \frac{k_{\text{obsd}1}[C]_1}{-K + \sqrt{K^2 + 4K[C]_1}} \quad (8)$$

It follows that a plot of  $k_{\text{obsd}1}[C]_1$  vs.  $[C]_1$  will be a smooth curve passing through the origin with the initial slope being equal to  $k_2$ . However,  $k_2$  is best determined by evaluating  $K$  by successive approximation:  $[X^-]_1$  and  $[X^-]_2$  are calculated from assumed values of  $K$  (eq. 7) until each yield the same  $k_2$  (eq. 8).

It will be observed when making such calculations that where  $[C]_2 > [C]_1$ ,  $k_{\text{obsd}1}[C]_1/[X^-]_1$  will be greater than  $k_{\text{obsd}2}[C]_2/[X^-]_2$  when the assumed value of  $K$  is too large and the reverse when the assumed value of  $K$  is too small.

The twofold variation in observed rate constants with a tenfold variation in concentration of lithium chloride gives a derived rate constant,  $k_2$ , which deviates by less than 1% when  $K$  is assumed to be 0.18(). This very close agreement was achieved without recourse to ionic strength corrections and, indeed, constant ionic strength was avoided since the addition of any salt would exert a buffering effect on the dissociation of the ion pair.

Inasmuch as eq. 7 is exact only at time zero, when  $[M^+] = [X^-]$ , the observed rate constants should be initial rate constants (often difficult to determine precisely). The observed rate constants reported here are calculated from

$$k = \frac{1}{b-a} \ln \frac{a[b-x]}{b[a-x]}/t$$

from a single determination of the extent of reaction at such a time as to provide a small but sufficient extent of reaction (10–20%) which would be accurately analyzable.

This single point method was chosen because, since the whole of the reaction was quenched and titrated, quantities and time were known exactly. There is sufficient evidence that nucleophilic substitutions in DMF at a primary or secondary carbon are bimolecular.<sup>11–17</sup> Thereon, the applicability of the integrated equation of a second-order reaction for the determination of the rate constant with only a single, but precise, determination of extent of reaction at an accurately known time seems warranted. Nevertheless, the reaction of lithium iodide with methyl tosylate was followed throughout 100% of the reaction by the aliquot method simply to demonstrate the validity of the integrated second-order rate equation to this system. (The rate constants derived therefrom are considered somewhat less precise since the procedure was not sufficiently practiced.)

It has been common practice to average rate constants over the whole of the reaction, either graphically or arithmetically. Further, an inert salt is frequently added to maintain constant ionic strength. Both procedures have the effect of masking the variation of rate constant with concentration of the nucleophilic reagent and were purposely avoided.

(11) A. J. Parker, *Quart. Rev.* (London), **16**, 163 (1962).

(12) J. Miller and A. J. Parker, *J. Am. Chem. Soc.*, **83**, 117 (1961).

(13) H. E. Zaugg, *ibid.*, **83**, 837 (1961).

(14) W. M. Weaver, Ph.D. Thesis, Purdue University, 1958.

(15) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6270 (1955).

(16) N. Kornblum, R. Seltzer, and P. Haberfield, *ibid.*, **85**, 1148 (1963).

(17) N. Kornblum, R. K. Blackwood, and J. W. Powers, *ibid.*, **79**, 2507 (1957).

Contrary to what is observed with time and concentration, the rate constants at a given concentration of the salt of the nucleophile were easily reproduced. The standard deviations,  $s$ , [based on  $(n - 1)$  determinations] are reported in Table I along with the averaged value of the rate constant. This high degree of reproducibility was obtained over slightly different percentages of reaction since the initial concentration of methyl tosylate was not identical (not required by eq. 4) from one duplicate to the next.

An attempt to evaluate dissociation constants of ion pairs from kinetic data apparently was first done by Bell and Prue.<sup>18</sup> The associated species, however, was not a reactant but a catalyst (metal hydroxide). Their approach, therefore, had limited application and became obscure.

The most recent evaluation of dissociation constants from kinetic data was made by Casapieri and Swart.<sup>19</sup>

This work is very pertinent since lithium chloride, radioactive, was allowed to react with benzyl chloride in DMF. Their procedure is considerably more complicated since the mean activity coefficient,  $f$ , is employed in the equilibrium expression.

Application of the simpler method given above to the data of Casapieri and Swart gives  $k_2$ 's which differ by only 2% (cf. Table II). The required dissociation constants,  $K$ , do differ significantly though.

TABLE II

COMPARISON OF SPECIFIC RATE CONSTANTS<sup>a</sup> EVALUATED WITH AND WITHOUT THE USE OF ACTIVITY COEFFICIENTS

$10^4 k_{\text{obsd}}$	$10^2 C$	$K^b = f^2 \alpha^2 C / (1 - \alpha) = 0.0171$		$K = \alpha^2 C / (1 - \alpha) = 0.037$	
		$\alpha$	$10^4 k_2$	$\alpha$	$10^4 k_2$
2.04	1.07	0.790	2.58	0.810	2.52
2.07	0.704	.831	2.49	.859	2.41
2.25	.343	.892	2.52	.921	2.44
2.45	.106	.955	2.57	.972	2.52
Av.		2.54 ± 0.04		Av. 2.47 ± 0.05	

<sup>a</sup> For the reaction of lithium chloride, radioactive, with benzyl chloride in DMF at 30°; data of Casapieri and Swart.<sup>19</sup> <sup>b</sup> Ion pair dissociation constant for lithium chloride in DMF at 30°.

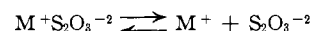
Although the omission of activity coefficients may give a less accurate value of  $K$ , the value so derived correlates the data equally well as the less useful  $K$  which is encumbered with activity coefficients. The prediction of  $f$  for solutions of 0.4  $M$  is hardly straightforward. Lichtin and Rao<sup>20</sup> have shown how difficult the prediction is even for dilute solutions.

The absence of any activity coefficient in the equilibrium expression employed in the procedure given here is best justified by the fact that activity coefficients are present also in the rate expression and are compensatory.<sup>21</sup> Stated in another way: since both the rate and equilibrium expressions are dependent on the activity of the anion, the activity rather than concentration of "free" anion is really calculated.

It remains to be seen how general the method herein described will be. The method, however, has been applied with limited success to the data of Fuchs, McCrary, and Bloomfield.<sup>22</sup> These workers have reported concentration-dependent rate constants for the reaction of benzyl chloride with sodium thiosulfate in a solvent consisting of 25% dimethyl sulfide-35% acetonitrile-40% water. Since thiosulfate is a divalent ion, the algebra is a little more complicated, but reasonably good correlation is obtained even though the system was further complicated by the addition of

20 mole % of potassium acetate as an acid buffer.

The ionic association is assumed to be simply the charged ion pair.



However, the concentration of the cation, sodium, is not that of the "free" thiosulfate but rather is equal to the stoichiometric concentration,  $[C]$ , of thiosulfate plus the "free" thiosulfate; *i.e.*

$$[M^+] = [C] + [S_2O_3^{2-}]$$

and

$$[M^+S_2O_3^{2-}] = [C] - [S_2O_3^{2-}]$$

Since

$$K = [M^+][S_2O_3^{2-}] / [M^+S_2O_3^{2-}]$$

then

$$[S_2O_3^{2-}] = \frac{-([C] + K) + \sqrt{([C] + K)^2 + 4K[C]}}{2}$$

In Table III are collected the results of Fuchs along with the computed  $k_2$  derived from  $K = 0.115$ . The greatest deviation is seen at 0.02  $M$   $Na_2S_2O_3$ . It can be observed in Fig. 1 that the observed rate constant for this concentration does not fall on the smooth curve connecting the other points and is probably too small.

TABLE III

OBSERVED AND DERIVED RATE CONSTANTS FOR THE REACTION OF SODIUM THIOSULFATE WITH BENZYL CHLORIDE IN 25% DMSO-35% ACETONITRILE-40% H<sub>2</sub>O AT 30°

$[Na_2S_2O_3]$ , mole l. <sup>-1</sup>	$10^4 \times k_{\text{obsd}}$ , l. mole <sup>-1</sup> sec. <sup>-1</sup>	$\alpha^a$	$k_2 \times 10^3$
0.004	27.0	0.94	28.8
.008	24.0	.88	27.2
.02	18.8	.76	24.6
.04	17.2	.64	27.8
.08	14.2	.49	28.9

<sup>a</sup> Derived from ion pair dissociation constant:  $K = 0.115$ .

The method has been applied also to the two rate constants reported by Miller and Parker<sup>12</sup> for the reaction of tetraethylammonium azide with *p*-fluoronitrobenzene in acetone at 25.1°. At  $[NEt_4N_3]_0 = 0.0187 M$ ,  $k_{\text{obsd}} = 49.6 \times 10^{-4}$  l. mole<sup>-1</sup> sec.<sup>-1</sup> and at  $[NEt_4N_3]_0 = 0.0270 M$ ,  $k_{\text{obsd}} = 47.4 \times 10^{-4}$  l. mole<sup>-1</sup> sec.<sup>-1</sup>. The specific rate constant and ion pair dissociation constant were computed to be:  $k_2 = 57.1 \times 10^{-4}$  l. mole<sup>-1</sup> sec.<sup>-1</sup> and  $K_{NEt_4N_3} = 0.11$ , provided the reported rate constants are close to initial rate constants.

(21) This is shown as follows: Let  $A$  be the substrate,  $X$  the nucleophile,  $M$  the cation,  $[C]$  the total salt concentration, and  $f_*$  the activity coefficient of the transition state.

$$\text{rate} = k_2[A][X]f_A f_X / f_* = k_{\text{obsd}}[A][C]$$

$$k_2 f_A / f_* = k_{\text{obsd}}[C] / f_X[X]$$

$$K = ([M][X] / [MX]) f_M f_X / f_{MX}$$

when  $[M] = [X]$

$$K = \frac{f_M f_X [X]^2}{f_{MX}[C] - f_{MX}[X]}$$

$$f_M f_X [X]^2 + f_{MX}[X]K - f_{MX}[C]K = 0$$

Multiplying through by  $f_X / f_M$

$$f_X^2 [X]^2 + \frac{f_{MX}}{f_M} f_X [X]K - \frac{f_{MX}}{f_M} f_X [C]K = 0$$

The ratio of any two activity coefficients in the same medium ought to be close to one.

$$f_X^2 [X]^2 + f_X [X]K - f_X K [C] = 0$$

$$f_X^2 [X]^2 + f_X [X]K - K [C] \approx 0$$

$$f_X [X] = [-K + (K^2 + 4K[C])^{1/2}] / 2$$

$$\frac{k_2 f_A}{f_*} = \frac{k_{\text{obsd}} [C]}{f_X [X]} = k_2 (f_A / f_* \approx 1)$$

$$k_2 = k_{\text{obsd}} C / (-K + \sqrt{K^2 + 4KC}) / 2$$

(22) R. Fuchs, G. E. McCrary, and J. J. Bloomfield, *J. Am. Chem. Soc.*, **83**, 4281 (1961).

(18) R. R. Bell and J. E. Prue, *J. Chem. Soc.*, 362 (1949).

(19) P. Casapieri and E. R. Swart, *ibid.*, 4342 (1961).

(20) N. N. Lichtin and K. N. Rao, *J. Am. Chem. Soc.*, **83**, 2417 (1961).

### Discussion

Hammett<sup>6</sup> very early explained the normally quoted order of reactivity of the halide ions in terms of solvation. Yet, in the most recent texts this order,  $I^- > Br^- > Cl^-$ , is explained in terms of polarizability thusly: "the greater polarizability of the larger ions permits an easier adjustment to the requirement of a stable transition state thereby lowering the activation energy."<sup>12</sup> This polarizability should then be an intrinsic property and persist from one medium to another. However, the reverse order is clearly visible in DMF. Parker<sup>9</sup> has suggested that we may not need polarizability but then allows it to enter the back door to explain the "common rate" observed for the reaction of chloride ion and bromide ion (together with a few other ions) with methyl iodide in DMF:  $k_{Cl} = 0.130$  and  $k_{Br} = 0.107$ .

This leveling effect on nucleophiles is ascribed to aprotic solvents, including DMF, solvating large anions, and large transition states because of the polarizability of the larger species. Our results show no such leveling.<sup>23</sup> The effect that Parker observed is probably due to the neglect of association and to the use of methyl iodide as the reference. The rate of reaction of methyl iodide with halides is 20–200 times faster than the rate of reaction of methyl tosylate with the halides and such a reactive substrate will be relatively insensitive to changes in nucleophilicity.

The addition of 9% water to DMF, which causes only a small dielectric change (37 to 46), clearly demonstrates the retardation caused by the solvation by protic solvents of anions of high charge density. It furthermore shows that the retardation is proportional to the charge density, *i.e.*, the small chloride ion with its high charge density is retarded 24-fold, whereas the large iodide with its lower charge density is retarded only twofold.

The need to invoke polarizability seems unnecessary as an explanation for the nucleophilic order usually observed in protic solvents for the halide anions and it might be best discarded.

The higher charge density of chloride ion, which also stabilizes the lithium chloride crystal as reflected by its higher m.p. and causes chloride to be more firmly coordinated in a complex ion than iodide (spectrochemical series<sup>24</sup>), causes lithium chloride to associate to ion pairs to a larger extent than lithium iodide. Thus in DMF, the dissociation constant for lithium chloride is one-tenth that of lithium iodide. In the solvent acetone with its smaller dielectric constant, the electrostatic forces are considerably stronger and lithium chloride is much more associated into ion pairs than lithium iodide.<sup>7</sup> (The dissociation constant for lithium iodide is 2000 times larger than that of lithium chloride.)

The association of lithium chloride in acetone is so much greater than lithium iodide that the rate of substitution by chloride is retarded to such an extent as to make chloride ion appear a weaker nucleophile than iodide ion. Substitution of a large tetraalkylammonium ion for the lithium cation weakens the electrostatic forces and the resultant association in acetone so that chloride ion is now visibly a stronger nucleophile than iodide.<sup>7</sup>

It is thus concluded that solvation of anions and ion-pairing both have a retarding effect on the rates of bimolecular substitution. This retardation<sup>25</sup> is most

(23) The rates of reaction of the halides with *n*-butyl *p*-bromobenzenesulfonate in acetone after correction for ion-pairing also fail to show such leveling and the apparent relative rates:  $[Cl^-] = 18 > Br^- = 4 > I^- = 1$  are quite similar to those visibly observed in DMF as reported above.

(24) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1962, p. 579.

effective with small anions with their high charge density.

Basic to the positions previously taken is the assumption that ion pairs are kinetically unreactive. This is both reasonable and justified by the data reported here. However, Ingold<sup>26</sup> has suggested that with salts of ambident anions, O-alkylation comes from the "free" anion and C-alkylation comes from the ion pair. Kornblum, *et al.*,<sup>16</sup> have pointed out that this conclusion is untenable. In addition, if the product variation in the alkylation of an ambident anion were dependent on the ratio of free ion to ion pair, then the observed variation in O- to C-alkylation with various alkyl halides would not be expected.

The kinetic inactivity of ion pairs is indicated, also, by the successful preparation of alkyl iodides from the reaction of alkyl chlorides with lithium iodide in acetone.<sup>27</sup>

Even though the reactivity of chloride ion is greater than that of iodide ion and the reactivity of alkyl iodides is greater than alkyl chlorides, in acetone the equilibrium is displaced toward the formation of alkyl iodide. This then must result from the ion pairs of the predominately associated lithium chloride being kinetically unreactive.

Where the association of lithium chloride and lithium iodide is more nearly the same, as in DMF, this displacement of equilibrium (because of the formation of a weakly dissociated species) no longer occurs. Thus the facile conversion of *n*-butyl iodide into *n*-butyl chloride in DMF is observed.

### Experimental

**Kinetic Measurements.**—Solutions of lithium halides (assayed at 99. + %) in DMF (spectroquality reagent, dried over LiH and vacuum distilled) were standardized at 0° by potentiometric titration with silver nitrate. A Leeds and Northrup pH meter [catalog No. 7401] was used in conjunction with a silver electrode and a  $Hg-Hg_2(OAc)_2$ , ( $NaClO_4-HOAc$ ) reference electrode<sup>28</sup> (superior to the ordinary calomel electrode for silver halide titrations since the electrolyte is not reactive toward silver ion). All lithium halide-DMF solutions were measured at 0° with calibrated pipets. To ensure temperature control, volumetric measurements and reactions were done from ice-water baths maintained in a refrigerator; cotton gloves were worn to inhibit heat transfer from the body. The reaction vessel was a 25-ml., glass-stoppered erlenmeyer flask to which there was affixed a drooping appendage, 3 cm. long, 1.5 cm. in diameter, and beginning 2 cm. from the base of the flask. Methyl tosylate ( $n_D^{20}$  1.5170, m.p. 27–28°, lit.<sup>29</sup> m.p. 27–28°) was introduced from a tared syringe into the appendage. Standardized lithium halide-DMF solution [10 ml.] was placed in the main body of the flask. After equilibrating for 1 hr. to 0°, the flask was shaken vigorously to initiate the reaction (methyl tosylate readily super cools and was always in the liquid state). At an appropriate time the reaction was stopped by rinsing the contents of the flask into a 150-ml. beaker containing 40 ml. of 10%  $H_2SO_4$ . In the lithium chloride runs the quench solution also contained a known excess of silver nitrate which was back titrated with standardized aqueous lithium chloride. In the lithium bromide runs the unreacted bromide ion was directly titrated with silver nitrate after quenching with 10%  $H_2SO_4$ . In the lithium iodide runs the quench solution was layered with 15 ml. of petroleum ether in order to isolate the produced methyl iodide from silver ion, and unreacted iodide ion was titrated directly with silver nitrate. All concentrations were corrected for the volume increase owing to methyl tosylate. Initial titers, however, are independent of total volume since the whole of the reaction system is titrated. Reaction times for chloride were 5–8 min.; for bromide, 12–20 min.; and for iodide, 20–45 min. A typical run: lithium bromide, 0.2171  $M = 5.03$  ml. of 0.4386  $N$   $AgNO_3$  (*b*) was allowed to react for 20 min. with methyl tosylate, 0.1194  $M = 2.77$  ml. of  $AgNO_3$

(25) To speak of aprotic solvents as having an accelerating effect on the rates of bimolecular substitution seems to be looking at things upside down. The view that protic solvents have a retarding effect on bimolecular substitutions seems to be much more consistent.

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(a). The unreacted halide was equal to 4.23 ml. of  $\text{AgNO}_3$ ,  $[b - x]$ . Substitution into  $k = \frac{2.303}{b - a} \log \frac{a [b - x]}{b [a - x]} / t$  gave  $k = 1.44 \times 10^{-3}$  l. mole<sup>-1</sup> sec.<sup>-1</sup>.

With those runs containing water, 1 ml. of water was added to the 10 ml. of lithium halide-DMF solution in the main body of the reaction flask. Concentrations were corrected for the volume increase. The reaction time for those runs containing water was 60-75 min.

For the extensive study of the rate of reaction of lithium iodide with methyl tosylate, the reaction vessel consisted of two 100-ml. round-bottom flasks joined by a bent adaptor fitted with two  $24/40$  standard tapered male joints. Fifty ml. of lithium iodide-DMF solution was placed in one flask and methyl tosylate in the other; 5-ml. aliquots were removed and titrated with  $\text{AgNO}_3$ .

After vacuum transfer of the remainder of the extensive reaction to free it of the nonvolatile salts, the remainder was vapor chromatographed. Only three substances were observed—methyl iodide, DMF, and methyl tosylate. The retention times were identical with those obtained from a synthetic mixture. The yield of methyl iodide was 82% of theoretical.

**Preparation of *n*-Butyl Chloride.**—To a solution of lithium chloride (8.2 g., 0.195 mole) in 90 ml. of DMF at room temperature in a 250-ml. erlenmeyer flask, *n*-butyl iodide (31.0 g., 0.168 mole) was added all at once and stoppered. All of the *n*-butyl iodide did not dissolve immediately but did so after shaking for 15 min. About this time, evolution of heat was noticed and the flask was cooled in ice for 5 min. and then returned to the air. After an hour the contents were added to 150 g. of ice and the organic phase separated without aid of a solvent, washed with three 10-ml. portions of water, and dried over calcium chloride.

TABLE IV

EXTENSIVE REACTION OF LITHIUM IODIDE WITH METHYL

TOSYLATE IN DMF AT 0°

$[\text{LiI}]_0 = 0.1871 M = 8.48 \text{ ml.}^a$ ;  $[\text{MeTos}]_0 = 0.3709 M = 16.81 \text{ ml.}^a$

<i>t</i> , sec.	$[\text{LiI}]^a$	$[\text{MeTos}]^a$	$10^3 k_{\text{obsd.}}$ l. mole <sup>-1</sup> sec. <sup>-1</sup>
0	8.48	16.81	...
955	6.94	15.27	0.596
1840	5.98	14.31	.557
3070	4.90	13.23	.548
3880	4.40	12.73	.531
8110	2.48	10.81	.529
10840	1.78	10.11	.528
14470	1.15	9.48	.537
24 hr.	0.00	...	...
			Av. 0.546

<sup>a</sup> Concentration in ml. of 0.1096 *N*  $\text{AgNO}_3$  per 4.965-ml. aliquot.

The yield of crude *n*-butyl chloride was 98% (15.0 g., 0.165 mole,  $n_D^{25}$  1.4025, lit.<sup>30</sup>  $n_D^{25}$  1.3995). Analysis of the *n*-butyl chloride by v.p.c. showed *n*-butyl iodide to be present to an extent less than 1%.

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[CONTRIBUTION FROM THE RESEARCH INSTITUTE FOR MEDICINE AND CHEMISTRY, CAMBRIDGE, MASS.]

## The Mechanism of the Barton Reaction<sup>1a</sup>

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A non-"cage," free-radical mechanism for the Barton reaction (Scheme I) has been proposed on the basis of the following experiment. Photolysis of a mixture of the nitrites ( $\text{N}^{15}$ -III) and ( $\text{N}^{14}$ -II) followed by rearrangement and oxidation gave a mixture of the ketonitriles VI and VII; the ratio  $\text{N}^{15}:\text{N}^{14}$  in these ketonitriles is 1:1.22 and 1:1.21 (in isooctane), respectively. Evidence for the existence of alkoxy radicals in the photolysis of nitrites is also presented.

Following the discovery by Barton and his co-workers of an intramolecular exchange reaction<sup>2</sup> of the type indicated in Scheme I ( $\text{X} = \text{NO}$ ), the principle underlying this reaction has been used in the synthesis of a number of organic molecules hitherto available only with difficulty.<sup>3</sup> The Barton reaction involving the photolysis of a suitably constituted organic nitrite results in an intramolecular exchange of the NO of the nitrite residue with a hydrogen atom attached to a carbon atom in the  $\gamma$ -position. The C-nitroso compounds thus formed can be isolated as the corresponding nitroso dimers or, after isomerization, as the oximes. We report studies relating to the mechanism of this reaction.

Random observations made during the application of the Barton reaction to various syntheses<sup>4</sup> strongly suggested that irradiation of a nitrite A leading to D (Scheme I) involves three discrete steps: first, the photochemical cleavage of the O-N bond to furnish the

alkoxy radical B and NO; second, the intramolecular abstraction of hydrogen to furnish the alkyl radical C; and finally, the combination of C with NO to furnish the product D. Quantum yield studies ( $\phi = 0.25$ )<sup>5</sup> and the nitrite concentration effects indicate that the free-radical reactions are not of a chain nature. The initial photochemical dissociation is illustrated by reaction 1, and the fact that the quantum yield is less than unity<sup>5</sup> is explicable in terms of reversibility of reaction 1. The mechanism of the nitrite photolysis leading to the exchange reaction  $\text{A} \rightarrow \text{D}$ , ( $\text{X} = \text{NO}$ , Scheme I) involves at least three possibilities.

**Mechanism 1.**—The two fragments, alkoxy radical and NO, initially formed remain bound within the solvent "cage"<sup>6</sup> until the completion of the exchange reaction, as illustrated in eq. 1 and 2. In this case, the NO group present in the final product D must originate from the NO group present in the parent molecule A.

**Mechanism 2.**—One may assume that in the reaction  $\text{A} \rightleftharpoons \text{B}$  (Scheme I), the reversible recombination of the alkoxy radical and NO takes place after the two species have broken out of their original environment, as illustrated by eq. 3. Then the product D, or its

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