255. Solvation of Ions. Part II.[1] Dipolar Aprotic Solvents as Media for Nucleophilic Substitution Reactions at a Saturated Carbon Atom.

By A. J. PARKER.

Kinetic experiments on the S_N2 reactions of methyl iodide with lithium chloride, tetraethylammonium (or sodium) azide, sodium picrate, sodium cyanide, potassium fluoride, potassium thiocyanate, and lithium bromide severally, in the protic solvents methanol, 10% dioxan–formamide, and *N*-methylformamide, and in the dipolar aprotic solvents dimethylformamide, dimethylacetamide, and acetone are reported. The solvolysis rates of methyl iodide in these solvents and the rate of S_N2 decomposition of trimethylsulphonium bromide in dimethylformamide have also been measured.

S_N2 rates increase by a factor of up to 10^7 as the hydrogen-bonding capacity of the solvent decreases from water to dimethylacetamide through a series of methyl-substituted amides, but solvolysis rates are little influenced by solvent change. Acetone is confirmed as a typical dipolar aprotic solvent.

The observed effects of solvents on rates are due to solvation differences, in the two types of solvent, of the anionic participants, not of the organic substrates.

Halogen and halogenoid ions in the absence of differential solvation (*i.e.*, deactivation) due to hydrogen bonding, have similar nucleophilic tendencies. A reappraisal of current ideas on nucleophilic tendency must be made. In dimethylformamide, reactivity towards methyl iodide is in the order $CN^- > F^-, Cl^-, N_3^-, Br^- > SCN^- >$ Picrate$^-$.

Some examples of increased yields and shorter reaction times, when dipolar aprotic solvents are the reaction media, are explained by a simple postulate.

MILLER and PARKER[1] have reported that aromatic nucleophilic substitution (S_NAr) reactions are up to 10^5 times faster in nine dipolar aprotic solvents than they are in three protic solvents. Rate constants (k_2) increased as the hydrogen-bonding capacity of the

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[1] Part I, Miller and Parker, *J. Amer. Chem. Soc.*, 1961, **83**, 117.

solvent decreased from methanol to dimethylacetamide. It was suggested that in dipolar aprotic solvents solvation of anions is in the reverse order to that accepted for protic solvents, *i.e.*, solvation decreases in the series of anions

$$\text{Transn. state ion} > \text{Picrate}^- > \text{I}^- > \text{SCN}^- > \text{Br}^- > \text{N}_3^-, \text{Cl}^- \gg \text{F}^-$$

We felt that this effect on rate, in the change from protic to dipolar aprotic solvent, should be general for anion–dipolar molecule reactions passing through a relatively large, negatively charged transition state. This work shows that such solvent influence is general for bimolecular nucleophilic substitutions such as (1) and (2):

$$\text{R–X} + \text{Y}^- \longrightarrow \text{RY} + \text{X}^- \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (1)$$

$$\text{R–X}^+ + \text{Y}^- \longrightarrow \text{RY} + \text{X} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (2)$$

where R = alkyl or aryl. R was chosen as methyl for the new results because it is the simplest for displacements at carbon, and because higher homologues eliminate HX readily in dipolar aprotic solvents.[2]

Reactions of Y^- have been studied to estimate qualitatively the effect of anion size, basicity, and polarizability on relative solvation, and thus reactivity, of anions in protic and dipolar aprotic solvents. It was hoped that the effect on rate, of solvation of Y^-, of RX, and of the transition state $[\text{Y} \cdots \text{R} \cdots \text{X}]^-$ in reaction (1), could be separated by varying RX in some series in which Y^- was constant.

It has been apparent for some years that the results of Ingold and his co-workers for rates of Finkelstein substitutions in acetone[3] can be used to calculate semi-quantitative rate constants[4] which allow for incomplete dissociation of salts in acetone, and give as good a picture as possible of the nucleophilic tendency of " free " halide ions in acetone. Winstein[5] has recently done this. The derived values of halides in acetone agree with those now experimentally observed in dimethylformamide.

The principles discussed here and in Part I explain some examples of increased yields and shorter reaction times in dipolar aprotic solvents. These hitherto unconnected examples are being reported more frequently and it is hoped that this series of papers will enable one to select the most suitable solvent in given circumstances.

RESULTS AND DISCUSSION

Table 1 records rate constants and solvent rate ratios for nucleophilic substitutions in various solvents. Anionic nucleophiles used were azide ion, a strong base in water and methanol, and chloride ion, a weak base in water and methanol. Both are strong bases in dipolar aprotic solvents[6] and form relatively strong bonds with carbon. Substrates were methyl iodide, which is slowly solvolysed by some solvents, and *p*-fluoronitrobenzene, which was recovered quantitatively from the solvents at the temperature used.[1] These are two of the simplest substrates for S_N2 and S_NAr reactions respectively. Displaced groups were weakly bound (iodide), and strongly bound (fluoride) to carbon.

The solvents methanol, formamide (I), *N*-methylformamide (II), *NN*-dimethylformamide (III), dimethylacetamide (IV), and acetone should form hydrogen bonds with a suitable anion in the order, MeOH > (I) > (II) ≫ (III) > (IV), COMe_2. In this work 10% dioxan–formamide was used since methyl iodide is only slightly soluble in formamide. This amount of dioxan does not greatly affect rates in methanol and water,[1] so it is assumed that rates in formamide and in 10% dioxan–formamide are comparable.

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[2] Parker and Hughes, unpublished work.

[3] de la Mare, Hughes, Ingold, *et al.*, *J.*, 1955, 3169—3200.

[4] Hughes, Ingold, and Parker, *J.*, 1960, 4400.

[5] Winstein, Savedoff, Smith, Stevens, and Gall, *Tetrahedron Letters*, 1960, No. 9, 24.

[6] Janz and Danyluck, *Chem. Rev.*, 1960, **60**, 209.

TABLE 1. *Rate constants* (10^4k_2, l. mole^{-1} sec.$^{-1}$) *at temperature shown for the reactions* (A) $CH_3I + LiCl \rightleftharpoons CH_3Cl + LiI$, (B) $p\text{-}NO_2{\cdot}C_6H_4F + NEt_4N_3 \longrightarrow p\text{-}NO_2{\cdot}C_6H_4{\cdot}N_3 + NEt_4F$ *in various solvents.* [*Equimolar concentrations* (0·035—0·045M) *of reactants for all new results. Solvolysis rates* (*expressed as* 10^6k_1[a]) *at* 25·1° *for methyl iodide at an initial concentration of* 0·050—0·057M.]

Solvent	Reaction A 10^4k_2	T	Ratio $\frac{k_2\text{ (solvent)}}{k_2\text{ (water)}}$ 0°	25°	Reaction B 10^4k_2	T	Ratio $\frac{k_2\text{ (solvent)}}{k_2\text{ (methanol)}}$ 25°	100°	Solvolysis 10^6k_1
H_2O	0·0011[c]	0·0°	1	—	—	—	—	—	
H_2O	0·032[c]	25·1	—	1	—	—	—	—	0·1[d]
MeOH	0·030	25·1	—	0·94	$6{\cdot}7 \times 10^{-4}$	25·1°	1	—	
MeOH	—	—	—	—	2·28	100·0	—	1	4×10^{-3}[g]
10% Dioxan–formamide...	0·40[e]	25·1	—	12·5	13·0	100·0	—	5·6	1·0
N-Methylformamide...	1·45[e]	25·1	—	45·3	36·0	100·0	—	15·7	1·1
$NMe_2{\cdot}CHO$ ...	1300	0·0	$1{\cdot}2 \times 10^6$	—	16·4	25·1	$2{\cdot}45 \times 10^4$	—	0·28
$NMe_2{\cdot}CHO$ ...	—	—	—	—	11,100	100·0	—	$4{\cdot}9 \times 10^3$	—
$NMe_2{\cdot}COMe$ ...	8100	0·0	$7{\cdot}4 \times 10^6$	—	59	25·1	$8{\cdot}8 \times 10^4$	—	0·26
$COMe_2$	50,000[f]	25·1	—	$1{\cdot}6 \times 10^6$	47·4	25·1	$2{\cdot}45 \times 10^4$	—	—

[a] See p. 1331. [b] Results from Part I. [c] Bathgate and Moelwyn-Hughes, *J.*, 1959, 2642. [d] Moelwyn-Hughes, *Proc. Roy. Soc.*, 1938, *A*, **164**, 295. [e] Results corrected to allow for solvolysis reaction (see text). [f] Calculated from the observed rate at 50% reaction (ref. 4) divided by the concentration of methyl iodide and of free chloride ions (see p. 1331), *i.e.* $k_i = k_2/\alpha$. The recorded rate constant is k_i, the rate constant for attack by free chloride ions, and k_2 is the observed rate constant calculated from stoicheiometric concentrations of reactants in the normal way; α is the degree of dissociation at 50% reaction calculated from the dissociation constants in acetone at 25°: $K_{LiCl} = 2{\cdot}03 \times 10^{-5}$, $K_{LiI} = 2{\cdot}85 \times 10^{-3}$. [g] Extrapolated from the observed k_1 of $2{\cdot}0 \times 10^{-7}$ sec.$^{-1}$ (Table 7) to give this semiquantitative figure. The recorded result is satisfactory for the discussion.

S_NAr reactions between *p*-fluoronitrobenzene and azide ion (Reaction B, Table 1) stop at the intermediate complex (V) in dipolar aprotic solvents, but fluoride is removed by protic solvents.[1] The S_N2 LiCl–CH_3I exchange proceeds at least 95% in the forward direction in all solvents,[4] except where solvolysis interferes. Table 1 includes rates $d[I^-]/dt$, expressed as k_1, for solvolysis of methyl iodide at an initial concentration of 0·02M, measured over the first 30% of reaction. The k_1 values are not constant (Table 8), but the downward drift is not more than 50%; however, as will be seen, they are satisfactory for our purpose.

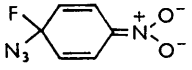
(V)

Table 2 gives k_2 values and solvent rate ratios for a variety of S_N2 and S_NAr reactions in dimethylformamide and methanol. All substrates and salts used were recovered from either solvent when treated separately with solvent for a period corresponding to reaction conditions of Table 2. The CH_3I–LiBr exchange had an equilibrium constant of 8·5 in

TABLE 2. *Rate constants* (10^5k_2, l. mole^{-1} sec.$^{-1}$) *at* 0° *unless otherwise stated, for some* S_N2 *and* S_NAr *reactions in methanol and dimethylformamide.*

Reactants	10^5k_2 in methanol	$NMe_2{\cdot}CHO$	Ratio $\frac{k_2\ (NMe_2{\cdot}CHO)}{k_2\text{ (methanol)}}$
$CH_3I + LiBr$	0·183[d]	10,700	$5{\cdot}8 \times 10^4$
$Me_3S^+Br^-$ [a]	0·0035[b,c]	125[b]	$3{\cdot}5 \times 10^4$[b,c]
$CH_3I + KSCN$	2·0	1100	$5{\cdot}5 \times 10^2$
$2,4\text{-}(NO_2)_2C_6H_3I + KSCN$ [e]	0·017	1·08	$6{\cdot}5 \times 10^1$
$CH_3I + NaN_3$	0·30	13,800	$4{\cdot}5 \times 10^4$
$p\text{-}NO_2{\cdot}C_6H_4I + NaN_3$ [e]	$4{\cdot}4 \times 10^{-7}$	0·020	$4{\cdot}6 \times 10^4$
$p\text{-}NO_2{\cdot}C_6H_4F + NaN_3$ [e]	$1{\cdot}55 \times 10^{-4}$	7·86	$5{\cdot}0 \times 10^4$

[a] At an ionic strength of 0·08M, buffered with 0·04M-$LiClO_4$. [b] At 59·8°. Calc. for a hypothetical alcoholic solvent of the same dielectric constant as D.M.F. (see p. 1331). [d] Moelwyn-Hughes, *Trans. Faraday Soc.*, 1939, **35**, 368. [e] Data calculated from the Arrhenius parameters given in Part I.

dimethylformamide at 0·0° (Table 5), and the decomposition of trimethylsulphonium bromide (Table 6) appeared to come to equilibrium also. For these reactions, rate constants were calculated over the first 40% of reaction. Other reactions proceeded to more than 70% completion.

Decomposition of trimethylsulphonium bromide is very susceptible to the ionic strength and the dielectric constant (D) of the medium.[2] The k_2 value in Table 2 for " methanol " is calculated from initial k_2 values in ethanol and methanol[2,7] at an ionic strength of 0·08M (buffered with 0·04M-lithium perchlorate) by extrapolation of a log k_2–$1/D$ plot[8] to the dielectric constant ($D = 37{\cdot}6$) of dimethylformamide.[9] The measured k_2 in dimethylformamide is compared with this hypothetical k_2 for the decomposition of trimethylsulphonium bromide in a hydroxylic solvent of the same dielectric constant at the same ionic strength.

Table 3 records k_2 and solvent rate ratios for S_N2 reactions of methyl iodide with some nucleophiles in methanol, water, dimethylformamide, and acetone. Swain and Scott's[10] nucleophilic constants η are included for comparison.

Table 4 gives semiquantitative specific rate constants, k_i, calculated from the rates of Ingold *et al.*[3] for Finkelstein reactions in acetone. Acree's formula,[11] in the absence of a better one, has been used to calculate k_i, which is the second-order rate constant for attack by " free " halide ions: *i.e.*, $k_i = k_2/\alpha$, where k_i = specific rate constant, k_2 = observed rate constant, and α = degree of dissociation of LiHal. Values of α were calculated from the mass-law expression with appropriate salt concentrations at 50% reaction and allowance for common-ion effects, and from the dissociation constants at 25°, *viz.*, $K_{\text{LiCl}} = 2{\cdot}03 \times 10^{-5}$,[12] $K_{\text{LiBr}} = 5{\cdot}22 \times 10^{-4}$,[13] $K_{\text{LiI}} = 2{\cdot}85 \times 10^{-3}$,[12] $(6{\cdot}9 \times 10^{-3})$,[14] and $K_{\text{LiClO}_4} = 1{\cdot}9 \times 10^{-4}$.[15] Incomplete dissociation of sodium, lithium, or tetraethylammonium salts at <0·04M does not affect rate constants by more than 10% in solvents of dielectric constant > 33.[1]

TABLE 3. *Anion nucleophilicity towards methyl iodide. Rate constants* (k_2, *l. mole*$^{-1}$ *sec.*$^{-1}$) *at temperature shown for the reaction* $CH_3I + Y^- \longrightarrow CH_3Y + I^-$ *in protic and dipolar aprotic solvents. Equimolar concentrations* (0·035—0·045M) *of reactants for all new results. Comparison with Swain and Scott's nucleophilic constants* η,[a] *and effect of solvent change on different anions.*

	η [a] of Y^-	$10^5 k_2$ at 0° in MeOH	$10^5 k_2$ at 0° in H_2O	$10^1 \times k_2$ at 0° in $NMe_2{\cdot}CHO$	$\frac{k_2\,(NMe_2{\cdot}CHO)}{k_2\,(\text{Protic})}$ at 0°	$\frac{k_2\,(COMe_2)}{k_2\,(H_2O)}$ [h] at 25°
Na picrate ...	1·9	1·8 [b]	—	$3{\cdot}6 \times 10^{-3}$ [b]	20 [b]	—
KSCN	4·77	2·0	—	0·11	$5{\cdot}5 \times 10^2$	—
LiI	5·04	—	1·6 [e]	—	—	$2{\cdot}5 \times 10^4$
LiBr............	3·89	—	0·18 [e]	1·07	$5{\cdot}5 \times 10^4$	$2{\cdot}1 \times 10^5$
NaN_3	4·00	0·30	—	1·36	$4{\cdot}5 \times 10^4$	—
NaCN	5·10	—	2·3 [f]	>10 [g]	$>5 \times 10^4$	—
LiCl	3·04	0·01	0·010 [e]	1·30	$1{\cdot}3 \times 10^6$	$1{\cdot}5 \times 10^6$
KF	2·0	—	7×10^{-3} [c, e]	>1 [c,d]	$>10^6$ [c]	—

[a] Refs. 9 and 10. [b] At 59·8°. [c] At 25°. [d] Estimated from the half-life of 5—10 min. (depending on stirring efficiency) for formation of iodide ion from 0·04M-CH_3I and 1 g. of finely divided solid KF suspended in dimethylformamide. [e] Ref. (*c*), Table 1. [f] Moelwyn-Hughes and Marshall, *J.*, 1959, 2640. [g] Reaction was complete 1 min. after mixing at 0·0°: equimolar amounts of CH_3I and NaCN in dimethylformamide. [h] Rate ratios taken from Table 4.

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[7] Budd, Thesis, London, 1952; Whittingham, Thesis, London, 1950.

[8] Laidler, " Chemical Kinetics," McGraw-Hill, New York, 1950, p. 128.

[9] Hine, " Physical Organic Chemistry," McGraw-Hill, New York, 1956.

[10] Swain and Scott, *J. Amer. Chem. Soc.*, 1953, **75**, 141.

[11] Acree, *Amer. Chem. J.*, 1912, **48**, 353.

[12] Blokker, *Rec. Trav. chim.*, 1935, **54**, 975.

[13] Evans and Sugden, *J.*, 1949, 270.

[14] Unpublished work by Savedoff, quoted in ref. 5.

[15] Accascina and Sckiavo, *Ann. Chim. (Italy)*, 1953, **43**, 695.

All the new substitutions, like the quoted reactions, of Tables 1—4 followed second-order kinetics over not less than 40% of reaction and gave the expected substitution products. Solvolysis, in reactions of methyl iodide in *N*-methylformamide and 10% dioxan–formamide, and in methanol for the reaction with sodium picrate only, was a minor reaction (<20%) and could be allowed for by using the formula of Hughes, Ingold, and Shapiro,[16] since solvolysis rates are known (Table 1). Solvolysis rates of methyl iodide by methanol and by methanol containing 0·04M-lithium perchlorate were within 10% of each other (Table 7), so that k_1 for solvolysis by pure solvent can be used to separate S_N2 rates from the overall rate of iodide-ion production. In the other reactions, each iodide ion formed from methyl iodide corresponded to a chloride, bromide, thiocyanate, cyanide, or azide ion consumed. No acid was detected. It is concluded that all new k_2 values, like the literature values of Tables 1—4, are for bimolecular additions of an anion to carbon, usually followed or accompanied by displacement from that carbon atom of some other group or neutral molecule.

Some rate constants at 25° and 100°, which were not used in Tables 1—4, are in Table 9. The temperatures used are common when comparing rate data, and since Arrhenius parameters have not been included, the results may be of value to other workers.

The following points should be noted:

(1) The two reactions (A and B) of Table 1 have the same solvent behaviour, although reaction A is more sensitive than B. As hydrogen-bonding capacity decreases, rate constants increase, as shown below:

Solvent	MeOH	$NH_2{\cdot}CHO$	$NHMe{\cdot}CHO$	$NMe_2{\cdot}CHO$	$NMe_2{\cdot}COMe$	$COMe_2$
Rel. rates (reaction A) ...	1	12·5	45·3	$1{\cdot}2 \times 10^6$	$7{\cdot}4 \times 10^6$	$1{\cdot}6 \times 10^6$
Rel. rates (reaction B) ...	1	5·6	15·7	$2{\cdot}4 \times 10^4$	$8{\cdot}8 \times 10^4$	$2{\cdot}4 \times 10^4$

(2) Specific rate constants for the reactions of " free " halide ions in acetone recorded in Tables 1, 3, and 4 suggest that acetone is a typical dipolar aprotic solvent like dimethylformamide and -acetamide, nitrobenzene, and the other solvents described in Part I.

TABLE 4. *Specific and observed rate constants (k_i and k_2, l. mole^{-1} sec.$^{-1}$) for Finkelstein substitutions in acetone and water at 25°.*

	[LiHal] (M)	α [e]	10^4k_2 [a] ($COMe_2$)	10^4k_i ($COMe_2$)	10^4k_2 [b] (H_2O)	$\frac{k_i\ (COMe_2)}{k_2\ (H_2O)}$
$CH_3Cl + Cl^-$	0·0275	0·027	0·388	14	0·0055	2500
$CH_3Br + Cl^-$	0·0503	0·010	59·5	5,950	0·046	$1{\cdot}3 \times 10^4$
$CH_3I + Cl^-$	0·0246	0·004	176 [c]	47,000	0·032	$1{\cdot}5 \times 10^6$
$CH_3Cl + Br^-$	0·0240	0·10	3·4	34	0·17	200
$CH_3Br + Br^-$	0·0240	0·10	1300	13,000	—	—
$CH_3I + Br^-$	0·0220	0·03	2700	90,000	0·44	$2{\cdot}1 \times 10^5$
$CH_3Cl + I^-$	0·0365	0·34	—	16 [d]	0·20	80
$CH_3Br + I^-$	0·0220	0·36	2500	7000	7·02	1000
$CH_3I + I^-$	0·100	0·24	20,000	80,000	3·3	$2{\cdot}5 \times 10^4$ [g]
$CH_3Br + F^-$	—	—	3400 [f]	>3400	$4{\cdot}6 \times 10^{-4}$	$>8 \times 10^6$

[a] Data from ref. 3 unless stated otherwise. [b] Data from Bathgate and Moelwyn-Hughes, *J.*, 1959, 2642 unless stated otherwise. [c] Ref. 4. [d] Aziz and Moelwyn-Hughes, *J.*, 1959, 2636. [e] α, the degree of dissociation of LiHal in acetone, has been calculated at 50% reaction with due allowance for the effect on α of the product LiHal, and of any added buffer salts, *e.g.*, $LiClO_4$, using the dissociation constants for salts in acetone given in the text. [f] Rimmer, unpublished work, quoted by Mackie, Thesis, London, 1955; α is not known and k_i is a minimum value. [g] This value agrees with that of Swart and Le Roux, *J.*, 1957, 406.

(3) Solvolysis rates of methyl iodide recorded in Table 1 exclude the possibility that an S_N1, or other process not dependent on the nucleophile, accounts for the observed rates. Solvent effects are similar for S_NAr and S_N2 reactions in a number of structurally different dipolar aprotic solvents,[1] which suggests that it is not a reactive CH_3I–solvent adduct which is reacting in the S_N2 process.

The mechanism of solvolysis was not studied, but amide solvolysis may involve

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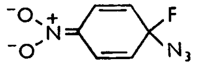
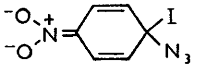
[16] Hughes, Ingold, and Shapiro, *J.*, 1936, 225.

reversible formation of a quaternary salt, followed by decompositions, either *in situ* or after water is added.[17] Solvolysis rates decrease by a factor of 20 from water to dimethylacetamide, but S_N2 rates increase by 10^7. The conclusion is that differential solvation of the forming iodide ion in solvolysis of methyl iodide is not very important to the rate, and that the enormous S_N2 solvent effect must be a property of relative nucleophile and/or transition-state solvation, rather than of solvation of methyl iodide.

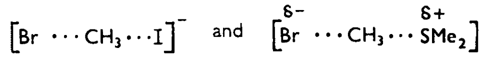
(4) Table 2 suggests that the solvent effect is associated with only the anionic nucleophile rather than with the transition state or substrate. The transition states:

$[N_3\cdots CH_3\cdots I]^-$



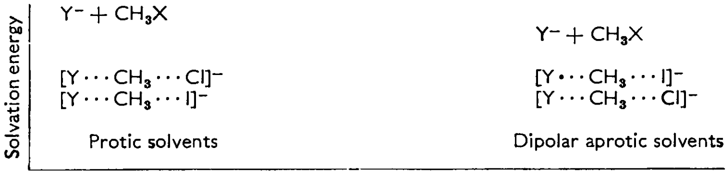


seem to be equally susceptible to the change of solvent from methanol to dimethylformamide, as do:



$$[Br\cdots CH_3\cdots I]^- \text{ and } [\overset{\delta-}{Br}\cdots CH_3\cdots \overset{\delta+}{SMe_2}]$$

However, the derived k_i values of Table 4 show that susceptibility to solvent is in the order MeI $\gg$ MeBr $>$ MeCl. The explanation may be that, in the reactions of Table 2, solvation of the leaving group is either not a kinetically significant step (*e.g.*, S_NAr reactions of anions other than thiocyanate[18]) or is not very different in protic or in dipolar aprotic solvents (as is the case with iodide ion[1] or dimethyl sulphide as leaving group). In such reactions, solvent effects will be mainly a function of solvation of the attacking anion. In S_N2 reactions of methyl chloride and, to a smaller extent, of the bromide, solvation of the departing halide ion, which decreases the energy of the transition state, is very much greater because of hydrogen bonding in protic than in dipolar aprotic solvents. The argument is summarized by the annexed scheme.



Qualitative representation of solvation energies in protic and dipolar aprotic solvents (X = I or Cl).

Since a well-solvated transition state increases rate, and strong solvation of Y^- decreases rate, it is apparent why methyl iodide is more susceptible to solvent change than is methyl chloride in S_N2 reactions. Reactions of methyl iodide should give a better picture of relative solvation of nucleophiles unobscured by transition-state effects than reactions of other methyl halides.

(5) Chloride ion is more susceptible to solvent change than the stronger base, azide ion (Table 3). This confirms that hydrogen bonding to smaller, densely charged anions, and not an acid–base interaction in water, reduces the reactivity of anions in protic solvents and accounts for the differences in solvation in protic and dipolar aprotic solvents.

The anions of Table 3 are susceptible to solvent change in the order, $F^- > Cl^-, CN^- > Br^-, N_3^- > I^- > SCN^- >$ Picrate$^-$. This corresponds roughly with their increasing size and polarizability and decreasing tendency to form hydrogen bonds with protic solvents. The order is the reverse of their expected interactions with dipolar aprotic solvents and fits the degrees of anion solvation shown in Fig. I of Part 1.[1]

[17] Kornblum and Blackwood, *J. Amer. Chem. Soc.*, 1956, **78**, 4037.

[18] Parker, " Sulfur Nucleophiles in S_NAr Reactions," in " Organic Sulfur Compounds," Pergamon, London, 1960.

(6) Nucleophilicity in dimethylformamide towards methyl iodide at 0·0° decreases, as shown in Table 3, in the order, $CN^- > F^-, Cl^-, N_3^-, Br^- > SCN^- >$ Picrate$^-$, relative rates being > 10, > 1, 1, 1, 1, 0·1, 0·004.

The nucleophilic tendencies of chloride, bromide, and iodide ions in acetone (Table 4), although not precisely observed values, follow a similar pattern to those in dimethylformamide. Thus in acetone (relative rates in parentheses) the apparent nucleophilic tendency at 25°

towards CH_3I is Br^- (2), I^- (2) > Cl^- (1);
towards CH_3Br is Br^- (2) > I^- (I), Cl^- (1);
towards CH_3Cl is Br^- (2) > I^- (1), Cl^- (1);
towards butyl *p*-bromobenzenesulphonates [5] is Cl^- (17) > Br^- (3) > I^- (1).

Winstein [5] has commented recently on nucleophilic tendencies in acetone.

Reassessment of current ideas is called for. Nucleophilic tendencies in dimethylformamide and other dipolar aprotic solvents cannot be correlated with Swain and Scott's nucleophilic constants,[10] or with relative rates towards methyl iodide in water [19] or towards the trimethylsulphonium ion in ethanol or methanol.[2]

It seems that sulphur nucleophiles, and others whose nucleophilic atoms are of high atomic number, are powerful nucleophiles in hydroxylic (protic) solvents simply because they do not form strong hydrogen bonds with the solvent, not because they are polarizable and can adjust their outer electron shell to the requirements of a " stable " transition state, as is generally assumed.[9,18] Fluoride and cyanide ions are strong nucleophiles, in the absence of deactivation by solvation, because they form strong bonds with carbon. It may be that polarizability should not be discounted entirely, since interactions of halides and related groups with electron-deficient atoms of dipolar aprotic solvents (which would reduce reactivity) should decrease in the order, $SCN^- > I^- > Br^-, N_3^- > Cl^- > F^-$. Such interactions could almost exactly cancel any advantage large anions might have, owing to their polarizability and diffuse orbitals, in forming bonds with electron-deficient carbon. This would explain the " common rate " for S_N2 reactions of a number of these ions in dimethylformamide and in acetone (Tables 3 and 4). Apparently dipolar aprotic solvents are levelling and protic solvents are differentiating for nucleophilic tendencies of anions, whereas it has been observed [6] that protic solvents are levelling and dipolar aprotic solvents are differentiating for basicity of anions towards the proton.

Our postulate,[1] that any bimolecular reactions of a small anion passing through a large polarizable transition state will be considerably accelerated in the change from protic to dipolar aprotic solvent, explains some examples of increased yields and shorter reaction times when dipolar aprotic solvents are used as the reaction medium: for the Gabriel phthalimide synthesis; [20] in alkylations of sodium acetylide,[21] of phenanthrene,[22] of phenothiazines,[23] of saccharin,[24] of 6-mercaptopurines,[25] and of imidazoles; [25] in diethyl malonate additions; [26] in synthesis of aromatic fluorides [27] and iodides,[28] of alkyl cyanates,[29]

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[19] Bathgate and Moelwyn-Hughes, *J.*, 1959, 2642.

[20] Sheehan and Bolhofer, *J. Amer. Chem. Soc.*, 1950, **72**, 2786; Vassel, U.S.P. 1956, 2,757,198; Donahoe *et al.*, *J. Org. Chem.*, 1957, **22**, 68; Billman and Cash, *Proc. Ind. Acad. Sci.*, 1953, **62**, 158; *J. Amer. Chem. Soc.*, 1954, **76**, 1944; Lo and Shropshire, *J. Org. Chem.*, 1957, **22**, 999.

[21] Rutledge, *J. Org. Chem.*, 1959, **24**, 840, U.S.P. 2,846,491/1958.

[22] Nelson and Garland, *J. Amer. Chem. Soc.*, 1957, **79**, 6313.

[23] Zaugg, Swett, and Stone, *J. Org. Chem.*, 1958, **23**, 1389.

[24] Rice and Pettit, *J. Amer. Chem. Soc.*, 1954, **76**, 302.

[25] Johnston, Holum, and Montgomery, *J. Amer. Chem. Soc.*, 1958, **80**, 6265.

[26] Schudy and Collins, *J. Org. Chem.*, 1959, **24**, 556; Burgstahler and Aiman, *ibid.*, 1960, **25**, 489.

[27] Finger and Kruse, *J. Amer. Chem. Soc.*, 1956, **78**, 6034; Finger and Starr, *ibid.*, 1959, **81**, 2674.

[28] Bunnett and Conner, *J. Org. Chem.*, 1958, **23**, 305.

[29] Himel and Richards, U.S.P. 2,866,801/1958.

sulphides,[30] nitriles,[31] and hence carboxylic acids and their derivatives,[32] of nitro-compounds [33] and benzoates; [34] in synthesis of cellulose esters [35] and cyclic sulphides; [36] and dehydrohalogenation of steroids and other cyclic halides by lithium chloride in dimethylformamide,[37] where presumably in this last example the very strong nucleophile—chloride ion in dimethylformamide—displaces a *cis*-toluene-*p*-sulphonate or halide in a S_N2 Walden inversion to give a *trans*-chloride, which eliminates readily, without competing S_N1 processes, in the presence of dimethylformamide [2] and non-hydrogen bonded chloride ions—both sufficiently powerful bases to neutralise hydrogen chloride and prevent its back-addition to the olefin produced. There is some evidence that eliminations in dipolar aprotic solvents are *cis*-four-centred processes.[2] Bromide ion in dimethyl sulphoxide should be even better for this reaction, despite the solvolyzing properties of dimethyl sulphoxide, but this remains to be tested.

TABLE 5. *A typical halogen exchange reaction in dimethylformamide at* 0·0°. $[CH_3I]_0 =$ 13·28 [a] *c.c.*, $[LiBr]_0 =$ 13·75 *c.c.* (*Concentrations in c.c. of* 0·0200N-$AgNO_3$ *for* 6·81 *c.c. sample. Rate constants,* k_2, *in l. mole*$^{-1}$ *sec.*$^{-1}$.)

t (min.)	$[I^-]$	$[I^- + Br^-]$	$10k_2$	t (min.)	$[I^-]$	$[I^- + Br^-]$	$10k_2$	t (min.)	$[I^-]$	$[I^- + Br^-]$	$10k_2$
0·0	4·00	13·70	—	2·0	6·80	13·70	1·17	8·0	8·95	13·76	0·75
0·5	4·67	13·68	0·96	3·0	7·30	13·82	0·99	120	9·80	13·75	—
1·0	5·40	13·70	0·99	4·0	7·75	13·71	0·91	180	9·82	13·79	—
1·5	6·15	13·72	1·10	6·0	8·62	13·82	0·86				

Mean k_2 over first 30—50% reaction = 1·05 × 10^{-1} l. mole^{-1} sec.$^{-1}$; equilibrium constant K = 8·48. A duplicate estimation, $[CH_3I]_0$ = 15·00 c.c., $[LiBr]_0$ = 15·00 c.c., gave k_2 = 1·07 × 10^{-1}, K = 8·5.

[a] $[CH_3I]$ initially, and at equilibrium, estimated by warming a sample with excess of LiCl in dimethylformamide and titrating iodide ion.

Dipolar aprotic solvents are, of course, useful media for the more obvious alkyl or aryl halogen (etc.) interconversions shown in Part I [1] and this paper. The specific solvent effects in the alkylation of enol anions discussed at length by Zaugg, Horron, and Borgwardt [38] can be given an additional explanation by the postulate.

TABLE 6. *Decomposition of trimethylsulphonium bromide in dimethylformamide at* 59·8° *at ionic strength* 0·08M. $[Me_3S^+ClO_4^-]_0 =$ 13·62 *c.c.*, $[LiBr]_0 =$ 13·62 *c.c.* (*Concentrations in c.c. of* 0·0200N-$AgNO_3$ *for* 6·81 *c.c. sample. Run in sealed tubes. Rate constants* k_2, *in l. mole*$^{-1}$ *sec.*$^{-1}$.)

t (hr.)	$[Br^-]$	10^3k_2	t (hr.)	$[Br^-]$	10^3k_2	t (hr.)	$[Br^-]$	10^3k_2
0·00	13·30	—	2·70	8·97	1·24	24·25	4·45	0·60
0·50	12·04	1·30	2·70	9·00	1·23	24·25	4·45	0·60
1·00	11·10	1·35	4·25	7·65	1·22	36·00	4·00	—

Mean k_2 = 1·25 × 10^{-3} l. mole^{-1} sec.$^{-1}$.

Provided reactants are soluble (dimethyl sulphoxide is often the best solvent), the examples quoted and many other reactions (*e.g.*, S_N2 displacements at elements other than carbon) should be equally rapid in other dipolar aprotic solvents besides those already

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[30] Carbon, *J. Amer. Chem. Soc.*, 1958, **80**, 6083.

[31] Copelin, U.S.P. 2,715,137/1955; Gahana, Schmidt, and Shah, *J. Org. Chem.*, 1959, **24**, 557; Newman and Otsuka, *ibid.*, 1958, **23**, 797; Smiley and Arnold, *ibid.*, 1960, **25**, 257; Friedman and Schechter, *ibid.*, 1960, **25**, 877.

[32] Hammond and Cram, " Organic Chemistry," McGraw-Hill, New York, 1959, p. 222.

[33] Kornblum and Powers, *J. Org. Chem.*, 1957, **22**, 455; Kornblum and Blackwood, *Org. Synth.*, 1957, **37**, 44; White and Considine, *J. Amer. Chem. Soc.*, 1958, **80**, 626; Fusco and Rossi, *Chem. and Ind.*, 1957, 1650; Belshaw, Howard, and Irving, U.S.P. 2,587,093/1952.

[34] Reist, Goodman, and Baker, *J. Amer. Chem. Soc.*, 1958, **80**, 5775.

[35] Blume, U.S.P. 2,705,710/1955.

[36] *Org. Synth.*, 1956, **36**, 89.

[37] Hoylsz, *J. Amer. Chem. Soc.*, 1953, **75**, 4432; *Org. Synth.*, 1958, **38**, 8; Chamberlin, Tristram, Utne, and Chemerda, *J. Amer. Chem. Soc.*, 1957, **79**, 456; Pederson, Johnson, Hoylsz, and Ott, *ibid.*, 1957, **79**, 1115; Hirschmann and Miller, U.S.P. 2,837,541/1958.

[38] Zaugg, Horron, and Borgwardt, *J. Amer. Chem. Soc.*, 1960, **82**, 2895, 2905.

reported. *Traces* of water (<0·2%) in dipolar aprotic solvents do not appear to affect rates of reaction.[1,39] The reactions are very sensitive to acid. Commercial nitrile and amide solvents contain traces of organic acids and, unless neutralized by lime and distillation, are apt to behave as protic solvents. Rates in commercial benzonitrile for the *p*-fluoronitrobenzene–azide ion reaction were immeasurably slow at 25°. Dimethyl-formamide and -acetamide should be freed by pumping from volatile, nucleophilic amines. Tetraalkylammonium salts seem to be the most soluble in dipolar aprotic solvents and thus the best source of nucleophiles.

EXPERIMENTAL

Materials.—Solvents, substrates, and salts of nucleophiles were prepared and/or purified by methods already described [1,4] or by recrystallization and drying. All reactants were analysed and were >99% pure. Solvents were neutral and contained no halogen or halogenoid ions, and amide solvents gave no deep yellow colour in a spot test for amines with 2,4-dinitro-1-fluorobenzene. Different batches of solvent gave identical rate constants.

Tetraethylammonium azide, sodium picrate, lithium chloride, lithium bromide, sodium azide, and sodium cyanide showed 100% purity after being heated at 100° for 3 hr. in all solvents studied. Methyl iodide was very slowly solvolysed by amide solvents and methanol (Tables 1, 7, and 8). Trimethylsulphonium perchlorate was unchanged in dimethylformamide at 59·8° after 24 hr.

Kinetics.—The technique has been described.[1,3,4] Reactions were quenched by pouring into ice-water, and halogenoids were titrated immediately with silver nitrate in the presence of barium nitrate. Typical runs are in Tables 5—8. Miscellaneous results are collected in Table 9.

TABLE 7. *A typical S_N2 reaction of methyl iodide in methanol accompanied by methanolysis at* 59·8°. (*Data for the reaction between sodium picrate and methyl iodide in methanol and for the methanolysis of methyl iodide measured simultaneously in methanol containing* 0·038M-LiClO$_4$. $[CH_3I]_0 = 13{\cdot}07$ *c.c.*, $[NaPic]_0 = 13{\cdot}07$ *c.c. Concentrations expressed in c.c. of* 0·0200N-AgNO$_3$ *for* 6·81 *c.c. sample. Rate constants, k_2, in l. mole^{-1} sec.$^{-1}$ and k_1 in sec.$^{-1}$.*)

S_N2 Substitution				Methanolysis			
t (hr.)	$[I^-]$, obs.	$[I^-]$, corr.	10^5k_2	t (hr.)	$[I^-]$	$[H^+]$	10^7k_1
0·0	0·05	0·00	—	0·0	0·05	0·00	—
1·7	0·15	0·05	—	1·7	0·10	0·05	—
22·0	1·10	0·70	1·04	22·0	0·40	0·40	3·9
72·5	2·75	2·00	1·82	72·5	0·75	0·75	2·3
93·0	3·37	2·56	1·90	93·0	0·81	0·80	2·0
165·0	4·17	3·27	1·50	165·0	0·90	0·92	1·3
237·0	5·88	4·83	1·80	237·0	1·05	1·05	1·0

Mean $k_2 = 1{\cdot}8 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$.

$k_1 = 2 \times 10^{-7}$ sec.$^{-1}$; k_1 in methanol without LiClO$_4$ = $1{\cdot}8 \times 10^{-7}$ sec.$^{-1}$.

TABLE 8. *Solvolysis of methyl iodide in* 10% *dioxan–formamide and* N-*methylformamide at* 25°. (*Concentrations in* c.c. *of* 0·0200N-AgNO$_3$ *for* 5·0 *c.c. sample. Rate constants, k_1, in sec.$^{-1}$.*

10% Dioxan–formamide. $[CH_3I]_0 = 12{\cdot}60$ c.c.						*N*-Methylformamide. $[CH_3I]_0 = 13{\cdot}50$ c.c.					
t (hr.)	$[I^-]$	10^6k_1	t (hr.)	$[I^-]$	10^6k_1	t (hr.)	$[I^-]$	10^6k_1	t (hr.)	$[I^-]$	10^6k_1
0·0	0·25	—	28·20	1·25	0·814	0·00	0·35	—	28·20	1·66	0·960
2·25	0·40	1·47	53·25	1·86	0·732	2·25	0·55	1·60	53·25	2·55	0·915
5·00	0·59	1·52	166·0	4·10	0·659	5·00	0·75	1·58	166·0	5·35	0·844
22·00	1·02	0·797	166·0	4·10	0·659	22·00	1·55	1·13	166·0	5·40	0·850

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[39] Cavell and Speed, *J.*, 1960, 1453.

TABLE 9. *Miscellaneous rate constants for some* S_N2 *reactions.* (*Initial concentrations of reactants* = 0·03—0·05M.)

CH_3I + Na Picrate in methanol at 25·1°	$k_2 = 6 \times 10^{-7}$ l. mole^{-1} sec.$^{-1}$
CH_3I + Na Picrate in D.M.F. at 25·1°	$k_2 = 3{\cdot}35 \times 10^{-5}$,, ,,
CH_3I + KSCN in methanol at 25·1°	$k_2 = 5{\cdot}26 \times 10^{-4}$,, ,,
CH_3I + NaN_3 in methanol at 25·1°	$k_2 = 7{\cdot}80 \times 10^{-5}$,, ,,
CH_3I + NaCl in methanol at 25·1°	$k_2 = 3{\cdot}0 \times 10^{-6}$,, ,,
CH_3I solvolysis by $NMe_2{\cdot}CHO$ at 100·0°	$k_1 = 2{\cdot}35 \times 10^{-5}$ sec.$^{-1}$
CH_3I solvolysis by $NMe_2{\cdot}COMe$ at 100·0°	$k_1 = 2{\cdot}0 \times 10^{-5}$,,

Reaction Products.—Methyl iodide–halogen (etc.) exchanges were substitutions, since total halogen was constant and no acid was formed. Each ion had a characteristic potential at the end-point of a silver-ion titration and was identified in this way.

Trimethylsulphonium bromide in dimethylformamide decomposed to dimethyl sulphide (identified by the mercuric chloride complex [7]), and bromide-ion consumption followed second-order kinetics, suggesting that methyl bromide was the other product.

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