THE EFFECTS OF SOLVATION ON THE PROPERTIES OF ANIONS IN DIPOLAR APROTIC SOLVENTS

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CHEMISTS need an understanding of the behaviour of ions in solution and it should be emphasised that the chemistry of anions in dipolar aprotic solvents differs greatly from their chemistry in water because anions are much less solvated in dipolar aprotic than in protic solvents[1] such as water.

In this Review, hydrogen-donors, *e.g.*, water, methanol, and formamide, are classed as protic solvents; solvents with dielectric constants > 15, which, although they may contain hydrogen atoms, cannot donate suitably labile hydrogen atoms to form strong hydrogen bonds with an appropriate species, are classed as dipolar aprotic. Common dipolar aprotic solvents are: dimethylformamide of dipole moment[2] $\mu = 3{\cdot}82$, dimethylacetamide $\mu = 3{\cdot}79$,[2] dimethyl sulphoxide $\mu = 4{\cdot}3$,[3] tetrahydrothiophen dioxide (sulpholane) $\mu = 4{\cdot}69$,[4] acetone $\mu = 2{\cdot}72$,[5] acetonitrile $\mu = 3{\cdot}37$,[5] and nitrobenzene $\mu = 3{\cdot}99$ D.[5]

The classification of solvents as hydrogen-donors explains our opening observation. There are four kinds of strong solvent–solute interaction: ion–dipole, dipole–dipole, π-complex-forming, and hydrogen bonding. In protic solvents, anions are solvated by ion–dipole interactions, on which is superimposed a strong hydrogen bonding which is greatest for small anions. Thus solvation by protic solvents decreases strongly in the series of anions[1] $OH^-, F^- \gg Cl^- > Br^- > N_3^- > I^- > SCN^- >$ Picrate. In dipolar aprotic solvents, anions are solvated by ion–dipole interactions, on which is superimposed an interaction due to the mutual polarisability of the anion and the solvent molecule, which is greatest for large anions. There is no significant contribution to solvation by hydrogen bonding in dipolar aprotic solvents. Solvation of anions by dipolar aprotic solvents thus decreases slightly, in the reverse order to that given above for protic solvents.[1]

That there are two distinct types of anion solvation has not been fully appreciated, and in this Review it is proposed to illustrate how the concept of differences of anion solvation in the two classes of solvent gives a consistent explanation of some solvent effects on rates of reaction, on polarographic data, on conductance, on acid and base strength, on basicity of anions, on solubility, and on spectra. Anion solvation explains

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

[2] "A Review of Catalytic and Synthetic Applications for DMF and DMAC," E.I. du Pont de Nemours and Co., Wilmington 98, Delaware, 1959.

[3] Schäfer and Schaffernicht, *Angew. Chem.*, 1960, **72**, 618.

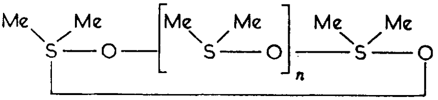
[4] Burwell and Langford, *J. Amer. Chem. Soc.*, 1959, **81**, 3799.

[5] Weissberger, "Organic Solvents," Interscience Publ., Inc., New York, 1955.

why many reactions with synthetical applications can be performed with advantage in dipolar aprotic solvents.

Properties of Solvents.—The dipolar aprotic solvents have large dielectric constants[5] (*e.g.*, propylene carbonate 65,[6] sulpholane 44,[4] dimethylformamide 37·6[2]) and large dipole moments (see above). They are high-boiling liquids with a large liquid range[2,3,5] and a variety of viscosities and refractive indices,[5] and are poor conductors of electricity.[2–5] Sulpholane, dimethylformamide, and dimethyl sulphoxide are highly associated liquids[2–4] and the Trouton constants of dimethylformamide[2] (33·4) and dimethyl sulphoxide[3] (29·5) are abnormally high.

Dimethyl sulphoxide possesses an ordered structure which breaks down sharply between 40° and 60°, as shown by the temperature-dependence of its refractive index, specific heat, density, and viscosity.[3] In this respect it resembles water, which has a distinct structural change at 37°. Sulpholane and dimethylformamide may also have structures which are temperature-dependent. Schäfer and Schaffernicht[3] suggest that the structure of dimethyl sulphoxide involves hydrogen bonds between polar oxygen and the hydrogen of the methyl groups. Although the molecules do not dimerise,[3,7] it is not unlikely that the structure may involve chains of sulphur and oxygen atoms of variable size such as (I);



(I)

these could break down on heating, or rearrange when a hydrogen-donor is added. Cryoscopic studies[7] suggest that dilute solutions in benzene contain chains of sulphoxide molecules. Bonding between first- and second-row elements of the same group analogous to that proposed here, is found in phosphonitriles, which polymerise readily. Dimethyl sulphoxide has a high entropy of fusion (10·4 cal. deg.$^{-1}$ mole^{-1}),[7] which supports the idea of a chain structure. Also the small heat of fusion of sulpholane, coupled with the large heat of vaporisation, suggests that there is little difference between the highly ordered liquid and the solid form of sulpholane.[4] Sulpholane has a large molal freezing-point-depression constant (66°/mole),[4] as has dimethyl sulphoxide (4·36°/mole),[7] and because so many substances are soluble, including inorganic complexes, these are useful solvents for semi-quantitative determination of molecular weight provided that the solvent does not react with solute.

1. Effect of solvation on solubility

Solvation ranges from one extreme, in which donor and acceptor properties result in definite, stable compounds, through the intermediate

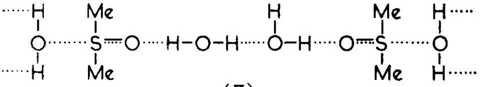
[6] Fuoss and Hirsch, *J. Amer. Chem. Soc.*, 1955, **77**, 6115.

[7] Kentamaa, Lindberg, and Nissema, *Suomen Kem.*, 1961, **34**, *B*, 98.

dipole associations and unstable co-ordination compounds, to the weak van der Waals interactions.[8] Solvation is influenced by entropy changes in the solvent and the solute. The classical principle of "*similia similibus solvuntur*" ("like dissolves like") has frequently "explained" unusual solubility effects, and may be a result of entropy changes favouring solvation and solubility.

(i) *Solubility of dipolar solutes.* Hydrogen bonding greatly influences the solubility of dipolar solutes in dipolar solvents, and in suitable systems outweighs the effect of dipole–dipole interactions. For example, nitrobenzene has a larger dipole moment than aniline or phenol, but is much less soluble in the strongly dipolar water, presumably because it does not form hydrogen bonds with water as do the latter.[8] Those dipolar molecules that can form strong hydrogen bonds with water, by accepting its hydrogen atoms, are completely miscible with water, but compounds such as nitromethane, which cannot form strong hydrogen bonds, are only slightly soluble in water. Doubly bound oxygen is usually a good hydrogen-acceptor.

When water is mixed with strong hydrogen-acceptors such as dimethyl sulphoxide and dimethylformamide, much heat is evolved, and, under certain conditions, the mixture becomes viscous for a short time.[9] This may result from breakdown of the sulphoxide rings and formation of a hydrogen-bonded structure such as (II).



(II)

Polar compounds, even insoluble ones such as some nitro-aromatic disulphides and diselenides,[9] dissolve readily in dimethylformamide,[2] dimethylacetamide,[2] dimethyl sulphoxide,[3] and sulpholane.[9] Thus alcohols, aldehydes, ketones, ethers, esters, aromatic and heterocyclic compounds, organic mercury derivatives, polymers (polyacrylonitrile, nitrocellulose, cellulose acetate, and wood extracts) are usually soluble in these solvents. Inorganic complexes, which are insoluble in most other solvents, frequently dissolve in dimethyl sulphoxide,[3] and/or sulpholane.[9] In some cases the complex is converted into a solvato-complex.

Gaseous polar molecules dissolve readily in dipolar aprotic solvents such as dimethylformamide,[2] dimethyl sulphoxide,[3] dimethylacetamide,[2] and acetone.[10] Acetylene, sulphur dioxide, nitrogen dioxide, ammonia, and hydrogen chloride can be separated from less polar and less soluble gases (ethane, methane, nitrogen, hydrogen, and oxygen) by solvent extraction

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[8] Remick, "Electronic Interpretations of Organic Chemistry," Chap. 10, John Wiley and Sons, London, 1947.

[9] Parker, unpublished observations.

[10] Seidell, "Solubilities of Inorganic Compounds," Van Nostrand, New York, 1940.

with dimethylformamide,[2] dimethylacetamide,[2] or dimethyl sulphoxide.[3] Sulphur trioxide forms a complex with dimethylformamide which is an extremely useful and convenient source of the trioxide for a variety of purposes.[2] Paraffins, saturated cyclic compounds, and long-chain alcohols are only very slightly soluble in dimethylformamide,[2] dimethylacetamide,[2] dimethyl sulphoxide,[3] or sulpholane.[9] It appears that polarisability of the solute is an important factor in the solubility of non-ionic species in dipolar aprotic solvents.

(ii) *Solubility of electrolytes and anion solvation.* A salt dissolves in a solvent if either the ion-pair solvation or the total of anion solvation, cation solvation, and "dissociating or ionizing power" of the solvent, which is usually reflected in its dielectric constant, exceeds the crystal energy of the salt. Ionic species are often soluble and are dissociated in dipolar aprotic solvents, but usually less so than in water. Most salts are dissociated even in acetonitrile,[11] which causes little solvation of anions or cations.

In water, anions have much greater solvation energies than cations of comparable size,[12] because of the hydrogen-bonding contribution to solvation of anions, but in dipolar aprotic solvents anions are poorly solvated and are often less solvated than cations.[13] Effects due to differences of anion solvation are found in the solubilities of many sodium and potassium salts in different solvents.[1] Thus potassium chloride is much less soluble in dimethylformamide than in methanol which is of comparable dielectric constant, but potassium iodide is more soluble in dimethylformamide than in methanol; this suggests that the iodide ion is at least as solvated in this dipolar aprotic solvent as in methanol, but that chloride ion is much more solvated in methanol than in the dipolar aprotic solvent.[1] The conclusion is supported by the fact that iodides and thiocyanates are the salts most soluble in acetonitrile,[11] and iodides are much more soluble than chlorides in dimethyl sulphoxide.[3] Hydroxides are very slightly soluble in acetonitrile,[14] dimethylformamide,[9] dimethyl sulphoxide,[9] sulpholane,[9,15] and dimethylacetamide,[9] suggesting that the hydroxide ion is poorly solvated and thus very active in these solvents.

(iii) *Cation solvation.* Cations are strongly solvated in highly polar solvents having a negative charge localised on a bare oxygen atom, as in dimethyl sulphoxide, dimethylformamide, sulphur dioxide, dimethylacetamide, 2-pyridones, 2-pyrrolidones, pyridine *N*-oxide, phosphorus oxides, and substituted tertiary amides.[16] Sodium and potassium ions in dimethylformamide and dimethyl sulphoxide are solvated, to give a solvodynamic unit equivalent in size to the tetra-n-propylammonium ion,

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[11] Kolthoff and Coetzee, *J. Amer. Chem. Soc.*, 1957, **79**, 870.
[12] Buckingham, *Discuss. Faraday Soc.*, 1957, **24**, 151.
[13] Prue and Sherrington, *Trans. Faraday Soc.*, 1961, **57**, 1796.
[14] Kolthoff and Coetzee, *J. Amer. Chem. Soc.*, 1957, **79**, 1852.
[15] Burwell and Langford, *J. Amer. Chem. Soc.*, 1960, **82**, 1503.
[16] Zaugg, *J. Amer. Chem. Soc.*, 1960, **82**, 2903.

indicating that strong K^+ and Na^+ solvent interactions take place.[17,18] Potassium iodide is less soluble than sodium iodide in methanol or water, but in dimethylformamide or dimethyl sulphoxide the reverse is true,[9] and this may be due to differences of cation solvation.

Cations are poorly solvated in, for example, nitroalkanes,[19] alkyl cyanides,[11] and t-butyl alcohol, presumably because the negative portion of the solvent dipole is dispersed, is on an unfavourable electron-donor atom, or is surrounded by bulky groups. If cation solvation by electron-donor solvents decreases in the series Me_2SO, $Me_2NAc > Me_2N{\cdot}CHO$, SO_2, $H_2O > COMe_2$, sulpholane, $> MeOH$, $\gg MeCN$; $MeNO_2 > PhCN$, $PhNO_2$,–[6,11,19,20] then some observations dependent on cation solvation are explained, as demonstrated in this Review.

Specific donor–acceptor interactions between cation and solvent interfere in generalisations about cation solvation. Thus many silver salts are more soluble in acetonitrile than in water,[14,21] and cuprous iodide dissolves in acetonitrile but not in water.[10,14] Acetonitrile readily forms complexes with silver and cuprous ions.[14] Silver-ion activity varies greatly with change of solvent,[8,22,23] suggesting that cation-solvation differences could be used to advantage in electrophilic reactions of cations, just as differences of anion solvation are utilised in nucleophilic substitutions.[1]

Lithium salts form solvates with many dipolar aprotic solvents, *e.g.*, acetone and dimethyl sulphoxide,[3] and their solutions are extremely viscous.[9] Lithium salts dissolve largely as ion pairs in acetone.[24] Dimethyl sulphoxide forms stable solvates with many transition-metal ions, *e.g.*, of $CuCl_2$, $FeCl_3$, $CrCl_3$, $CoCl_2$, $NiBr_2$, and $AlCl_3$.[3,25] In all cases oxygen is the donor atom, except for the dimethyl sulphoxide–palladium complexes in which sulphur is the donor.[25]

Dimethylformamide acts as a Lewis base and forms complexes with sulphur trioxide[2] and iodine cyanide.[26] Dimethylacetamide is a much better base towards iodine than is acetone,[27] and basicity of the solvent molecule towards cobalt in the dichlorobisethylenediaminecobalt(III) cation decreases in the series of solvents $H_2O > Me_2SO > MeOH > Me_2NAc > Me_2N{\cdot}CHO$.[28] Lewis acids are generally more soluble in dimethyl-formamide and -acetamide than is indicated by their dielectric constants, and

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[17] Sears, Wilhoit, and Dawson, *J. Phys. Chem.*, 1955, **59**, 373.

[18] Sears, Lester, and Dawson, *J. Phys. Chem.*, 1956, **60**, 1433.

[19] Hammett and Looy, *J. Amer. Chem. Soc.*, 1959, **81**, 3872.

[20] Sears, Wilhoit, and Dawson, *J. Phys. Chem.*, 1955, **59**, 373.

[21] Hammond, Hawthorne, Waters, and Graybill, *J. Amer. Chem. Soc.*, 1960, **82**, 704.

[22] Koch, *J.*, 1928, 269.

[23] Koch, *Phil. Mag.*, 1931, **11**, 579.

[24] Parker, *J.*, 1961, 1328.

[25] Cotton and Francis, *J. Amer. Chem. Soc.*, 1960, **82**, 2986; Drago and Meek, *J. Phys. Chem.*, 1961, **65**, 1446.

[26] Haszeldine, *J.*, 1954, 4145.

[27] Carson, Rose, and Wenz, *J. Amer. Chem. Soc.*, 1961, **83**, 3572; Schmullbach and Drago, *J. Amer. Chem. Soc.*, 1960, **82**, 4478.

[28] Watts and Tobe, personal communication.

some Lewis acid reactions, *e.g.*, of thionyl or sulphuryl chloride, halogens, or carbonyl chloride, are much more effective when performed in these solvents.[2,9]

2. Polarography

Cations are reduced at more positive potentials, and anions are depolarised at more negative potentials, at the dropping-mercury electrode, as they become less solvated.[11]

It is difficult to compare half-wave reduction potentials of cations secured in different solvents.[29] Where different reference electrodes are involved, the $E_{\frac{1}{2}}$ values cannot be expected to be the same, or even to be directly related in any absolute sense.[29,30] Relative values for a series of cations, however, have significance.[11,29,31]

Kolthoff and Coetzee, on the basis of relative $E_{\frac{1}{2}}$ values, conclude that cations are generally much less solvated in acetonitrile than in water,[11] but that cuprous and silver ions, which strongly interact with acetonitrile, are much more solvated than in water.[14] Solvation of cations in acetonitrile does not depend on charge density, to the same extent, or in the same way, as in water. The proton is very much less solvated in acetonitrile than in water and would be expected to have a much greater activity in acetonitrile.[32]

The $E_{\frac{1}{2}}$ values for simple cations show that dimethylformamide solvates cations much more readily than acetonitrile does[31,33] and it is claimed that water is more efficient in this respect than dimethylformamide.[31] The polarographic method appears to be a useful means of studying cation solvation, especially since ultraviolet spectra, solvent basicity, and molar refractions of solvents do not reflect the ability to solvate cations.[16]

The anodic dissolution potentials (E_A, Table 1) referred to an external calomel electrode[14] show that anions are much less solvated in acetonitrile (a dipolar aprotic solvent) than in water. The difference is greatest for small, slightly polarisable anions. Hydroxide ion has a very much greater activity (*i.e.*, is less solvated) in acetonitrile than in water, since the difference between the E_A's for hydroxide ion in these solvents is twice as great as for any other anion studied. Only fluoride ion might be expected to show a comparable effect. Kolthoff and Coetzee[14] found by polarography that in acetonitrile trihalide ions were more stable than the corresponding halide ions. This agrees with our postulate[1] that large polarisable anions, as in transition states, are more solvated than smaller anions by dipolar aprotic solvents. Trihalide ions could be regarded as intermediates resembling the transition state for displacement by Hal^- of Hal^- at a univalent halogen atom.

[29] Schaap, Messner, and Schmidt, *J. Amer. Chem. Soc.*, 1957, **79**, 870.
[30] Popov and Geske, *J. Amer. Chem. Soc.*, 1957, **79**, 2074.
[31] Brown and Al-Urfali, *J. Amer. Chem. Soc.*, 1958, **80**, 2113.
[32] Kolthoff and Coetzee, *J. Amer. Chem. Soc.*, 1957, **79**, 6110.
[33] Wawzonek and Runner, *J. Electrochem. Soc.*, 1952, **99**, 457.

TABLE 1. *Anodic dissolution potentials* (E_A, *in* V) *of mercury* vs. *an external calomel electrode at* 25°.[14]

Anion	E_A H_2O	E_A MeCN	ΔE_A ($H_2O - MeCN$)
OH^-	0·0	−0·90	0·90
Cl^-	+0·2	−0·25	0·45
Br^-	+0·1	−0·35	0·45
I^-	−0·1	−0·45	0·35
SCN^-	+0·1	−0·10	0·20

3. Conductance

Recent measurements of conductance in dimethylformamide[13,20,34,35] dimethylacetamide,[36] dimethyl sulphoxide,[3,18] and sulpholane[4] illustrate some anion and cation solvation effects. Prue and Sherrington[13] have compared the Stokes-law radii of anions and cations in solvents with their crystallographic radii, and conclude that cations carry a large solvation sheath in dimethylformamide, dimethylacetamide, and dimethyl sulphoxide, whereas anions are naked in these dipolar aprotic solvents.

Sears, Wilhoit, and Dawson[20] had earlier arranged limiting cationic conductances in dimethylformamide in the increasing order: $Bu_4N^+ < Pr_4N^+ < Na^+ < K^+ < Me_3PhN^+ < H{\cdot}CO{\cdot}NMe_2H^+ < Et_3NH^+ < Et_4N^+ < EtNH_3^+ < Me_4N^+$. The lithium cation is less conducting than tetrabutylammonium cation in dimethylformamide.[13] Inasmuch as the cationic conductance of a species is related inversely to the effective cation size, this series suggests that lithium, sodium, and potassium cations are well solvated by dimethylformamide. The partially substituted ammonium cations are apparently solvated by hydrogen bonding to the oxygen of the amide. Limiting cationic conductances in acetone[37,38] fall into the same series arrangement as in dimethyl-formamide and -acetamide, pyridine, and dimethyl sulphoxide,[13,18]

Limiting cation conductances in a number of solvents are compared in Table 2. It is apparent that the alkali-metal cations are well solvated by dimethylformamide, dimethyl sulphoxide, water, and methanol, because the solvodynamic units are less conducting than some large alkylammonium cations. Sodium ions have larger solvation sheaths than potassium ions.

Anion solvation is well illustrated by its effect on limiting equivalent anionic conductances, as also shown in Table 2. Anions are as conducting as cations of similar crystallographic radii in methanol and water, but anions are much more conducting than cations in the dipolar aprotic solvents dimethylformamide, dimethyl sulphoxide, and acetone.

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[34] Ames and Sears, *J. Phys. Chem.*, 1955, **59**, 16.
[35] Sears, Wolford, and Dawson, *J. Electrochem. Soc.*, 1956, **103**, 633.
[36] Lester, Gover, and Sears, *J. Phys. Chem.*, 1956, **60**, 1076.
[37] Reynolds and Kraus, *J. Amer. Chem. Soc.*, 1948, **70**, 1709.
[38] McDowell and Kraus, *J. Amer. Chem. Soc.*, 1951, **73**, 3293.

Schäfer and Schaffernicht[3] observed that, although chloride ion and potassium ion were of comparable size in water and methanol, the chloride ion is much smaller than the potassium ion in dimethyl sulphoxide.

The relative conductances of chloride, bromide, iodide, and picrate ions in methanol follow quite a different pattern from that in dimethylformamide and dimethyl sulphoxide. This is because the negative solvodynamic units are hydrogen-bonded and large in methanol, whereas in dimethylformamide and dimethyl sulphoxide the anions are bare and of a size comparable with their crystallographic radii. Thus chloride ion is more conducting than iodide ion in the two named solvents, but less conducting in methanol and water.

Dissociation.—Most sodium and potassium salts, except the chlorides and nitrates are completely dissociated in $< 10^{-3}$M-solution in dimethylformamide[34,15] dimethyl sulphoxide,[3,18] sulpholane,[4] and acetonitrile.[11] Dissociation constants in protic and dipolar aprotic solvents reflect anion-solvation effects. Thus chlorides tend to be weak electrolytes in the differentiating solvents,[39] dimethylformamide,[40,13] dimethyl sulphoxide,[3] and acetone,[4,37] but iodides and picrates in these solvents are much stronger.

TABLE 2. *Limiting ionic conductivities in solvents at 25°.*

Ion	$\lambda_0(Me_2N{\cdot}CHO)$	$\lambda_0(Me_2SO)$	$\lambda_0(H_2O)$[a]	$\lambda_0(MeOH)$
Li^+	25·0[13]	—	38·7	39·8[a]
Na^+	29·9[13]	13·8[18]	50·1	45·2[a]
K^+	30·8[13]	14·4[18,3]	73·5	52·4[a]
Me_4N^+	38·9[20]	—	44·9	66·7[b]
Pr_4N^+	29·1[34]	—	23·4	43·9[b]
Bu_4N^+	26·2[13]	11·2[18]	19·5	36·9[b]
Me_3PhN^+	32·2[20]	14·1[18]	—	—
Cl^-	55·1[13]	36·3[3]	76·3	52·4[a]
Br^-	53·6[13]	24·2[18]	78·4	56·5[a]
I^-	52·3[13]	23·8[18]	76·8	62·7[a]
SCN^-	59·8[34]	29·2[18]	—	64·7[b]
Picrate	38·1[35]	17·3[18]	30·4	49·2[b]

[a] Robinson and Stokes, "Electrolyte Solutions," Butterworths Scientific Publns., London, 1959. [b] Evers and Knox, *J. Amer. Chem. Soc.*, 1951, **73**, 1739.

However, in methanol—a levelling solvent—dissociation constants of chlorides, bromides, iodides and picrates are almost equal.[20] Potassium chloride in methanol is a stronger electrolyte than potassium picrate in methanol,[20] but in dimethyl sulphoxide potassium picrate is stronger than potassium chloride,[18] suggesting that the chloride ion is much more solvated in methanol than in dimethyl sulphoxide by comparison with picrate ion in methanol and the sulphoxide.

Cations with a labile proton available for hydrogen bonding (*e.g.*,

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

[40] Sears, Wilhoit, and Dawson, *J. Chem. Phys.*, 1955, **23**, 1274.

R_3NH^+) form strongly hydrogen-bonded structures with a suitable anion in differentiating (*i.e.*, dipolar aprotic) solvents,[19,41,42] where there is no other source of protons for this purpose. The result is that partly substituted ammonium salts such as NHR_3X, but not R_4NX,[42] are weakly dissociated in acetone,[41] nitromethane,[19] nitrobenzene,[43] acetonitrile,[41] and dimethylformamide.[35] These salts are strong electrolytes in solvents which compete with R_3NH^+ to provide hydrogen bonds for X^-, such as water, methanol, and ethanol.[41] Since salts RNH_3X are such weak electrolytes in dipolar aprotic solvents, the use of indicators such as the substituted anilines, for acid–base studies in dipolar aprotic solvents is more complicated than it appears at first to be.

Taylor and Kraus[43] have shown that even the picrate ion has a tendency to form hydrogen bonds with labile hydrogen from the accompanying cation, leading to incomplete dissociation of ammonium picrates in nitrobenzene (Table 3). In dimethylformamide, which solvates cation more efficiently than nitrobenzene does, triethylammonium picrate is completely dissociated, but partially substituted ammonium bromides in dimethylformamide are weak electrolytes.[20]

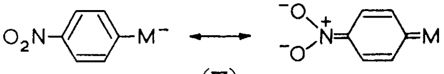
TABLE 3. *Dissociation constants of picrates in nitrobenzene at* 25°.[43]

Cation	Me_4N^+	$MeO{\cdot}NMe_3^+$	$HO{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_3^+$	$NHMe_3^+$	$HO{\cdot}NMe_3^+$
10^4K	400	250	70	1·5	0·17

4. Spectra and solvent effects

Dimethyl sulphoxide is more transparent than water in the visible portion of the spectrum and is transparent throughout the region 400—1800 mμ.[3] Dimethylformamide and dimethyl sulphoxide are transparent in the near-ultraviolet region.[9]

A pronounced red shift (100 mμ) of the absorption maxima for the charge-transfer-transition (III) (where M is a Group VI atom) occurs in



(III)

the change from a protic to a dipolar aprotic solvent.[44] The shift is greatest when M is selenium. It has also been observed that a number of charge-transfer processes involving anions X^- and aromatic systems have very much smaller transition energies (*i.e.*, absorb nearer the red region) in dipolar aprotic solvents than in protic solvents.[9] These observations conform with our postulate that dipolar aprotic solvents solvate large polarisable anions

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[41] Wynne-Jones, *J.*, 1931, 795.
[42] P. Walden, "Salts, Acids and Bases," McGraw-Hill, New York, 1929.
[43] Taylor and Kraus, *J. Amer. Chem. Soc.*, 1947, **69**, 1731.
[44] Parker, *Acta Chem. Scand.*, 1962, in the press.

better than they solvate small anions having localised charge, whereas in protic solvents the reverse is true[1]. Solvation of excited states involves, of course, only mutual polarisability of the loosely held electrons of the solvent and the excited state, since other processes, *e.g.*, solvent re-orientation, require periods much longer than the transition time, but apparently such polarisability interactions are strong in dipolar aprotic solvents.

The position of the charge-transfer absorption band of l-alkylpyridinium iodide complexes is remarkably sensitive to the nature of the solvent in which it is measured.[45] Kosower[45] has adopted the transition energies of this process as an empirical measure of solvent polarity called Z values. As with so many theories of solvent effects,[46] Z values give good correlations for a number of observations in a series of protic solvents but, as with ion association data,[45] kinetic measurements,[47] and transition energies of iodide ion,[48] two behaviour patterns emerge, one for protic solvents, the other for dipolar aprotic solvents. This may be due to differences of solvation of iodide ion in the two classes of solvent. Z values are much higher in solvents than in dipolar aprotic solvents of comparable dielectric constant, indicating that the iodide ion is stabilised by hydrogen bonding in the protic solvents.

Spectral shifts illustrate the existence and magnitude of ion-solvent interactions, such as hydrogen bonding.[49-53] Both the O–H stretching and the bending frequencies of water are shifted strongly by negative ions, including iodide, but are unaffected by positive ions.[50] The shifts increase in magnitude with increasing ability to form hydrogen bonds with water in the series $I^- < Cl^- < F^-$. The idea that the proton-acceptor in hydrogen-bond formation must be an element of small atomic radius and strong electronegativity, although true for the strong hydrogen bonding to anions, cannot be extended to the much weaker hydrogen bonding with covalently bound electronegative atoms.[54] The O–H stretching frequency of methanol in carbon tetrachloride is shifted most in the infrared region for RI and least for RF in a series of alkyl halides.[54] This has important applications to our understanding of solvent effects on the initial and the transition states of S_N1 and S_N2 reactions. Since in the final state Cl^- is more solvated by hydrogen bonding than I^-, but in the initial state the halogen in RI is more solvated than in RCl, the question arises, at what stage in the S_N1 ionisation in protic solvents do hydrogen bonding forces change from

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[45] Kosower, *J. Amer. Chem. Soc.*, 1958, **80**, 3253.

[46] Hughes and Ingold, *J.*, 1935, 244.

[47] Kosower, *J. Amer. Chem. Soc.*, 1958, **80**, 3267; Smith, Fainberg, and Winstein, *J. Amer. Chem. Soc.*, 1961, **83**, 618.

[48] Kosower, *J. Amer. Chem. Soc.*, 1958, **80**, 3261.

[49] Bale, Davies, Morgans, and Monk, *Discuss. Faraday Soc.*, 1957, **24**, 94.

[50] Waldron, *J. Chem. Phys.*, 1957, **26**, 809; Cavell and Speed, *J.*, 1961, 226.

[51] Badger, *J. Chem. Phys.*, 1937, **5**, 839.

[52] Lord, *J. Chem. Phys.*, 1953, **21**, 166.

[53] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492.

[54] Schleyer and West. *J. Amer. Chem. Soc.*, 1959, **81**, 3164.

favouring ionisation of RI more than that of RCl to the reverse? Most important, does this change occur before or after the transition state is reached? A similar question arises for S_N2 reactions.

$$\mathrm{RCl} \rightleftharpoons \overset{\delta+}{\mathrm{R}}\ldots\overset{\delta-}{\mathrm{Cl}} \rightleftharpoons \mathrm{R}^+ + \mathrm{Cl}^-$$

$$\mathrm{RI} \rightleftharpoons \overset{\delta+}{\mathrm{R}}\ldots\overset{\delta-}{\mathrm{I}} \rightleftharpoons \mathrm{R}^+ + \mathrm{I}^-$$

Cation–water interactions in acetonitrile, as observed by infrared measurements, are large when the cation is small, but are small when the cation is large, *e.g.*, tetra-alkylammonium.[55] Nuclear magnetic resonance measurements show that the $^{23}\mathrm{Na}^+$ ion forms complexes with amides such as *N*-methylformamide.[56] Iodine complexes at the oxygen atom of dimethylacetamide as shown by the carbonyl band shift in the infrared spectrum.[57] Here iodine is a Lewis acid and oxygen acts as the donor atom.

5. Acids and bases

Dissociation of HX.—The conductance of hydrogen halides in anhydrous polar organic solvents has been reviewed recently.[39] Two groups of solvents may be distinguished: levelling solvents, in which the members of a series of electrolytes are approximately of the same strength, *e.g.*, hydrogen halides in methanol; and differentiating solvents, in which the members possess markedly different strengths, *e.g.*, hydrogen halides in dimethylformamide, dimethyl sulphoxide, pyridine, acetonitrile, acetone, nitrobenzene, and nitromethane.[39] It appears that differentiating solvents have this property because, being dipolar aprotic, they do not efficiently solvate small anions but are slightly more efficient for large than for small anions. The levelling (protic) solvents solvate small anions strongly (*i.e.*, those which form the strongest bonds with hydrogen) because of hydrogen-bonding solvent-anion interactions. It is apparent, therefore, that solvation of A^- in protic solvents most assists dissociation of acids with the strongest H–A bonds, and thus levels (*i.e.*, distorts) the "absolute" acid strength,[11] which is the tendency of HA to dissociate into ions in the absence of other molecules. Solvation of A^- in dipolar aprotic solvents slightly assists dissociation of acids with the weakest H–A bonds (largest, most polarisable A^-) and reinforces the "absolute" acid strength of HA. To illustrate this, the pK_a values of hydrogen bromide and chloride in acetonitrile[58] are 5·51 and 8·94, respectively; conductivities of 10^{-3}M-hydrogen halides in acetonitrile[59] increase in the ratio 1:20:60 from hydrogen chloride to hydrogen iodide; hydrogen bromide ($K_a = 1{\cdot}7 \times 10^{-2}$ at 25°) is much stronger than hydrogen chloride ($K_a = 2{\cdot}8 \times 10^{-4}$ at 25°)

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[55] Scherba and Sukhotin, *Zhur. fiz. Khim.*, 1959, **33**, 2401.
[56] Takeda and Stejskal, *J. Amer. Chem. Soc.*, 1960, **82**, 27.
[57] Schmullback and Drago, *J. Amer. Chem. Soc.*, 1960, **82**, 4478.
[58] Kolthoff, Bruckenstein, and Chantooni, *J. Amer. Chem. Soc.*, 1961, **83**, 3927.
[59] Janz and Danyluck, *J. Amer. Chem. Soc.*, 1959, **81**, 3854.

in dimethylformamide,[35,60] but the differences in acid strength of these three halogen acids in the levelling solvent, methanol, are less than 100%.[39]

If A^- is small and capable of accepting hydrogen bonds, HA will be a very weak acid in dipolar aprotic solvents, even although HA may be strong in protic solvents of comparable dielectric constant. Hydrogen chloride is a strong acid in methanol,[61] but a weak one in dimethylformamide,[35,60] acetonitrile,[58,59] nitrobenzene,[62] and nitromethane[63] despite the very similar dielectric constants of all these solvents. These observations cannot be entirely explained by differences in proton solvation, since dimethylformamide appears to solvate protons better than methanol does. Perchloric acid is strong in acetonitrile, and hydrogen bromide is much weaker.[58]

Many acids (HA) in dipolar aprotic solvents form hydrogen bonds from A^- through a proton to a solvent molecule to form, *e.g.*, $Me_2S{=}O \ldots HA$, $MeCN \ldots HA$, $Me_2C{=}O \ldots HA$, or to another anion to form HA_2^-. Molecular complexes of HA and organic solvents are known,[39] and dihalide ions (HA_2^-) are a common and stable species[39] in nitromethane,[19,64] nitrobenzene,[19] acetonitrile,[58,65] and other dipolar aprotic solvents.[58,66]

Picric acid is stronger ($K_a = 6{\cdot}3 \times 10^{-2}$ at 25°) than hydrogen bromide ($K_a = 1{\cdot}7 \times 10^{-2}$ at 25°) in dimethylformamide,[35] and as strong as hydrogen chloride in acetonitrile,[58] but in water the halogen acids are much stronger than picric acid. This is in agreement with the order of anion solvation Picrate $>$ Br^- $>$ Cl^- in dipolar aprotic solvents, and Cl^- $>$ Br^- $>$ Picrate in protic solvents.[1]

Hammett and Looy[19] have studied acid–base reactions in nitromethane and suggest that the dissimilarity of these reactions from corresponding reactions in water should be attributed to the lack of hydrogen-donor properties of nitromethane, and that, conversely, the familiar properties of acid–base systems in water-like solvents are due much more to the quality of these solvents as hydrogen-donors, and much less to their relatively high dielectric constants than has usually been appreciated. Kolthoff, Bruckenstein, and Chantooni, in a paper on acid–base equilibria in acetonitrile,[58] point out that an interpretation of differences in acid strength in different solvents must consider the formation and dissociation of ion pairs, and the degree of solvation of anions, in addition to the basic character of the solvent and its dielectric constant.

Reactivity of Anions towards Hydrogen.—Turning from acid and base strength, in terms of dissociation of HA, to acidity and basicity, in terms

[60] Thomas and Rochow, *J. Amer. Chem. Soc.*, 1957, **79**, 1843.
[61] Ogston, *Trans. Faraday Soc.*, 1936, **32**, 1679.
[62] Beckmann and Lockemann, *Z. phys. Chem.*, 1907, **60**, 390.
[63] Hartley, Murray-Rust, and Wright, *J.*, 1931, 199.
[64] Pocker, *J.*, 1960, 1292.
[65] Janz and Danyluck, *J. Amer. Chem. Soc.*, 1959, **81**, 3850.
[66] Kaufler and Kunz, *Ber.*, 1909, **42**, 385.

of the reactivity of H^+ and A^-, we find that anions in dipolar aprotic solvents are much more reactive towards hydrogen than in protic solvents. Cram, Rickborn, Kingsbury, and Haberfield[67] have shown that the sodium methoxide-catalysed H–D exchange at carbon α to CN, $CO{\cdot}NR_2$, or CO_2R is 10^9 times faster in dimethyl sulphoxide than in methanol. They attribute the rate increase to the fact that methoxide ion is strongly solvated by hydrogen bonding in methanol, but is poorly solvated in dimethyl sulphoxide. Sodium methoxide in sulpholane was less reactive than in the sulphoxide, but much more reactive than in methanol. It is interesting that potassium t-butoxide in dimethyl sulphoxide displaces carbanions from hydrogen 10^{12} times faster than does potassium methoxide in methanol.[67] Cram and his co-workers[67] point out that a large number of organic reactions involve the breaking of carbon–hydrogen bonds as the rate-determining step, and it is probable that the rates of many such reactions could be dramatically increased by substitution of dimethyl sulphoxide for the usual hydroxylic solvents. Base-catalysed eliminations (*e.g.*, carbene, aryne, olefin, and acetylene formation), certain condensations, prototropic rearrangements, and nucleophilic substitutions might be subject to enhancement of rate and possibly yield. Other dipolar aprotic solvents could be used in place of dimethyl sulphoxide, if stable to alkali.

Fluoride ion is a strong base when not stabilised by hydrogen bonding, and in dimethylformamide, dimethyl sulphoxide, and sulpholane extracts a proton even from primary halides to give olefins.[68] Tetraethylammonium fluoride decomposes to ethylene and hydrogen fluoride when warmed in aprotic solvents.[69] Chloride, bromide, and azide ions accelerate decomposition of *t*-butyl bromide to isobutene, and, by forming HA_2^-, prevent the back-addition of the proton to olefin in acetone,[9,70] acetonitrile,[9] and nitromethane[9,64] because they are strong bases in these solvents.

Reactivity of a Proton towards Bases.—This depends on the electron-donor properties of the solvent, *i.e.*, its ability to solvate protons.[71] Proton solvation, ranging from salt formation in pyridine to weak hydrogen bonding between anions and solvent molecules in acetonitrile,[39,59,65] reduces hydrogen-ion activity, and this solvation varies in amount considerably from one solvent to another.[72]

Sulphuric acid in sulpholane is much more acidic than the corresponding aqueous solution.[15] Powell and Whiting[72a] suggest that H_0 values in the range -4 to -8 would be found for the system sulpholane–hydrogen tetrafluoroborate. They observed that *trans*-Δ^1-octalin was converted into

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[67] Cram, Rickborn, Kingsbury and Haberfield, *J. Amer. Chem. Soc.*, 1961, **83**, 3687; Cram, Kingsbury, and Rickborn, *J. Amer. Chem. Soc.*, 1961, **83**, 3688.

[68] Parker and Banthorpe, unpublished work.

[69] Miller, Fried, and Goldwhite, *J. Amer. Chem. Soc.*, 1960, **82**, 3091.

[70] Fuchs and Nisbett, *J. Amer. Chem. Soc.*, 1959, **81**, 2371.

[71] Mulliken, *J. Amer. Chem. Soc.*, 1952, **74**, 811.

[72] Braude and Stern, *J.*, 1948, 1976.

[72a] Powell and Whiting, *Proc. Chem. Soc.*, 1960, 412.

Δ^9-octalin by hydrogen tetrafluoroborate in 1:2 benzene–sulpholane 8×10^4 times as fast as in 1:2 benzene–acetic acid. The proton is extremely active in nitromethane[19] and the solvated proton in acetonitrile is a "super acid."[32] The indicators *o*-nitroaniline and *o*-nitrodiphenylamine are 5×10^4 times stronger in acetonitrile than in water,[68] *i.e.*, the proton is added much more efficiently in acetonitrile. Acidity functions (H)[73] of 0·02M-hydrogen chloride towards *p*-nitroaniline in various solvents are given in Table 4. More positive values denote greater acidity. Although uncertainties in the absolute values are introduced by incomplete dissociation of hydrogen chloride (which tends to make H more negative),[73] this does not change the conclusion that the proton is well solvated in dimethyl sulphoxide, poorly solvated, *i.e.*, most active, in nitromethane, with intermediate behaviour in acetone.

TABLE 4. *Acidity functions* (H)[73] *and acid strengths of* 0·02M-HCl *at* 25°.

Solvent:	$Me_2N{\cdot}CHO$[a]	H_2O[73]	EtOH[73]	Me_2CO[73]	$MeNO_2$[19]
H:	−2·4	−1·7	−1·36	−1·05	+2·14
Acid strength:	Weak	Strong	Weak	Very weak	Very weak

[a] Dessy, Reynolds, and Kim, *J. Amer. Chem. Soc.*, 1959, **81**, 2683.

6. Rates and mechanisms of reactions

Most anions in dipolar aprotic solvents are much less solvated than in protic solvents, but polarisable charged transition states in dipolar aprotic solvents are more solvated than in protic solvents.[1] The result is that the bimolecular reactions of anions, which pass through a large polarisable transition state containing that anion, are much faster in dipolar aprotic solvents than in protic solvents,[1,24,74] Reactions of small anions are most accelerated, and reactions of large polarisable anions are least accelerated, in the change from protic to dipolar aprotic solvent.[1,24]

The effect of hydrogen-bonding forces on rate is illustrated in Table 5. The effect is general for S_N2 and S_NAr anion–dipole reactions[24] and for S_N2 and S_NAr anion–cation reactions[75], *i.e.*, for a variety of transition states. Bimolecular substitutions not involving anions are much less susceptible to changes in solvent structure, provided that the dielectric constant does not change appreciably.[76,77] Pyridine and butyl bromide react together at substantially the same rate in dipolar aprotic solvents and in water–methanol mixtures of the same dielectric constant at the same ionic strength.[77] Although pyridine is not solvated by hydrogen-bonding in dipolar aprotic solvents but is so solvated in protic solvents, this rate-

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[73] Braude, *J.*, 1948, 1971.
[74] Cavell and Speed, *J.*, 1961, 226.
[75] Beringer and Mausner, *J. Amer. Chem. Soc.*, 1958, **80**, 4535.
[76] Palit, *J. Org. Chem.*, 1947, **12**, 752.
[77] Parker, *J.*, 1961, 4398.

enhancement is nullified by the fact that the departure of bromide ion in the transition state is assisted less in the dipolar aprotic solvents. The trimethylamine–trimethylsulphonium cation reaction is twenty times faster in nitromethane than in methanol.[78] This may be because in methanol hydrogen bonding reduces the reactivity of trimethylamine but does not assist the departure of dimethyl sulphide from the transition state, because neutral sulphur accepts only weak hydrogen bonds. The reaction is therefore slower in the protic solvent.

TABLE 5. *Relative rates*[24] *in solvents for the reactions at* 25°.

A: $CH_3I + Cl^- \rightarrow CH_3Cl + I^-$
B: $p\text{-}NO_2{\cdot}C_6H_4F + N_3^- \rightarrow p\text{-}NO_2{\cdot}C_6H_4{\cdot}N_3 + F^-$

Solvent:	MeOH	$NH_2{\cdot}CHO$	$Me{\cdot}NH{\cdot}CHO$	$Me_2N{\cdot}CHO$	Me_2NAc
Relative rates of reaction A:	1	12·5	45·3	$1{\cdot}2 \times 10^6$	$7{\cdot}4 \times 10^6$
Relative rates of reaction B:	1	5·6	15·7	$2{\cdot}4 \times 10^4$	$8{\cdot}8 \times 10^4$

The accepted order for carbon nucleophilicity is $CN^- > I^- > SCN^- > N_3^- > Br^- > Cl^- > F^-$, but this is only true for "protic solvated" anions.[24,79] This series is a function of solvation rather than of size, polarisability, or ability to form bonds at large separations of reactants.[24,77] Dipolar aprotic solvents exert a "levelling effect" on this series of nucleophiles, in that small, slightly polarisable anions are most activated by the change from protic to dipolar aprotic solvent.[24] Protic solvents differentiate the nucleophilicity and level the basicity of anions towards carbon and hydrogen.[80] It appears that the complex $[Y \cdots R \cdots Cl]^-$ in the transition state is more solvated because of hydrogen bonding than is $[Y \cdots R \cdots I]^-$ in protic solvents. The reverse is true in dipolar aprotic solvents.[24]

Anionic reactions are much faster in dipolar aprotic solvents, but positions of equilibria, which are thermodynamically controlled, are similar in protic and in dipolar aprotic solvents, unless the displacing and the displaced groups have very different polarisabilities and sizes or are of different charge types.[77,80] Thus halide ion–alkyl halide exchanges have comparable equilibrium constants in protic and in dipolar aprotic solvents,[80] but the equilibrium $RX + R_2S \rightleftharpoons R_3SX$ lies much further to the left in dipolar aprotic solvents than in protic solvents of the same dielectric constant.[9]

Protic molecules added in concentrations slightly greater than an anionic reactant do not sharply lower rates of reaction in acetone,[81,82] dimethyl-

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[78] Hughes ad Whittingham, *J.*, 1960, 806.
[79] Winstein, Savedoff, Smith, Stevens, and Gall, *Tetrahedron Letters*, 1960, No. 9, 24.
[80] Parker, *Proc. Chem. Soc.*, 1961, 371.
[81] Cavell and Speed, *J.*, 1960, 1453.
[82] Le Roux and Sugden, *J.*, 1939, 1279.

formamide,[1] dimethyl sulphoxide,[67,70] or acetonitrile.[74] The solvent molecules, as well as the reactant anions, are hydrogen-acceptors and, being much more numerous than the anions, effectively compete for the added protic molecules. Protic additives exert a rate-diminishing influence which increases with their increasing hydrogen-donor ability.[74,83,84]

TABLE 6. *Compounds synthesised with advantage in dipolar aprotic solvents.*

Solvents are denoted: DMF = $Me_2N\cdot CHO$; DMAC = Me_2NAc; DMSO = Me_2SO; Sn = sulpholane.

Reaction: $RX + CN^- \rightarrow RCN + X^-$

RCN	X	Solvent	Reference
Primary and secondary alkyl cyanides and dinitriles	Hal, $Me\cdot SO_3$	DMF, DMAC, DMSO, Sn	111–115, 24, 6–1, 6–2
Aromatic nitriles	Br	DMF, 1-methylpyrrolidone	89, 90
Cyanodithioformate	Addition to CS_2	DMF	6–3
"Nylon"	Addition to RNCO	DMF, DMAC, $(EtO\cdot CH_2\cdot CH_2)_2O$	110

Reaction: $RX + NO_2^- \rightarrow RNO_2 + X^-$

RNO_2	X	Solvent	Reference
Primary and secondary nitroparaffins	Hal	DMF, DMSO	116, 117, 6–4, 6–5, 6–6
Primary and secondary dinitroparaffins	Br	DMF	116, 6–7
Nitroquinones	Cl	DMF	6–8
β-Nitro-ketones	Hal	DMF	6-9
Cycloalkyl nitrites	Br, I	DMF, DMSO	123
α-Nitro-esters	Br	DMF	6–10, 6–11

Reaction: $RX + R'_2N^- \rightarrow NRR'_2 + X^-$

NRR'_2	X	Solvent	Reference
Phthalic acid derivatives	Hal	DMF, DMAC	2, 119, 120,

References in addition to those cited also in the text:
6-1 Lawton and McRichtie, *J. Org. Chem.*, 1959, **24**, 26.
6-2 Cahana, Schmidt, and Shah, *J. Org. Chem.*, 1959, **24**, 557.
6-3 Bahr and Schleitzer, *Chem. Ber.*, 1955, **88**, 1771.
6-4 Kornblum, Blackwood, and Mooberry, *J. Amer. Chem. Soc.*, 1956, **78**, 1501.
6-5 Kornblum and Blackwood, U.S.P. 2,791,694/1956.
6-6 White and Considine, *J. Amer. Chem. Soc.*, 1958, **80**, 626.
6-7 Stille and Vessel, *J. Org. Chem.*, 1960, **25**, 478.
6-8 Belshaw, Howard, and Irving, U.S.P. 2,587,093/1952.
6-9 Fusco and Rossi, *Chem. and Ind.*, 1957, 1650.
6-10 Kornblum and Blackwood, *Org. Synth.*, 1957, **37**, 44.
6-11 Kornblum and Weaver, *J. Amer. Chem. Soc.*, 1958, **80**, 4333.

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[83] Leary and Kahn, *J. Amer. Chem. Soc.*, 1959, **81**, 4173.
[84] Pocker, *J.*, 1959, 1179.

TABLE 6.—*continued*

Reaction: $RX + R'_2N^- \rightarrow NRR'_2 + X^-$

NRR'_2	X	Solvent	Reference
(Gabriel synthesis)			6–12, 6–13, 6–14, 6–15
10-Propylphenothiazine	Br	DMF	6–16
5-Arylalkylidene-3-isobutylthiazolidine-2,4-diones	Br, I	DMF	6–14, 6–17
N-Alkylpurines	Hal	DMF	6–18
N-Alkylurethanes	Br	DMF	6–19
N-Alkylnaphthalimides	Hal	DMF	6–20

Reaction: $R'X + R_3C^- \rightarrow CR_3R' + X^-$

CR_3R'	X	Solvent	Reference
Alkynes	Br	Xylene–DMF, DMAC, $2PO(NMe_2)_3S$	93
14-Hydroxy-18,19-bisnorprogesterone	I	DMF	94
α-Alkylacetoacetates	Hal	DMSO, $(EtO{\cdot}CH_2{\cdot}CH_2)_2O$, *NN*-disubst. amides, *N*-oxides, *P*-oxides	91, 92
(±)-Baikiain	Cl	DMSO–C_6H_6	95
Acylbenzenes	Br	$(EtO{\cdot}CH_2{\cdot}CH_2)_2O$, $HO{\cdot}CH_2{\cdot}CH_2{\cdot}OH$	97
Et_2 malonate derivatives	Br	DMF	6–18

Reaction: $RX + R'O^- \rightarrow ROR' + X^-$

ROR′	X	Solvent	Reference
Alditol ethers	Hal	DMF	6–21, 6–22
Aldose benzoates	Tosylate	DMF	6–23
Alkyl glycosides	Hal	DMF	122
α-Alkoxy-γ-lactones	Hal	DMF	6–24
Alkylcelluloses	I	DMF	6–25
Benzyl esters	Cl	DMF	6–26
Di-(2-hydroxethyl) terephthalate	Addition to ethylene oxide	DMF	6–27

6-12 Donahoe, Seiwald, Neumann, and Kimura, *J. Org. Chem.*, 1957, **22**, 68.
6-13 Billman and Cash, *J. Amer. Chem. Soc.*, 1954, **76**, 1944.
6-14 Lo and Shropshire, *J. Org. Chem.*, 1957, **22**, 999.
6-15 Gabriel, *Ber.*, 1908, **41**, 1127.
6-16 Zaugg, Swett, and Stone, *J. Org. Chem.*, 1958, **23**, 1389.
6-17 Lo, Shropshire, and Croxall, *J. Amer. Chem. Soc.*, 1953, **75**, 4845.
6-18 Schudy and Collins, *J. Org. Chem.*, 1959, **24**, 556.
6-19 Dannley and Sukin, *J. Org. Chem.*, 1957, **22**, 268.
6-20 Devereux and Donahoe, *J. Org. Chem.*, 1960, **25**, 457.
6-21 Wolfrom, Juliano, Toy, and Chaney, *J. Amer. Chem. Soc.*, 1959, **81**, 1446.
6-22 Segaller, *J.*, 1914, **105**, 113.
6-23 Reist, Goodman, and Baker, *J. Amer. Chem. Soc.*, 1958, **80**, 5775.
6-24 Stacy, Cleary and Cortatouski, *J. Org. Chem.*, 1957, **22**, 765.
6-25 Barth and Timell, *J. Amer. Chem. Soc.*, 1958, **80**, 6320.
6-26 Fekekte, U.S.P. 2,830,078/1958.
6-27 Kolb, U.S.P. 2,901,505/1959.

TABLE 6.—*continued*

Reaction: $RX + R'O^- \rightarrow ROR' + X^-$

ROR′	X	Solvent	Reference
Triscarbamates	Addition of cellulose to alkyl isocyanates	DMF	6–28

Reaction: $RX + R'S^- \rightarrow RSR' + X^-$

RSR′	X	Solvent	Reference
Alkylthiopurines	Cl	DMF	121
4,7-Dimercapto-1-methylimidazo[4,5-*d*] pyridazine	Cl	DMF	6–29
Isothiouronium 2-halogenoacetamidates and 2-halogenoacetates	Hal	DMF, $COMe_2$	6–30, 6–31
Tetrahydrothienyl	Cl	DMF	6–32
Vinyl sulphides	Addition of $R'S^-$ to acetylenes	DMF	6–33

Reaction: $RX + Hal^- \rightarrow RHal + X^-$

RHal	X	Solvent	Reference
Alkyl and aryl halides and *ψ*-halides	Hal	Cf. ref. 5	1, 24
Aromatic fluoro-nitro-compounds	Cl	DMF, DMSO, MeCN	87
2-Fluoropyridines	Cl	DMF, DMSO	6–34
Aromatic iodo-nitro-compounds	Cl	DMF, DMSO	6–43
Aromatic bromo-nitro-compounds	I	DMF, $COMe_2$	9
Steroids halides	Tosylate	DMF	6–35
SF_4	Cl	MeCN, Sn, PhCN	88, 6–36
Fluoro-olefins	Cl	$NH_2{\cdot}CHO$, $COMe_2$	69, 107
$CF_3{\cdot}SCl$	Cl	Sn, MeCN	106, 6–37
Polymers	Addition of Cl^- to acrylonitrile	DMF	109

6-28 Pikl, U.S.P. 2,668,168/1954.
6-29 Carbon, *J. Amer. Chem. Soc.*, 1958, **80**, 6083.
6-30 Speziale and Hamm, *J. Amer. Chem. Soc.*, 1956, **78**, 5580.
6-31 Speziale, *J. Org. Chem.*, 1958, **23**, 1231.
6-32 *Org. Synth.*, 1956, **36**, 89.
6-33 Truce and Heine, *J. Amer. Chem. Soc.*, 1959, **81**, 592.
6-34 Finger and Starr, *J. Amer. Chem. Soc.*, 1959, **81**, 2674.
6-35 Blickenstaff and Chang, *J. Amer. Chem. Soc.*, 1958, **80**, 2726.
6-36 Tullock, Fawcett, Smith, and Coffman, *J. Amer. Chem. Soc.*, 1960, **82**, 539.
6-37 Sheppard and Harris, *J. Amer. Chem. Soc.*, 1960, **82**, 5106.

TABLE 6.—*continued*

Miscellaneous reactions:

Compound prepared	X	Solvent	Reference
Alkyl and aryl nitrates	Halogen	MeCN	6–38, 21
Alkyl isocyanates	Cl	DMF, DMAC	6–39
Phosphonitrilic isothiocyanates	Cl	DMF, DMAC, SO_2, $COMe_2$, RCN	6–40
Addition to fluoro-olefins	—	DMF	6–41
5-Substd tetrazoles	Addition of N_3^- to nitriles	DMF, DMSO	6–42

6-38 Ferris, McLean, Marks, and Emmons, *J. Amer. Chem. Soc.*, 1953, **75**, 4079.
6-39 Himel and Richards, U.S.P. 2,866,801/1958.
6-40 Tesi, Otto, Sherif, and Audrieth, *J. Amer. Chem. Soc.*, 1960, **82**, 528.
6-41 England, Melby, Dietrich, and Sindsey, *J. Amer. Chem. Soc.*, 1960, **82**, 5116.
6-42 Finnegan, Henry, and Sofquist, *J. Amer. Chem. Soc.*, 1958, **80**, 3908.
6-43 Bunnett and Connor, *J. Org. Chem.*, 1958, **23**, 305; *Org. Synth.*, 1960, **40**, 34.

7. Reactions of anions and application to synthesis

Reactions for which dipolar aprotic solvents have been reported to give higher yields and require shorter reaction times than conventional solvents are illustrated in Table 6. In each case one of the reactants is an anion and the reactions are probably bimolecular in mechanism. The solvent effect must be largely due to the greater reactivity of anions poorly solvated relative to the transition states of their reactions, in dipolar aprotic solvents; but there are also other advantages in the use of such solvents. Most organic compounds, except hydrocarbons and related non-polar species, are soluble in dipolar aprotic solvents, as are many electrolytes. Those dipolar aprotic solvents which solvate cations efficiently are completely miscible with water, which is an advantage when water-insoluble products are to be isolated. Dimethyl-formamide and -acetamide can be recovered from aqueous solution by distillation, since they do not form azeotropes.[2] Higher reaction temperatures (150—200°) are possible, since the highly associated solvents have an extensive liquid range.

Solvolysis of reactants by dipolar aprotic solvents is slower than by water or alcohols.[24] S_N1 ionisation in dipolar aprotic solvents is not common because both ionised groups are weakly solvated, the anion because it cannot form a hydrogen bond with the solvent, the cation (carbonium ion) because it has a well-shielded charge. An S_N1-like process is proposed for chloride exchange of platinum(II) complexes in dimethyl sulphoxide, nitromethane, acetonitrile, dimethylformamide, acetone, and ethanol[85] and triphenylmethyl chloride is appreciably ionised in sulphur dioxide,[86] which solvates cations efficiently, and according to Pocker[86] anions also.

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[85] Pearson, Gray, and Basolo, *J. Amer. Chem. Soc.*, 1960, **82**, 787.
[86] Pocker, *Proc. Chem. Soc.*, 1959, 386.

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Why sulphur dioxide solvates efficiently is not made clear and is unexpected since it cannot form hydrogen bonds with anions. The ionising power of protic and dipolar aprotic solvents has been discussed by Smith *et al.*[47]

The best sources of anions for reaction in dipolar aprotic solvents seem to be lithium or tetra-alkylammonium salts since these are most soluble. The latter salts (R_4NX) have the advantage that they often can be prepared *in situ*. Well-stirred, finely powdered suspensions of dry sodium or potassium salts are satisfactory sources of nucleophiles in the synthesis of aryl fluorides in dimethylformamide and dimethyl sulphoxide[87] and of sulphur tetrafluoride in acetonitrile.[88] When a cation forms a complex with the solvent, large amounts of the accompanying anion can be obtained in solution, as with silver salts in acetonitrile, and cuprous salts in dimethylformamide[89] or 1-methylpyrrolidone.[90]

Small amounts of water do not greatly affect the aprotic properties of dipolar aprotic solvents, but traces of acid or nucleophilic impurities (*e.g.*, dimethyl sulphide in dimethyl sulphoxide, dimethylamine in dimethylformamide) should be removed by distillation.[24] Dipolar aprotic solvents are readily purified by passage through molecular sieves.[13,47,67,77]

Some reactions of Table 6 deserve more detailed discussion.

(a) *Alkylation of Carbanions:* $R_3C^- + R'X \rightarrow CR_3R' + X^-$.—A striking increase of rate and yield in the alkylation of enolates,[91,92] acetylides,[93] and other carbanions[94,95] takes place when some dipolar aprotic solvents are added to an inert solvent such as benzene, xylene, dioxan or tetrahydrofuran. Zaugg and his co-workers[16,91] suggest that the additives

$$^-CHR{\cdot}CO_2Et + R'X \rightarrow CHRR'{\cdot}CO_2Et + X^-$$

break up ionic aggregates, which form in solvents of low dielectric constant, releasing very slightly solvated, reactive anions. Only solvents that solvate cations well (*i.e.*, molecules with regions of high π-electron density, preferably on oxygen) are suitable additives,[16] and protic solvents protonate carbanions, so are not satisfactory. Dimethyl sulphoxide, tertiary amines, and the covalent phosphorus, sulphur, and nitrogen oxides were the best additives of those studied.[91] Some rate measurements have been reported.[96]

Dipolar aprotic solvents need not be merely additives for alkylations. Thus enol anions are alkylated smoothly in mono- and di-ethylene glycol,[97]

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[87] Finger and Kruse, *J. Amer. Chem. Soc.*, 1956, **78**, 6034.

[88] Tullock, Smith, Muetterties, Hasek, Fawcett, Engelhardt, and Coffman, *J. Amer. Chem. Soc.*, 1959, **81**, 3165.

[89] Friedman and Schechter, *J. Org. Chem.*, 1961, **26**, 2522.

[90] Newman and Boden, *J. Org. Chem.*, 1961, **26**, 2525.

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

[92] Marshall and Cannon, *J. Org. Chem.*, 1956, **21**, 245.

[93] Rutledge, *J. Org. Chem.*, 1959, **24**, 840.

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

[95] Burgstahler and Aiman, *J. Org. Chem.*, 1960, **25**, 489.

[96] Zaugg, *J. Amer. Chem. Soc.*, 1961, **83**, 837.

[97] Zook and Russ, *J. Amer. Chem. Soc.*, 1960, **82**, 1258.

and much more rapidly in dimethylformamide and diemthyl sulphoxide than in benzene,[96] presumably because in the solvents of high dielectric constant ion pairs are not formed and carbanions, although stable, are poorly solvated (*i.e.*, active). The following reaction is 75% complete after 3 minutes in diethylene glycol dimethyl ether, whereas in ether this requires 234 hours:[97]

$$\mathrm{Et{\cdot}CHNa{\cdot}COPh + EtBr \rightarrow CHEt_2{\cdot}COPh + NaBr}$$

(b) *Dehydrohalogenation:* $\mathrm{B\colon + R{\cdot}CH_2{\cdot}CH_2X \rightleftharpoons R{\cdot}CH{:}CH_2 + BH^+ + X^-}$.—As already discussed, halide ions in dipolar aprotic solvents are both strong bases and powerful nucleophiles, and many dipolar aprotic solvents (*e.g.*, dimethylformamide and dimethyl sulphoxide) solvate cations efficiently and readily act as hydrogen acceptors. A basic halide ion assists elimination by an *E*2 mechanism, and formation of hydrogen-bonded species such as $\mathrm{HHal_2^-}$, $\mathrm{(DMF)_2H^+}$ and (DMF)HHal (where DMF = dimethylformamide) in, for example, dimethylformamide, deactivates the proton for back addition to the product olefin. It is not surprising, therefore, that halide ions in dimethylformamide, dimethyl sulphoxide, and acetone are such good dehydrohalogenating agents.

Halide exchanges are rapid in dipolar aprotic solvents.[24] The resulting Walden inversion may give a more favourable orientation[98] of X and H, as is required in some cyclic structures for elimination of HX. It is clear that the basicity and the nucleophilicity of halide ions in dipolar aprotic solvents together account for their ability to act as dehydrohalogenating agents. Some applications of this property are the synthesis of cortisone acetate[99] and corticosterone acetate[100] which were prepared by dehydrochlorination with lithium chloride in dimethylformamide. A solution of lithium chloride in this solvent and formamide (a protic solvent) did not cause dehydrohalogenation.[99] 3α-Acetoxy-20-bromobisnorcholan-22-al has been dehydrobrominated with dimethylformamide and lithium chloride,[101] and 3β-acetoxy-20-bromo-5α-chlorobisnorcholan-22-al is selectively dehydrobrominated by dimethylformamide alone, although with added lithium chloride both hydrogen chloride and hydrogen bromide are eliminated.[102] Other metal halides are effective, and dimethylacetamide is an equally effective solvent.[103] The dehydrohalogenation of 2-chloro-2-methylcyclohexanone by lithium chloride in dimethylformamide has been described in *Organic Syntheses*.[104] Elimination of telomer iodides:

$$\mathrm{C_2F_5{\cdot}CH_2{\cdot}CF_2I \rightarrow C_2F_5{\cdot}CH{=}CF_2 + HI}$$

was clean and gave high yields in dimethylformamide or dimethyl sulphoxide with LiCl, KF, NaBr, ICl, KSH, NaCN, $\mathrm{NaNO_2}$, or NaSPh as

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[98] Winstein, Darwish, and Holness, *J. Amer. Chem. Soc.*, 1956, **78**, 2915.

[99] Hoylsz, *J. Amer. Chem. Soc.*, 1953, **75**, 4432.

[100] Chamberlin, Tristram, Utne, and Chemerda, *J. Org. Chem.*, 1960, **25**, 295.

[101] Pederson, Johnson, Hoylsz, and Ott, *J. Amer. Chem. Soc.*, 1957, **79**, 1115.

[102] Chamberlin, Tristram, Utne, and Chemerda, *J. Amer. Chem. Soc.*, 1957, **79**, 456.

[103] Chemerda, Chamberlin, and Tristram, U.S.P. 2,833,790/1958.

[104] *Org. Synth.*, 1957, **37**, 10.

added base or nucleophile.[105] The halide salts were the most effective additives because they do not react with the product, *i.e.*, do not displace fluoride ion from doubly bonded carbon. Hauptschein and Oesterling[105] discarded the *E*2 mechanism because they believed that halides were not strong bases in the solvents used. The above reaction could, however, proceed by an *E*2 mechanism, by S_N2 displacement of iodide followed by a *cis*-elimination, or by a merged S_N2 elimination like that suggested by Winstein and his co-workers[98] for the reaction of 4-t-butylcyclohexyl toluene-*p*-sulphonate with lithium bromide in acetone.

(c) *Synthesis of Fluoro-compounds:* $RX + F^- \rightarrow RF + X^-$.—Fluoride ion in dipolar aprotic solvents is a powerful nucleophile and a strong base. Eliminations compete with substitution by fluoride ion,[9] except in the synthesis of non-eliminating compounds such as MeF,[9] SF_4,[88] ArF,[87] $CF_2{:}CClCF_3$,[69] and $CF_3{\cdot}SCl$[106] from the appropriate chloride, bromide, iodide, or nitro-compound. Exchanges are sensitive to moisture and do not take place in hydroxylic solvents.[87]

Fluoride ion in formamide is a strong nucleophile[69,107] and metal fluorides are soluble. Although formamide is a protic solvent, hydrogen bonding is less effective than in hydroxylic solvents,[1,24] so that fluoride ion is less solvated, *i.e.*, more reactive, in formamide than in water.

(d) *Anionic Polymerisation.*—Vinyl compounds polymerise in the presence of strong bases (B^-) and chain growth occurs in the absence of proton-donor solvents. The reactions involve anions rather than radicals, and can be described by the sequence:

$$\begin{array}{ll} \text{Initiation:} & B^- + CH_2{=}CHX \rightarrow B{\cdot}CH_2{\cdot}CHX^- \\ \text{Propagation:} & B{\cdot}CH_2{\cdot}CHX^- + CH_2{\cdot}CHX \rightarrow B{\cdot}CH_2{\cdot}CHX{\cdot}CH_2{\cdot}CHX^- \\ \text{Termination:} & B{\cdot}[CH_2{\cdot}CHX]_n{\cdot}CH_2{\cdot}CHX^- + H^+ \rightarrow B{\cdot}[CH_2{\cdot}CHX]_n{\cdot}CH_2{\cdot}CH_2X \end{array}$$

It is not surprising that dipolar aprotic solvents are the best media for such reactions.[108] They are not proton donors, reactants and products are soluble, the propagation step is rapid because the carbanion is very reactive (being poorly solvated and not in an ion pair with the cation), and the common initiators [chloride and cyanide ion (B^-)] are very strong bases and nucleophiles in such solvents.

It is well known[108] that acrylonitrile with cyanide ion as initiator readily gives Orlon in dimethylformamide, sulpholane, or α-methoxy-*NN*-dimethylacetamide, and that Dynel is formed from vinyl chloride and acrylonitrile in acetone with chloride or cyanide as initiator. The explanations given above are not so well known.

Bamford, Jenkins, and Johnston[109] found that acrylonitrile polymerised in dimethylformamide when initiated by lithium chloride, nitrate, or

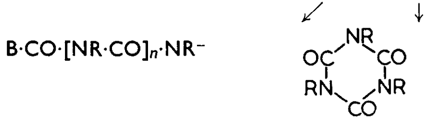
[105] Hauptschein and Oesterling, *J. Amer. Chem. Soc.*, 1960, **82**, 2868.
[106] Tullock, U.S.P. 2,884,453/1959.
[107] Fried and Miller, *J. Amer. Chem. Soc.*, 1959, **81**, 2078.
[108] Hammond and Cram, "Organic Chemistry," McGraw-Hill, New York, 1959.
[109] Bamford, Jenkins, and Johnston, *Proc. Roy. Soc.*, 1957, *A*, **241**, 364.

perchlorate, the efficiency decreasing in that order. Perchloric acid suppressed the polymerisation. The initiators and the anions involved in propagation are strong nucleophiles in dimethylformamide unless protons are present, and this explains their observations.

Nylon-like polymers are best formed at low temperatures. Shashoua, Sweeny, and Tietz[110] proposed the reaction scheme:

Initiation: $RNCO + B^- \rightarrow {}^-NR{\cdot}CO{\cdot}B$

Propagation: $B{\cdot}CO{\cdot}NR^- + RNCO \rightarrow B{\cdot}CO{\cdot}NR{\cdot}CO{\cdot}NR^-$



Termination: $B{\cdot}CO{\cdot}[NR{\cdot}CO]_n{\cdot}NR^- + H^+ \rightarrow B{\cdot}CO{\cdot}[NR{\cdot}CO]_n{\cdot}NHR$

At low temperatures (−50°) the required polymer is formed, at higher temperatures only the cyclic trimer. Dimethylformamide and its mixtures with dimethylacetamide and diethylene glycol dimethyl ether, with sodium cyanide or naphthalide as initiator, gave high yields of the polymer.[110] In these solvents, low temperatures could be used, presumably because of the high nucleophilicity of the initiators and of the intermediate $B{\cdot}CO{\cdot}NR^-$. As might be expected, formamide, a protic solvent, inhibited polymerisation, and acids terminated it.

(e) *Nitrile Synthesis:* $RX + CN^- \rightarrow RCN + X^-$.—Cyanide ion reacts $> 5 \times 10^5$ faster with methyl iodide in dimethylformamide than in water.[24] Primary and secondary alkyl halides[111] or methanesulphonates,[112] and presumably toluene-*p*-sulphonates, react rapidly and cleanly with alkali-metal cyanides in dimethyl sulphoxide,[113,114] dimethyl-formamide[113] and -acetamide,[115] sulpholane,[111] and dimethylsulpholane[111] to give nitriles in 60—90% yield. No isocyanide is formed.[111] Even neopentyl and neophyl halides react without rearrangement, but t-butyl chloride gives only isobutene,[111] emphasising the extreme reluctance of t-butyl compounds to take part in S_N2 reactions.

Sodium cyanide is preferred to potassium cyanide, because it is more soluble, and dimethyl sulphoxide dissolves more sodium cyanide than other dipolar aprotic solvents.[111] However, suspensions of alkali-metal cyanides in less ionising dipolar aprotic solvents (*e.g.*, dimethylformamide) give good yields.[112] Aromatic nitriles can be prepared in high yield from the bromo-analogue by using cuprous cyanide in dimethylformamide[89] or in 1-methylpyrrolidone[90] as the source of soluble cyanide ion.

[110] Shashoua, Sweeny, and Tietz, *J. Amer. Chem. Soc.*, 1960, **82**, 867.
[111] Friedman and Schechter, *J. Org. Chem.*, 1960, **25**, 857.
[112] Newman and Otsuka, *J. Org. Chem.*, 1958, **23**, 797.
[113] Cava, Little, and Napier, *J. Amer. Chem. Soc.*, 1958, **80**, 2260.
[114] Smiley and Arnold, *J. Org. Chem.*, 1960, **25**, 257.
[115] Copelin, U.S.P. 2,715,137/1955.

Synthesis of Nitro-compounds: $RX + NO_2^- \rightarrow RNO_2 + X^-$.—Kornblum and his co-workers[116] found that nitrite ion and 1-iodo-octane in dimethylformamide gave 57% yield of 1-nitro-octane after 2·5 hours at room temperature, but in ethanol the yield was only 39%, with 5% of iodo-octane still unchanged after 108 hours.[116] To their surprise[117] phloroglucinol (a strongly hydrogen-bonding additive) decreased the rate considerably, and in some cases completely suppressed the reaction. Rates in dimethyl sulphoxide and in nitromethane were similar to those in dimethylformamide, and are measurable at –20°.[116] The products are nitro-compounds rather than nitrates.[116]

Since nitrite ion in dipolar aprotic solvents is a strong base, labile hydrogen atoms may be extracted from the reactants, as in the following reaction:[118]

$$Ph\cdot CH_2\cdot NO_2 + NO_2^- \longrightarrow {}^-CHPh\cdot NO_2 + HNO_2 \rightarrow Ph\cdot CO_2H$$

t-Butyl compounds give isobutene.[116]

Lithium nitrite is the most soluble alkali-metal nitrite, but sodium nitrite is soluble in dimethyl sulphoxide, and is more soluble than potassium nitrite in dimethylformamide. Yields in the former are slightly lower than in the latter solvent.[117]

Some highly explosive nitro- and dinitro-alkanes, as well as nitroethylene, could no doubt be synthesised by nitrite–halide exchange. There seems no reason why the S_NAr reactions should not take place readily in dimethyl sulphoxide or dimethylformamide:

$$2,4\text{-}(NO_2)_2C_6H_3I + NO_2^- \rightarrow 1,2,4\text{-}(NO_2)_3C_6H_3 + I^-$$

(f) *Halogen Exchanges*: $RX + X'^- \rightleftharpoons RX' + X^-$ or $ArX + X'^- \rightleftharpoons ArX' + X^-$ (where X = F, Cl, Br, I, SCN, or N_3).—S_N2 reactions of methyl iodide with fluoride ion are on the average 10^7 times faster, with chloride ion 10^6 times faster, with bromide and azide ions 5×10^4 times faster, with iodide ion 10^4 times faster, and with thiocyanate ion 10^2 times faster in dipolar aprotic solvents than in water or alcohols.[24] For this reason, and because of favourable solubility factors, halogen exchanges are usually highly successful in dipolar aprotic solvents, provided the reaction is favoured thermodynamically.[80]

Iodide ion is the most solvated halide in dipolar aprotic solvents and is displaced from carbon by all other halides.[80] Alkyl iodides are the most reactive alkyl halides in S_N2 reactions, and are most susceptible to the change from protic to dipolar aprotic solvent,[24] and are thus the best source of alkyl groups for alkylation.

[116] Kornblum, Larson, Blackwood, Mooberry, Oliveto, and Graham, *J. Amer. Chem. Soc.*, 1956, **78**, 1497.

[117] Kornblum and Powers, *J. Org. Chem.*, 1957, **22**, 455.

[118] Kornblum, Blackwood, and Powers, *J. Amer. Chem. Soc.*, 1957, **79**, 2507.

(g) *Phthalimide Synthesis*.—The Gabriel phthalimide synthesis of phthalic acid derivatives in dimethylformamide has been extensively studied[2] since the pioneer work of Sheehan and Bolhofer.[119] The yield of 1,4-diphthalimidobutane, which was used in the preparation of putrescine, prepared from 1,4-dichlorobutane was 88% in dimethylformamide (containing potassium carbonate to form potassium phthalimide), 47% in benzyl alcohol, 51% in ethylene glycol, and 22% in xylene. Lower temperatures could be used with dimethylformamide, and the product was readily isolated by pouring the mixture into water.[120]

(h) *Miscellaneous Syntheses*.—In dimethylformamide containing potassium carbonate 6-mercaptopurine reacts much faster than in aqueous systems with suitable akyl halides; the solvent affords the reactive thioanion.[121] The alkylation occurs at sulphur only, in high yield. Under some conditions, *N*-alkylation of the imidazole ring of purines takes place readily in dipolar aprotic solvents.[121]

Alkyl halides react rapidly and cleanly with the sodium derivative of saccharin in dimethylformamide, to give alkyl derivatives of saccharin.[122] In protic solvents, or solvents of low dielectric constant, yields are poor. A variety of alkyl aryl, dialkyl, and diaryl ethers and sulphides can be synthesised rapidly in high yield in dimethylformamide or dimethyl sulphoxide reactions,[9] $RO^- + R'I \rightarrow ROR'$, and $RS^- + R'I \rightarrow RSR'$.

Cellulose esters of excellent quality are produced in dimethylformamide. One reason, of several postulated, is that this solvent reduces the hydrogen bonding between cellulose chains, permitting more rapid diffusion of the reagents to the reaction site.[123] This conforms with other observations that dimethylformamide is a good hydrogen-acceptor. Dipolar aprotic solvents such as dimethyl-formamide and -acetamide and dimethyl sulphoxide, which are good hydrogen-acceptors, may have applications in the study of other complex hydrogen-bonded systems.

Table 6 contains a by no means exhaustive survey of anion–dipole reactions in dipolar aprotic solvents, but it does indicate how solvation energy can be used to assist a variety of reactions. Explanations have rarely been given in the literature for the solvent effects noted, and it is hoped that the principles of this Review can be applied to many related bimolecular substitution reactions.

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[119] Sheehan and Bolhofer, *J. Amer. Chem. Soc.*, 1950, **72**, 2786.

[120] Vassel, U.S.P. 2,757,198/1956.

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

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

[123] Blume and Swezey, *TAPPI*, 1954, **37**, 481.