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Dipolar Aprotic Solvents in Bimolecular Aromatic Nucleophilic Substitution Reactions¹

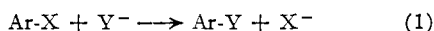
By J. MILLER² AND ALAN J. PARKER

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Rates of reactions of sodium azide, tetraethylammonium azide, potassium thiocyanate, lithium bromide and lithium iodide in some bimolecular aromatic nucleophilic substitutions have been measured in the protic solvents methanol, 10% dioxane-formamide and N-methylformamide, and in the dipolar aprotic solvents dimethyl sulfoxide (DMSO), dimethylformamide (DMF), dimethylacetamide (DMAC), acetone, tetramethylene sulfone, acetonitrile, benzonitrile, nitromethane and nitrobenzene. Rate constants for reactions in dipolar aprotic solvents are 10⁶ times greater than for reactions in protic solvents. Rate constants increase as the hydrogen bonding capacity of the solvent decreases from that of methanol through a series of methyl substituted amides. The solvent effect can be explained if solvation of anions in dipolar aprotic solvents is the reverse of that accepted for hydroxylic (protic) solvents; *i.e.*, trans. state⁻, picrate⁻ > I⁻ > SCN⁻ > Br⁻ > N₃⁻, Cl⁻ >> F⁻. The contribution of hydrogen bonding to solvation of small anions in protic solvents, and "steric resistance" to solvation of small anions in dipolar aprotic solvents are discussed. Polarizability and basicity differences of an anion lead to different specific interactions between an anion and the two classes of solvent. The effect on rate in the change—protic to dipolar aprotic solvent—should be general for anion-dipolar molecule reactions passing through a relatively large negatively charged transition state. Solubilities and conductivities in dipolar aprotic solvents are considered in terms of the "reversed" solvation, as are some rates for Finkelstein substitutions. Evidence for the existence and stabilization of an S_NAr intermediate complex is presented.

Introduction

The effect of pure solvents on reaction rates and the solvation of ions in solvents other than water are subjects which have received only limited attention. Studies of ion-dipole reactions, particularly S_NAr reactions^{3,4} (eq. 1) have been confined in general to water and the simpler alcohols, or to mixtures of these with some inert solvent, *e.g.*, dioxane or benzene, where the hydroxylic solvent is still the active solvating medium.



(Ar = a nitro substituted aromatic compound)

Theoretical treatments^{5,6} have been concerned with the variation of dielectric constant (*D*) and lead to a linear relationship in which $d \log k_2/d 1/D$ should be small and positive for reactions like 1.

The qualitative Hughes-Ingold solvent theory⁷ is, however, still the most generally applicable and this predicts that for bimolecular substitutions of type 1 an increase in ion solvating power of the medium should *slightly* retard reaction.

"Ion solvating power" is not determined by dielectric constant alone: the dielectric constant determines the magnitude of forces between well separated ions in solution. Solvation—the specific interaction between solvent molecules and ions—depends on two factors⁸: (1) Solvation increases with increasing dipole moment of the solvent. (2) Solvation decreases with increased shielding of dipole charges in the solvent. We propose 3 as an

(1) (a) Taken in part from A. J. Parker's doctoral thesis, University of Western Australia, May, 1958. (b) To be regarded as "The S_N Mechanism in Aromatic Compounds, Part XXVI," and "Solvation of Ions, Part I." (Part II, *J. Chem. Soc.*, in press).

(2) Department of Chemistry, University of Khartoum, Khartoum, Sudan. Reprints from A. J. P., University College, London, Gower St., W. C. 1, England.

(3) R. Heppollette, I. Lantzke and J. Miller, *Austral. J. Chem.*, **9**, 299 (1955).

(4) J. F. Bunnett and R. J. Morath, *THIS JOURNAL*, **77**, 5051 (1955).

(5) K. J. Laidler, "Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1950.

(6) E. R. Swart and L. J. le Roux, *J. Chem. Soc.*, 406 (1957).

(7) E. D. Hughes and C. K. Ingold, *ibid* 244 (1935).

(8) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953.

extension of 2. (3) Solvation depends on the nature of the atoms carrying the dipole charge in the solvent. The importance of 2 and 3 is shown by water and nitrobenzene. Water solvates ions more than nitrobenzene although molecular dipole moments suggest the reverse.⁸

This work is intended to show that there is a very great difference in "ion solvating power," and a reversal of the normally accepted order of solvation of anions, between the two classes of solvent—protic (alcohols, some amides) and dipolar aprotic⁹ (acetone, dimethylformamide). Rates of aromatic nucleophilic substitution reactions in the solvents methanol, 10% dioxane-formamide, N-methylformamide, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAC), tetramethylene sulfone (sulfolane), acetonitrile, benzonitrile, nitromethane, nitrobenzene, acetone and dimethyl sulfoxide (DMSO), have been determined. Solubility data for methanol and acetone, conductivity, acidity and base strength in the two classes of solvent,¹⁰ and rates of other substitution reactions¹¹⁻¹⁴ can be used to support the conclusions derived.

Results and Discussion

Kinetic data are in Table I and new rate constants in Table III. Features such as incomplete dissociation of reagents^{12,15} are discussed in the Experimental section.

The following points should be noted: (a) Dipolar aprotic solvents are "faster" than protic solvents, and the effect is much greater than predicted by the Hughes-Ingold solvent theory. The theory *is*

(9) Sometimes referred to as electron donor solvents.¹⁰ Many are classed²⁸ as "dissociating solvents."

(10) P. G. Sears, *et al.*, *J. Phys. Chem.*, **59**, 16 (1955); **60**, 1433 (1956); **59**, 373 (1955); *J. Electrochem. Soc.*, **103**, 633 (1956).

(11) P. B. de la Mare, *et al.*, *J. Chem. Soc.*, 3169 (1955).

(12) F. Aziz and E. A. Moelwyn-Hughes, *ibid.*, 2636 (1959).

(13) N. Kornblum, *et al.*, *THIS JOURNAL*, **78**, 1497 (1956).

(14) R. Fuchs and A. Nisbett, *ibid.*, **81**, 2371 (1959).

(15) A. Streitwieser, Jr., *Chem. Revs.*, **56**, 572 (1956). In both DMSO and DMF ions follow the Kohlrausch law of independent migration,¹⁰ and alkali metal halides are strong electrolytes in acetonitrile.¹⁶ It is felt therefore that electrolytes of Table I are effectively dissociated in solvents of dielectric constant >30 at concentrations <1 × 10⁻² M.

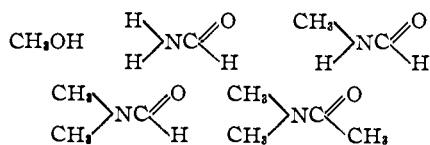
(16) I. M. Kolthoff, *THIS JOURNAL*, **79**, 870 (1957).

TABLE I
 SOLVENT EFFECTS IN S_NAr ION-DIPOLE REACTIONS

Reagents	Solvent	$k_2 \times 10^4$, m. ⁻¹ sec. ⁻¹ T, °C.	E_a , kcal./ mole	log B	k_2 solvent/ k_2 methanol 100°	T°, C.
4-Iodonitrobenzene						
NaN ₃	CH ₃ OH	0.034	27.8	10.9	1
NaN ₃	DMF	117	22.2	11.0	3.4 × 10 ³
NaN ₃	DMSO	1 × 10 ³	3 × 10 ³
		25°	100°			100°
4-Fluoronitrobenzene						
NaN ₃	Methanol	0.00067	2.28	24.1	10.5	1
NaN ₃	10% dioxane-formamide ^c	13.0	5.6
NaN ₃	N-Methylformamide	36.0	15.7
NEt ₄ N ₃	Nitromethane	1.84
NEt ₄ N ₃	Nitrobenzene	16.3
NEt ₄ N ₃	Acetonitrile	5.4
NEt ₄ N ₃	Benzonitrile	12.5
NaN ₃	DMSO	5.68
NaN ₃	DMF	16.3	11,100	19.3	11.4	4.9 × 10 ³
NEt ₄ N ₃	DMAC	59.0
NEt ₄ N ₃	Acetone	>48.0°
NaOPh ^a	Methanol	34.7	21.6	10.2	1
NaOPh ^a	Ethanol	31.6	19.6	9.0	0.91
NaOPh ^a	Isopropyl alcohol	26.9	18.3	8.2	0.71
		59.8°	100°			100°
1-Iodo-2,4-dinitrobenzene						
KSCN ^b	Methanol	1.45	33.0	20.0	9.3	1
KSCN	Nitromethane	402	12.2
KSCN	Acetonitrile	31.5
KSCN	DMSO	21.2
KSCN	Sulfolane	54.0
KSCN	DMF	78.2	1,900	19.8	10.9	58.0
KSCN	Acetone ^d	420	12,000	18.2	10.1	360
LiBr	Methanol	0.045	1
LiBr	Acetone ^d	930	22.6	11.2	2.07 × 10 ⁴
			100°			(100°)
1-Bromo-2,4-dinitrobenzene						
KI	Methanol	0.15	24.9	9.8	1
LiI	Acetone ^d	252	24.0	11.8	1680
LiI	Methanol	0.16	1

^a E. Della, Hons. Thesis, University of Western Australia, 1957. ^b J. Miller, A. J. Parker and B. A. Bolto, THIS JOURNAL, 79, 93 (1957). ^c Observed k_2 is a minimum value, should be divided by α for NEt₄N₃ in acetone at 25° (see text). ^d Observed k_2 (but not Arrhenius parameters) has been recalculated to allow for incomplete dissociation in acetone. ^e Dioxane is needed to dissolve 4-fluoronitrobenzene. This amount of dioxane does not affect rates of S_NAr reactions in protic solvents; cf. ref. 1a.

applicable to reactions *within* a series of protic or dipolar aprotic solvents of very different structures and dielectric constants. (b) Reactions of thiocyanate and iodide ions are less sensitive to solvent change than reactions of the smaller and less polarizable azide or bromide ions. (c) In the series of methyl substituted formamides and methanol, *i.e.*



the hydrogen bonding capacity of the solvent decreases as shown. The rate constants (k_2) for the 4-fluoronitrobenzene-azide exchange increase correspondingly. A less gross but comparable effect is observed between nitromethane which can hydrogen bond *via* the *aci* form, and nitrobenzene which

cannot. An even smaller difference in the expected direction exists between acetonitrile and benzonitrile. (d) There is no apparent correlation between rate and many properties of solvents which might have been expected to influence rate, such as: dielectric constant, dipole moment, polarizability, viscosity, molecular weight, polarity and solvent association. (e) A decreased energy of activation is responsible in many cases for the increase in rate in the change protic-dipolar aprotic solvent.

Additional information not conveniently summarized by Table I is: (f) Reactions of sodium azide in DMF (and the other dipolar aprotic solvents) with 4-fluoronitrobenzene were first order in azide ion, followed second-order kinetics, and proceeded until a mole of azide per mole of 4-fluoronitrobenzene was consumed. A deep red color was produced, but no sodium fluoride was precipitated.¹⁷

(17) A separate experiment showed that sodium fluoride was extremely insoluble in DMF (less than 0.1 g./100 ml. at 25°). Reac-

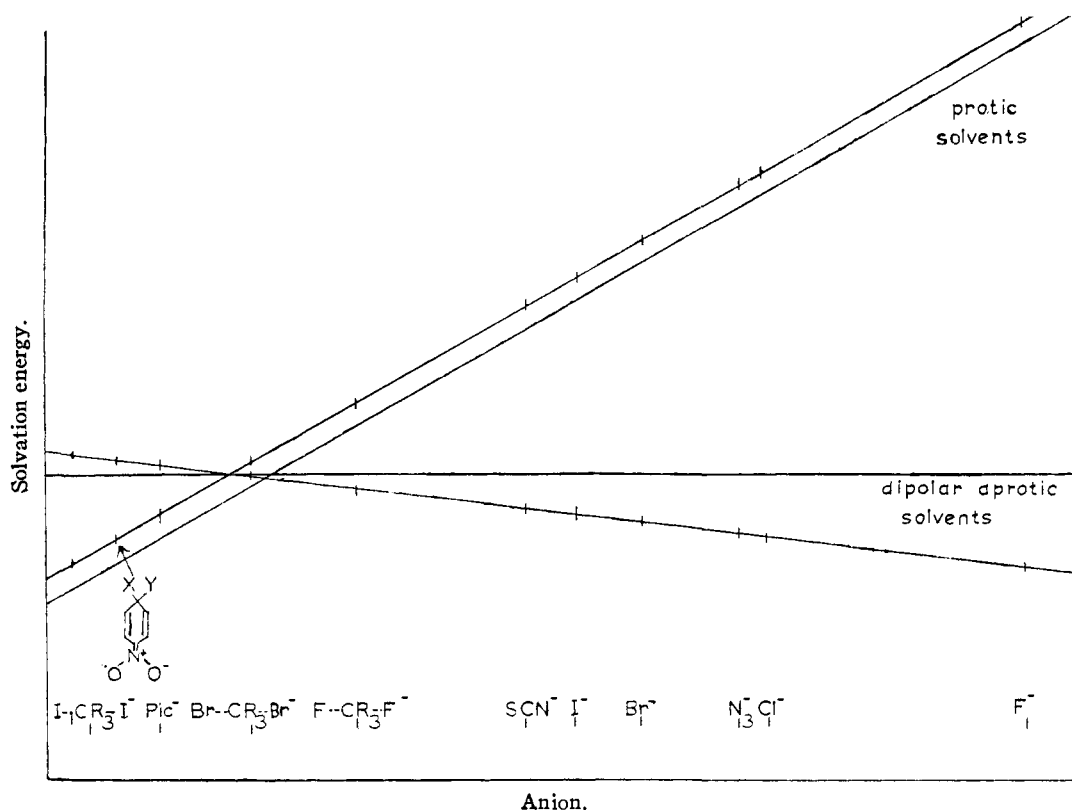
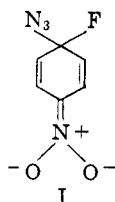


Fig. 1.—Relative solvation of anions in protic and in dipolar aprotic solvents (Pic⁻ is picrate anion). The line showing relative solvation in dipolar aprotic solvents could lie anywhere within the area shown. The results require only that it have less slope than the lines for protic solvents. It may intersect the protic area near where indicated. Our discussion leads us to believe that it may have negative slope; certainly not a positive slope.

Addition of 5 ml. of water per 100 ml. of DMF precipitated sodium fluoride. The solution fluoresced strongly when poured into excess water and 4-nitrophenylazide, m.p. 74°, precipitated in quantitative yield. We therefore conclude that a stable intermediate complex I^{18,19,26} is formed and only liberates fluoride ion when a protic solvent is available to "solvate off" the fluoride ion. Evidence for the formation of this complex is given in the Experimental section. (g) Iodide and thiocyanate ions in acetone and DMF do not displace fluoride from 1-fluoro-2,4-dinitrobenzene. Complex decomposi-



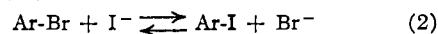
tions occur at elevated temperatures²⁰ but the consumption of nucleophile always corresponded to less than 10% reaction with iodide and 45% with tions carried out in the presence of a weighed amount of sodium fluoride produced no change in weight, showing that the reaction mixture was not supersaturated with sodium fluoride, nor was a colloidal suspension of sodium fluoride formed.

(18) The existence of these complexes has been doubted, or they were thought to be very unstable. The stability of similar complexes of picryl derivatives in protic solvents has been further demonstrated recently (R. C. Farmer, *J. Chem. Soc.*, 3425 (1959)).

(19) (a) J. F. Bunnett and R. Zahler, *Chem. Revs.*, **49**, 273 (1951); (b) J. Miller, *Rev. Pure Appl. Chem. (Australia)*, **1**, 171 (1951).

(20) Similar observations were made by P. Pierens, *et al.*, *Bull. soc. chim. Belg.*, **64**, 717 (1955), and by B. A. Bolto in this Laboratory.

thiocyanate. This occurs despite the fact that thiocyanate reacts readily with 1-iodo-2,4-dinitrobenzene in both solvents. Fluoro aromatics do not react with thiocyanate or iodide ions in methanol, because the bond breaking step is not sufficiently assisted by the nucleophile²¹; in acetone and DMF the lack of solvation of fluoride makes the bond-breaking step even more difficult. (h) The reaction of iodide ion with equimolar 1-bromo-2,4-dinitrobenzene reached equilibrium after 67% forward reaction in methanol, and after 53% forward reaction in acetone.



This could be explained if iodide were more solvated relative to bromide ion in acetone than in methanol. (i) Fluoride ion, in dipolar aprotic solvents, is a surprisingly powerful nucleophile. Even in heterogeneous reactions with potassium fluoride, S_NAr fluoride-halogen exchanges are at least 10³ times faster in dipolar aprotic solvents than in alcohols.²² Our explanation is that fluoride ion is much less solvated (thus more nucleophilic) in the former solvents. Work in progress suggests that fluoride-alkyl halide exchanges (S_N2) are facile in DMF.

The data a to i can be explained if solvation of anions varies as schematically represented in Fig. 1. It is not essential to the explanation that the two lines actually cross. Solvation energies of

(21) A. J. Parker, "Sulfur Nucleophiles in S_NAr Reactions," in "Organic Sulfur Compounds," Pergamon, London, 1960. Methanolysis takes place preferentially.

(22) G. C. Finger and C. W. Kruse, *THIS JOURNAL*, **78**, 6034 (1956).

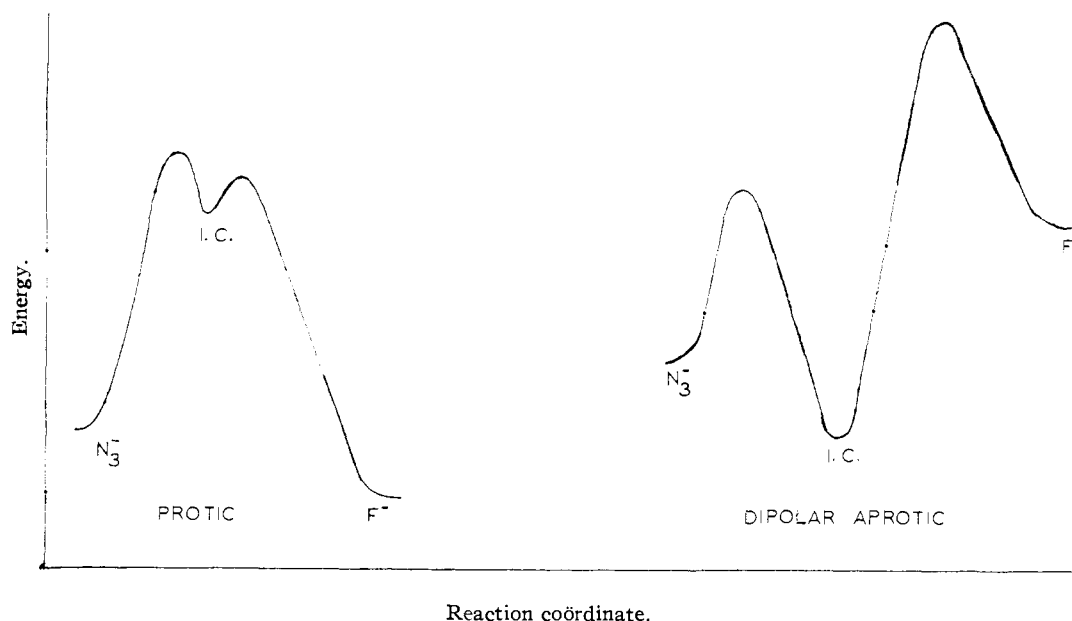


Fig. 2.—Energy-reaction coordinate diagram (ref. 25) for the reaction in protic (methanol) and dipolar aprotic (acetone, DMF) solvents. Energy levels are based on expected relative solvation energies of anionic participants (Fig. 1).

simple ions in dipolar aprotic solvents (*e.g.*, acetonitrile)²³ are lower than in water. We think it likely that some large polarizable anions have greater solvation energies in dipolar aprotic solvents than in protic solvents.

The picrate anion is used as a model for the S_NAr intermediate complex. It has a dispersed negative charge, dipolar nitro groups, a large percentage of cyclohexadienide character and is of comparable size.²⁴ Solvation of the picrate ion should resemble that of the S_NAr intermediate complex, and the structurally similar¹⁹ transition state. The expected positions of some aliphatic S_N2 transition states [X---CR₃---Y]⁻ in Fig. 1 are shown also. We believe that large polarizable anionic transition states are most solvated in dipolar aprotic solvents, so that solvation decreases from [I---CR₃---I]⁻ through structures like [Br---CR₃---Cl]⁻ to [F---CR₃---F]⁻. The consequences of this will be discussed in Part II of this series.¹

The azide ion-4-fluoronitrobenzene reaction (f) can be explained by Fig. 1. Our version of the free energy-reaction coordinate diagram²⁵ for this reaction (Fig. 2) shows the effect of solvation on the stability of the various components of the reaction. It can be seen easily why the reaction is faster (has less activation energy) in dipolar aprotic solvents than in methanol or formamide, why it stops at the intermediate complex²⁶ in DMF (and presumably other dipolar aprotic solvents) and why fluoride is

released from the complex only when a protic solvent is present to solvate it off. The high nucleophilicity of fluoride ion in S_NAr displacement of Cl⁻ and I⁻ in dipolar aprotic solvents²² can be predicted from Figs. 1 and 2.

The iodide ion and thiocyanate ion reactions with 1-fluoro-2,4-dinitrobenzene (g) have been discussed elsewhere,²¹ and can be explained if solvation of fluoride and iodide or thiocyanate ions is as represented in Fig. 1. Support for the relative solvation energies in Fig. 1 can be found in the solubilities of salts in the two classes of solvent (Table II). It is well known also that picrates, perchlorates, iodides and thiocyanates are much more soluble than nitrates or chlorides in acetonitrile. Further work on solubilities is in progress.

TABLE II
SOLUBILITIES OF SALTS IN ACETONE,^a DMF^b
AND METHANOL^a AT 25°

Salt	Methanol	DMF	Acetone	Methanol Acetone	Methanol DMF
KSCN	Soluble	18.2	20.75
NaSCN	40	29.2	8.5	5	1.4
NaN ₃	1	...	<10 ⁻²	>10 ²	..
KI	17.4	>25.0	2.93	6	< 0.7
KBr	2.52	...	0.023	10 ²	..
KCl	0.53	< 0.05	.00087	6 × 10 ²	>10
KF	.19000025	8 × 10 ²	..
K picrate	.27	...	1.080	0.25	..

^a A. Seidell, "Solubilities of Inorganic Compounds," Vol. 1, D. Van Nostrand Co., Inc., New York, N. Y., 1940.
^b "D. M. F. Product Information," du Pont Booklet, 1957.

The methanol/acetone and methanol/DMF ratios of Table II are a direct consequence of the solvation of the anions. The crystal energy term does not enter into the order of these ratios, and the potassium cation is considered throughout. Thus the picrate anion must be more solvated in acetone than in methanol, whereas fluoride ion is considerably less solvated in acetone than in

(23) I. M. Kolthoff and L. F. Coetzee, *ibid.*, **79**, 6110 (1957).

(24) One important difference is that picrate contains a polarizable and nucleophilic oxygen atom where the complex has the groups X and Y. Thus, effects due to direct interaction of polarizable atoms with the solvent cannot be extended from picrate to the intermediate complex.

(25) G. Hammond, *THIS JOURNAL*, **77**, 334 (1955).

(26) R. Bolton, J. Miller and A. J. Parker, *Chem. and Ind.*, 1026 (1960), have demonstrated the stability and >90% formation of this complex by a spectrophotometric examination of the reaction mixture at 397 mμ.

TABLE III

Reaction	Solvent	SNAr REACTIONS OF HALOGENOIDS IN VARIOUS SOLVENTS			
		Measured rate constants ($10^4 k_2$) $M^{-1} \text{sec.}^{-1}$ at ionic strength ^a shown (temp., °C).			
4-I-C ₆ H ₄ NO ₂ + NaN ₃	CH ₃ OH	0.034 (100.3)	0.215 (120.6)	0.65, 0.58 (131.4)	1.12 (138.8)
		1.04 (138.2)			
4-I-C ₆ H ₄ NO ₂ + NaN ₃	DMF	118, 120 (100.1)	8.58 (70.1, 0.04 M)	8.58 (70.1, 0.02 M)	
		31.0, 29.5 (84.2)			
4-F-C ₆ H ₄ NO ₂ + NaN ₃	CH ₃ OH	2.35, 2.40 (100.3)	5.78, 5.72 (110.8)	46.8, 45.7 (138.2)	
4-F-C ₆ H ₄ NO ₂ + NaN ₃	DMF	86.8, 86.8 (41.5)	17.2, 16.4 (25.0)	2.74, 2.74 (9.8)	
4-F-C ₆ H ₄ NO ₂ + NaN ₃	10% dioxane- formamide	13.0 (0.0450 M, 100.0)			
	N-Methyl- formamide	36.0 (0.0450 M, 100.0)	36.1 (0.0570 M, 100.0)		
	DMSO	5.68 (0.043 M, 25.1)			
4-F-C ₆ H ₄ NO ₂ + NEt ₄ N ₃ ^b	Acetone	49.6 (0.0187 M, 25.1)	47.4 (0.0270 M, 25.1)		
	DMF	17.5 (0.044 M, 25.1)			
	Nitromethane	1.84 (0.0240 M, 25.1)			
	Nitrobenzene	16.6 (0.0267 M, 25.1)	16.3 (0.0465 M, 25.1)		
	Acetonitrile	5.4 (0.0385 M, 25.1)			
	Benzonitrile	13.0 (0.0285 M, 25.1)			
	DMAC	59.0 (0.0571 M, 25.1)	59.0 (0.0286 M, 25.1)		
1-I-2,4-(NO ₂) ₂ C ₆ H ₃ + KSCN	Nitromethane	402 (0.0198 M, 100.0)			
	Acetonitrile	31.5 (0.0195 M, 59.8)			
	DMSO	21.2 (0.0198 M, 59.8)			
	Sulfolane	54.0 (0.0200 M, 59.8)			
	Acetone	179, 176 (60.4, 0.044 M)	106 (0.024 M)	74.2 (0.044 M)	(50.6)
		44.9 (0.044 M)	(45.0)	7.5 (0.044 M)	(25.0)
	DMF	186, 186 (69.8)	13.4 (0.044 M)	(41.5)	13.3 (0.024 M, 41.5)
		13.4 (0.044 M) (41.5)			
1-Br-2,4-(NO ₂) ₂ C ₆ H ₃ + LiI	Acetone	82.0, 83.4 (100.0)	(0.054 M)	13.1, 13.0 (80.0)	(0.054 M)
		5.00, 490 (69.9) (0.054 M)			
1-Br-2,4-(NO ₂) ₂ C ₆ H ₃ + KI or LiI*	CH ₃ OH	0.160 (100.5)	0.151 (100.3)	0.853, 0.850,* (120.6)	
		3.88, 3.40, 3.40* (138.8)			
1-F-2,4-(NO ₂) ₂ C ₆ H ₃ + KSCN ^c	Acetone	1.17, 1.15 (25.0)	(0.044 M)	9.20, 9.23 (45.0)	(0.044 M)
		37.0, 33.0 (60.4) (0.044 M)			

^a Given for reactions in acetone, where k_2 depends on concentration of salt, and to show that salts are completely dissociated in other solvents. No buffer salts were added. ^b Rates for formation of complex, estimated after pouring into water (see text). ^c Initial rates; probably not measuring the SNAr displacement reaction (see text).

methanol. Other ratios fit the solvation differences (protic solvent-dipolar aprotic solvent), shown in Fig. 1.

Conductivities in dipolar aprotic solvents¹⁰ confirm some interesting differences in degrees of dissociation, which could have been predicted from Fig. 1. Thus in water, HBr is a stronger acid than picric acid; in DMF and acetonitrile the reverse is true. Bromide salts are more dissociated than iodide in water; in DMF, DMSO and acetonitrile, iodides are more dissociated. It should be noted also that hydroxide ion is 10^7 times more basic in tetramethylene sulfone than in water.²⁷ The similarity to anion nucleophilicity is obvious.

Why should solvation of anions be so different in the two classes of solvent? We feel that the most important factors are: (a) steric resistance to solvation of *small* anions (less important for large anions) by bulky dipoles with charges on large atoms such as carbon, sulfur, nitrogen and oxygen. These atoms have electron shells and adjacent π -electron clouds and cannot fit closely around small anions. When solvation is by the small unshielded proton of protic solvents, steric resistance is negligible, so that small anions are highly solvated by the close fitting protic solvent dipoles. One can imagine small solvent "holes" in the protic solvents

and large solvent holes in the highly associated dipolar aprotic solvents. A small ion in a large hole will be poorly solvated. (b) Specific interactions of highly polarizable (I⁻, SCN⁻) or highly basic (F⁻, N₃⁻) anions with the polarizable solvent molecules and, in particular, the solvent atoms carrying the positive portion of the dipole. These would reduce the free energy of an anion. Iodide ion complexes with acetone,²⁸ acetonitrile and dimethyl sulfoxide are known and the interaction energy has been estimated at 19.3, 16.0 and 13.4 kcal./mole, respectively.²⁹ Thiocyanate solutions in dipolar aprotic solvents slowly develop a yellow color and a yellow solid precipitates after a few weeks. Apparently SCN⁻ interacts strongly with this class of solvent. Anions like picrate, having a polarizable "organic" structure, appear to interact strongly with electron donor solvents.^{10,30} Presumably highly polarizable "organic" transition states (X---CR₃---I)⁻ also interact. Hydrogen bonding in protic solvents, although recognized in the extreme case of HF₂⁻ and HF formation in water, has not been fully appreciated. The results of Table I confirm that hydrogen bonding makes an

(28) K. Shipsey and A. Werner, *J. Chem. Soc.*, 1255 (1913).

(29) E. Kosower, *THIS JOURNAL*, **80**, 3256 (1958); **80**, 3261 (1958).

(30) C. A. Kraus, *Ann. N. Y. Acad. Sci.*, **51**, 789 (1949).

(27) Dr. C. H. Langford, personal communication.

important contribution to the solvation of other small anions in protic solvents.

The role of entropy changes in the two classes of solvent is not clear, but it is significant that dipolar aprotic solvents have a highly ordered structure. Added electrolytes greatly increase this order, as shown by the increased viscosity. Perhaps ions of structure comparable to solvent molecules have considerably less entropy in that solvent than have ions of very different size and structure. The expression "like dissolves like" comes readily to mind.

Experimental

Measurement of Reaction Rates.—The procedure for S_NAr reactions of halogenoids has been outlined previously.³¹ New rate data are given in Table III. Equimolar proportions of nucleophile and aromatic substance were used in all cases. The concentration of both attacking halogenoid and displaced halogenoid was estimated,³² and total halogenoid was constant throughout reaction. Solid barium nitrate was added to the titrant to prevent coprecipitation of silver halogenoids during their estimation. Solutions were not acidified when estimating azide ion. Blank experiments showed that all combinations of halogenoids found in this study could be estimated individually to within 1%, and their concentration was not changed by interactions with glass or the solvents at 100°. Solvolysis of aryl halides does not occur at the temperatures used to measure reaction rates, as shown by blank experiments. A close check on acidity and total halogenoid was made for all reactions.³²

For reactions which came to equilibrium at less than 60% forward reaction, rate constants were calculated as for comparable Finkelstein reactions.¹¹ In all other cases normal second-order expressions were used.

Conductivity measurements have shown that the tetraethylammonium, potassium and sodium salts considered here are effectively dissociated in acetonitrile,³³ methanol,³⁴ DMF¹⁰ and DMSO¹⁰ at the concentrations used (< 0.05 M). Initial rate constants at 0.05 M and 0.025 M NaN₃, NEt₄N₃ or KSCN in DMF, DMAC or sulfolane were identical for the same reaction, as expected if dissociation was complete. As already discussed, dissociation of salts in acetone is not complete and observed rate constants increase with increasing dilution (Table IV). Specific rate constants (*k*₁) are calculated from the expression³⁵

$$k_2 = k_{1\alpha}, \text{ where } \alpha = \text{degree of dissociation}$$

Dissociation constants are known for salts in Grade 1⁸⁶ acetone at 25°, *i.e.*, $K_{KCl}^{36} = 8.02 \times 10^{-3}$, $K_{LiCl}^{36} = 2.85 \times 10^{-3}$, $K_{LiClO_4}^{37} = 2.03 \times 10^{-5}$, $K_{LiClO_4}^{37} = 1.9 \times 10^{-4}$, $K_{LiBr}^{36} = 5.02 \times 10^{-4}$, $K_{KSCN}^{36} = 3.83 \times 10^{-2}$. The dissociation constant of NEt₄N₃ is not available at present.

In Table IV are calculated specific rate constants for the reaction between KSCN and 1-iodo-2,4-dinitrobenzene in Grade 2 acetone. The effect of incomplete dissociation and improved rate constant is apparent.

TABLE IV

INCOMPLETE DISSOCIATION OF KSCN IN ACETONE

Effect on the S_NAr reaction between KSCN and 1-iodo-2,4-dinitrobenzene; observed rate constants, *k*₂, and specific rate constants, *k*₁, at 25°

$k_2 \times 10^3$ (M ⁻¹ sec. ⁻¹)	[KSCN] _{init} (mole/liter)	α_{25}^a	$k_1 \times 10^3$ (M ⁻¹ sec. ⁻¹)
0.680	0.0445	0.254	2.67
.824	.0240	.328	2.52

^a Degree of dissociation calculated from the dissociation constant for KSCN in acetone at 25, $K_{25} = 3.83 \times 10^{-2}$.

(31) J. Miller, A. J. Parker and B. A. Bolto, *THIS JOURNAL*, **79**, 93 (1957).

(32) Except for reactions involving fluoride ion, although in earlier work by this group, displacement of fluoride has been confirmed by direct estimation.

(33) I. M. Kolthoff, *THIS JOURNAL*, **79**, 870 (1957).

(34) A. R. Gordon, *et al.*, *ibid.*, **75**, 2855 (1953).

(35) E. R. Swart and L. J. le Roux, *J. Chem. Soc.*, 1475 (1955).

(36) M. B. Reynolds and C. A. Kraus, *THIS JOURNAL*, **70**, 1709 (1948).

(37) A. Accascina and S. Schiavo, *Ann. chim. Rome*, **43**, 695 (1953).

With NEt₄N₃ in acetone, rate constants at two different ionic strengths were similar (Table III). This suggests that NEt₄N₃ is more dissociated in acetone than is KSCN, although this is surprising.¹⁰ At 100° dissociation constants are not known, but in their absence, observed initial rate constants at a standard ionic strength (0.0445 M) have been multiplied by 3, 4 and 10 in Table I for reactions of LiI, KSCN and LiBr, respectively, in acetone. It is apparent that specific rate constants could be up to 100% in error, but since gross differences in rate (10%) are being compared, this is not as serious to our purpose as it might appear. No correction has been made to the Arrhenius parameters observed for the reactions in acetone. Rate constants for NEt₄N₃ in acetone may be many times greater than the observed values recorded in Table I. We await a value for $K_{NEt_4N_3}$ in acetone.

Equilibrium constants were estimated wherever possible. The lithium iodide-aryl bromide exchange in acetone reached equilibrium at 53% consumption of iodide (and displacement of bromide). This exchange in methanol reached equilibrium at 67% consumption of iodide and displacement of bromide.

Recorded rate constants (Table I) for lithium bromide-aryl iodide exchanges in methanol and acetone are not directly observed values but are calculated from the equilibrium constant and the rate of the back reaction. This assumes that dissociation of LiI and LiBr is the same (which it is not in acetone) but once again results are satisfactory for our discussion.

Reagents.—These were prepared and/or purified by standard procedures. Solvents were dried in different batches with appropriate drying agents,³⁸ fractionated twice (at reduced pressure if b.p. > 100°) and stored in a dry-box. It is not claimed that any solvent was completely free of water. However, the reproducibility of rate constants from different batches of solvent suggest that there is insufficient residual water to have any important effect. The clearly separate character of all batches of all dipolar aprotic from protic solvents also supports our contention. The effect of small quantities of water on solvation in dipolar aprotic solvents is being investigated.

Reaction Products.—Infinity tubes gave the following materials from reactions of:

Sodium Azide with 4-Fluoro- or 4-Iodonitrobenzene.—4-Nitrophenyl azide (m.p. 74°) was obtained in 100% yield from all the dipolar aprotic solvents after pouring into water or alcohol. In methanol or formamide the product was impure (m.p. 65–70°) as a result of decomposition of 4-nitrophenyl azide at > 100°. With the iodo compound in all solvents, iodide production was equivalent to azide consumption.

Potassium Thiocyanate with 1-Iodo- or 1-Bromo-2,4-dinitrobenzene.—2,4-Dinitrophenyl thiocyanate (m.p. 140°) was obtained in 80% yield together with 10% bis-(2,4-dinitrophenyl) sulfide in sulfolane, acetonitrile, acetone or DMF. The latter product is common in such reactions.²¹ KBr was precipitated from the reaction of the bromo compound.⁴⁰ In all cases the amount of SCN⁻ consumed was equivalent to the I⁻ or Br⁻ produced.

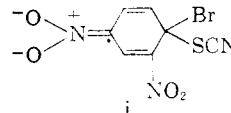
Potassium fluoride with 1-iodo-2,4-dinitrobenzene gave 75% 1-fluoro-2,4-dinitrobenzene (m.p. 25°) in acetone after 24 hours shaking at 100° and removal of acetone.

Potassium thiocyanate with 1-fluoro-2,4-dinitrobenzene in acetone gave 50% bis-(2,4-dinitrophenyl) sulfide⁴¹ (m.p. 194°), unchanged 1-fluoro-2,4-dinitrobenzene (30%) and

(38) A. Weissberger, "Organic Solvents," Interscience Publishers, Inc., New York, N. Y., 1955.

(39) Shown by a separate experiment.

(40) Bromide ion is displaced from the complex i in acetone, and since iodine is less strongly bound to carbon than bromine, and iodide



more solvated in acetone than bromide, iodide is displaced also, but is not precipitated. Unlike reactions of fluoroaromatic substances with thiocyanate, the reaction does not stop at the intermediate complex.

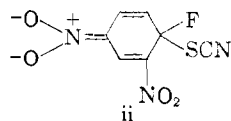
(41) From sealed tube reactions. With open flasks the disulfide was formed (40%) and no monosulfide could be detected.

2,4-dinitrophenyl thiocyanate (8%), when poured into water. After 20% reaction KF began to precipitate.⁴² In methanol the reaction gave 2,4-dinitroanisole and became acidic. No thiocyanate ion was consumed.

Potassium or lithium iodide with 1-bromo-2,4-dinitrobenzene in acetone at 100° gave 1-iodo-2,4-dinitrobenzene (95% with KI,⁴³ 45% with LiI). With LiI, 45% 1-bromodinitrobenzene was recovered unchanged. In methanol at 120°, 1-bromo-2,4-dinitrobenzene and 1-iodo-2,4-dinitrobenzene were recovered in proportions corresponding closely to the equilibrium value (67 and 33%, respectively). It made no difference whether LiI or KI was used.

Potassium or lithium iodide with 1-fluoro-2,4-dinitrobenzene gave a black tar, some hydrogen fluoride and unchanged 1-fluoro-2,4-dinitrobenzene⁴⁴ (80%) when poured into water after heating in acetone at 121° for 24 hours.

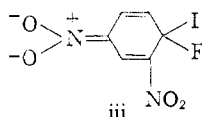
(42) This reaction is not a simple S_NAr displacement. It would not proceed beyond 40% consumption of thiocyanate ion. We assume



that the complex ii is formed, but not in high concentration. Decomposition of the complex via other paths involving displacements from sulfur²¹ accounts for the products and the consumption of SCN⁻.

(43) Precipitation of KBr in acetone drives the equilibrium to the right.

(44) The complex iii is formed in low concentration, apparently



cannot dispose of fluoride in the usual (S_NAr) way, and decomposes slowly by some other (radical?) path at high temperature.

The Existence of an S_NAr Intermediate Complex.—A 0.05 M red solution of sodium azide and 4-fluoronitrobenzene in DMF was warmed at 60° for 1 hour. A yellow homogeneous solution resulted and no sodium fluoride could be seen. The solution absorbed strongly at 397 mμ⁴⁵ although neither 4-nitrophenyl azide (361 mμ) nor 4-nitrofluorobenzene (367 mμ) absorb at this wave length in DMF. In all other dipolar aprotic solvents intense red colors developed, with a transient blue color in acetone.

The following experiments were performed on 50-ml. portions of the reaction mixture: (a) Poured into excess water at 25°⁴⁶; no azide ion was present and pure 4-nitrophenyl azide (100%) was obtained. The solution fluoresced and for a few moments became quite viscous. (b) A little water (1 ml.) was added. Crystals of sodium fluoride appeared on warming. These were insoluble in anhydrous DMF or the original reaction mixture. The experiment was repeated using acetone in place of water, but the solution remained homogeneous. The 397 mμ absorption slowly disappeared when 1 ml. of water was added.⁴⁷ (c) A weighed portion of NaF was added and warmed. It was recovered by filtration without change in weight.⁴⁸ Attempts are now being made to isolate the sodium salt of this complex.

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(45) Measurements made by Mr. R. Bolton.

(46) Azide ion was not consumed by 4-fluoronitrobenzene in 50% aqueous DMF at 25° after 2 hours.

(47) It should be possible to measure the rate of formation and of decomposition of the complex spectrophotometrically.

(48) Sodium fluoride was not present as a colloidal suspension or a supersaturated solution in the reaction mixture.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY, CHICAGO 16, ILL.]

Acylium Ion Formation in the Reactions of Carboxylic Acid Derivatives. II. The Hydrolysis and Oxygen Exchange of Methyl Mesitoate in Sulfuric Acid^{1a}

BY MYRON L. BENDER^{1b,c} HARRY LADENHEIM AND MARK C. CHEN

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The hydrolysis and oxygen exchange of methyl mesitoate-carbonyl-*O*¹⁸ have been studied at 25, 35, 45 and 90°, and at 3.09, 5.78, 9.8 and 11.5 M sulfuric acid. A spectrophotometric method has been developed for the determination of the kinetics of this hydrolytic process. The half-life of the hydrolysis of methyl mesitoate in 11.5 M sulfuric acid at 25° is 9 minutes, utilizing conditions considerably milder than those reported previously for obtaining high yields of mesitoic acid. The kinetic results at the higher acidities agree well with the Hammett-Zucker correlation between logarithm of the rate constant and *H*₀. The enthalpy and entropy of activation of the hydrolytic reaction in 9.8 and 11.5 M sulfuric acid are 28.4 kcal./mole and 17.0 e.u. and 22.5 kcal./mole and 4.1 e.u., respectively. Carbonyl oxygen exchange is absent at 3.09, 5.78 and 11.7 M sulfuric acid. Most significant is the absence of exchange at the lowest acidity where another path, such as a bimolecular mechanism, would offer most competition. The *H*₀ correlation, the entropies of activation and the lack of oxygen exchange indicate that the reaction proceeds by a unimolecular heterolysis, presumably because of particularly favorable conditions of structure and solvent.

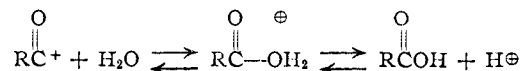
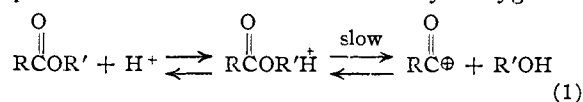
Introduction

The purpose of this continuing study is to provide an insight into the conditions and mechanism of acylium ion formation, using kinetic and oxygen-18 tracer techniques. The plan of the program is given in detail in a previous publication²; briefly, it is to generalize the use of oxygen exchange results as corroborative evidence for various types of hydrolytic reaction mechanisms. In reactions involving acylium ion formation, it is

(1) (a) This research was supported by a grant from the National Science Foundation. (b) Alfred P. Sloan Foundation Research Fellow. (c) Dept. of Chemistry, Northwestern University, Evanston, Ill.

(2) H. Ladenheim and M. L. Bender, *THIS JOURNAL*, **82**, 1895 (1960).

predicted that concurrent carbonyl oxygen ex-



change and hydrolysis will *not* occur, in contrast to the results occurring in reactions involving the formation of a tetrahedral addition intermediate.³ Therefore, in a reaction where an acylium ion path occurs, absence of carbonyl oxygen exchange should serve as a non-kinetic criterion of mechanism.

(3) M. L. Bender, *Chem. Revs.*, **60**, 53 (1960).