Solvation of Ions. XVIII.[1] Protic–Dipolar Aprotic Solvent Effects on the Free Energies, Enthalpies, and Entropies of Activation of an SnAr Reaction

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Abstract: The effects of solvent transfer on free energies, enthalpies, and entropies of activation of an aromatic nucleophilic substitution (SnAr) reaction are examined. Hexamethylphosphoramide is an excellent solvent for SnAr reactions. The enhanced rate of transfer from protic to dipolar aprotic solvents is more a function of decreased enthalpy than that of increased entropy of activation. The transfer of a SnAr transition-state anion from methanol to a dipolar aprotic solvent is usually exothermic by about 5 kcal mol^{-1}, and this exerts a strong influence on the rate of reaction. The enthalpy of transfer of reactant anions is also significant in determining a solvent effect on the rate of SnAr reactions.

In 1961 we first noted the enormous increase in rate when aromatic nucleophilic substitution reactions (eq 1) of azide ion with 4-fluoronitrobenzene were

$$\mathrm{ArF} + \mathrm{N_3^-} \longrightarrow \mathrm{ArN_3} + \mathrm{F^-} \qquad (1)$$
$$\mathrm{Ar} = \text{4-}\mathrm{NO_2C_6H_4}$$

transferred from protic to dipolar aprotic solvents.[3] This and related observations on solvent effects on rates of the general reaction 2 at 25° have been explained

$$\mathrm{Y^-} + \mathrm{RX} \rightleftharpoons \mathrm{YRX^{\ddagger-}} \longrightarrow \mathrm{YR} + \mathrm{X^-} \qquad (2)$$

and analyzed as in eq 3[4] in terms of the solvent activity coefficients, ${}^{s_1}\gamma^{s_2}$ for transfer from solvent s_1 to solvent s_2 of reactant anions Y^-, reactant molecular species RX, and transition-state anions $YRX^{\ddagger-}$. An alternative to eq 3 is to analyze the solvent effect (ΔG_{tr}) on

$$\log k^{s_1}/k^{s_2} = \log {}^{s_1}\gamma^{s_2}{}_{RX} + \log {}^{s_1}\gamma^{s_2}{}_{Y^-} - \log {}^{s_1}\gamma^{s_3}{}_{YRX^{\ddagger-}} \qquad (3)$$

the free energies of transfer of reactants and transition states at 25° from reference solvent s_1 to another solvent s_2 as in (4).

$$\Delta G_{tr}{}^{\ddagger} = \Delta G_{tr}(Y^-) + \Delta G_{tr}(RX) - \Delta G_{tr}(YRX^{\ddagger-}) \qquad (4)$$

The question of solvent effects on rate at temperatures other than 25° and the effect of solvent transfer on the enthalpy and entropy of activation of reaction 2 have received some attention,[3,5] but we know of no systematic investigation which provides information as detailed as that which is available for solvent effects on free energies of activation at 25°. The situation has been clouded by uncertainties about heats of solution of salts in methanol and in dimethylformamide, key examples of protic and dipolar aprotic solvents, respectively. Recent work by Krishnan and Friedman has[6] removed these uncertainties.[1]

In this paper we make a detailed study of the solvent effects on $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ of reaction 1, in a variety of solvents. The treatment is in terms of the popular extrathermodynamic assumptions[7,8] that $\Delta G_{tr}(\mathrm{Ph_4As^+}) = \Delta G_{tr}(\mathrm{Ph_4B^-})$, $\Delta H_{tr}(\mathrm{Ph_4As^+}) = \Delta H_{tr}(\mathrm{Ph_4B^-})$, and $\Delta S_{tr}(\mathrm{Ph_4As^+}) = \Delta S_{tr}(\mathrm{Ph_4B^-})$. The reasons for adopting these assumptions are discussed in parts XVI[8] and XVII.[1]

Experimental Section

Reaction Rates. Conventional methods of measuring and treating rate data were used. Reactions 1 were followed either by titration of N_3^- with standard $AgNO_3$ using reactant concentrations of about 4×10^{-2} *M* NBu_4N_3 and 2×10^{-2} *M* 4-fluoronitrobenzene, or spectrophotometrically by following the increase in absorption at 330 mμ with a Gilford 2400 spectrophotometer. All spectrophotometric measurements were carried out under pseudo-first-order conditions with [NBu_4N_3] about 10^{-2} *M*, except in water where it was 10^{-1} *M*, and [4-fluoronitrobenzene] about 1×10^{-4} *M*. It was assumed that at these concentrations, NBu_4N_3 was a strong electrolyte in all solvents used. Rate constants for reaction 1 are in Table I.

Table I. Rate Constants k (M^{-1} sec^{-1}) for SnAr Reactions (1) of NBu_4N_3 (0.01 *M*) with 4-Fluoronitrobenzene (10^{-4} *M*) at the Temperatures Shown in Parentheses

Solvent[a]	10^3k, M^{-1} sec^{-1}
DMSO	0.57 (27.1);[b,c] 1.62 (34.7); 9.11, 8.90 (53.9); 24.8, 24.6 (65.1)
CH_3CN	0.54 (25.1);[b,c] 0.61 (26.2); 1.53 (33.8); 5.70 (52.7); 6.30[b] (53.0); 7.06, 6.97 (53.9); 19.8, 20.7 (65.2)
TMS	3.32 (32.1), 7.19 (41.0), 13.8 (50.3), 29.7 (59.3)
PC	1.06, 1.00 (32.0); 1.59[b] (36.5); 3.45, 3.79 (44.6); 7.70, 7.61 (53.8); 10.9[b] (60.0); 14.0, 14.5 (65.0)
$MeNO_2$	0.184 (25.1), 0.415 (33.0), 1.06 (45.4), 2.74 (53.4), 6.64 (64.4)
Water[d]	0.0051 (64.0), 0.028 (79.9), 0.185 (101.1)
HMPT	39.2 (16.7); 85.5 (25.8); 181.0 (35.6); 384 (44.3)

[a] DMSO, dimethyl sulfoxide; PC, propylene carbonate; TMS, tetramethylene sulfone; HMPT, hexamethylphosphoramide. [b] Reaction followed by titration of N_3^- with $AgNO_3$; others were followed spectrophotometrically. [c] Reference 3. [d] These reactions were carried out in sealed tubes at an ionic strength of 0.1 *M* and were analyzed spectrophotometrically.

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[1] Part XVII: B. G. Cox and A. J. Parker, *J. Amer. Chem. Soc.*, **95**, 402 (1973).

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[3] J. Miller and A. J. Parker, *J. Amer. Chem. Soc.*, **83**, 117 (1961).

[4] A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).

[5] P. Haberfield, L. Clayman, and J. S. Cooper, *J. Amer. Chem. Soc.*, **91**, 787 (1969).

[6] C. V. Krishnan and H. L. Friedman, *J. Phys. Chem.*, **75**, 3606 (1971).

[7] E. Grunwald, G. Baugham, and G. Kohnstam, *J. Amer. Chem. Soc.*, **82**, 5801 (1960).

[8] R. Alexander, A. J. Parker, J. H. Sharp, and W. E. Waghorne, *ibid.*, **94**, 1148 (1972).

Heats of Solution of 4-Fluoronitrobenzene. Heats of solution of 4-fluoronitrobenzene were obtained by conventional methods of calorimetry, using a Guild solution calorimeter of design essentially as described by Arnett, Bentrude, Burke, and Duggelby.[9] The concentration of 4-fluoronitrobenzene ranged between 5×10^{-3} and 2×10^{-2} *M*. Results are in Table II.

Table II. Heats of Solution (ΔH_s kcal mol^{-1}) in Different Solvents and Enthalpy of Transfer from Methanol ΔH_{tr}(ArF) of 4-Fluoronitrobenzene (ArF) at 23 ± 1°

Solvent[a]	$\Delta H_s(\pm 0.15)$	$\Delta H_{tr}(ArF)(\pm 0.3)$
Cyclohexane	+2.87	+1.8
MeOH	+1.04[b]	0.0
H_2O	+0.88	−0.2
$MeNO_2$	+0.64	−0.4
DMSO	+0.43	−0.6
CH_3CN	+0.41	−0.6
PC	+0.24	−0.8
TMS[c]	+0.03	−1.0
DMF	−0.37[b]	−1.4
DMAC	−0.52	−1.6
HMPT	−2.14	−3.2

[a] Abbreviations as in Table I; DMF is dimethylformamide and DMAC is dimethylacetamide. [b] Reference 5. [c] Measurements in sulfolane were at 30°.

The purification of materials either has been described previously[10] or was accomplished by standard procedures of distillation or recrystallization.

The rate constants log *k*, the free energies $\Delta G^{\neq} = 2.303RT \log (k_BT/h) - 2.303RT \log k$, the enthalpies $\Delta H^{\neq}$, and the entropies $-298\Delta S^{\neq}$ of activation of the SNAr reactions (1) at 25° are recorded in Table III.

Table III. Activation Parameters[a] for the SNAr Reactions (1) in Different Solvents at 25°

Solvent[b]	−Log k[c]	$\Delta G^{\neq}$	$\Delta H^{\neq}$	$-298\Delta S^{\neq}$
DMSO	3.28	21.8	18.7	3.1
CH_3CN	3.26	21.8	17.1	4.7
DMF[b]	2.76	21.1	18.5	2.6
H_2O	7.4	28.1	24.1	4.0
MeOH[b]	7.2	27.5	23.6	3.9
TMS	2.76	21.1	15.9	5.2
PC	3.19	21.7	15.7	6.0
$MeNO_2$	3.74	22.6	18.6	4.0
HMPT	1.10	18.8	14.8	4.0

[a] Values in kcal mol^{-1}. Abbreviations as in Table II. [b] Reference 3. [c] *k* in l. mol^{-1} sec^{-1}.

Discussion

Hexamethylphosphoramide (HMPT) should be noted as an excellent solvent for performing SNAr reactions quickly. It appears to have a very strong dispersion force and/or dipole–dipole interactions with polar and polarizable solutes. Reaction 1 is 50 times faster, the enthalpy of activation is 1 kcal mol^{-1} less, and the heat of solution of 4-fluoronitrobenzene is 1.6 kcal mol^{-1} more exothermic in HMPT than in any other solvent studied by us. As shown in Table IV, the cyclohexadienide like transition-state anion for reaction 1 is very strongly solvated by HMPT.

We have suggested[4] that a decrease in the enthalpy of activation $\Delta H^{\neq}$, rather than an increase in the entropy of activation $\Delta S^{\neq}$, is the major reason for the increased rate of general reaction 2, on transfer from a protic to a dipolar aprotic solvent. This suggestion was made on limited evidence, but the data in Table IV confirm it for reaction 1. Most of $\Delta G^{\neq}{}_{tr}$ is reflected in $\Delta H^{\neq}{}_{tr}$; that is, $-298\Delta S^{\neq}{}_{tr}$ is usually small in Table IV.

Assuming the validity of several extrathermodynamic assumptions for determining single-ion free energies of transfer,[8] it has been shown that large changes in $\Delta G^{\neq}{}_{tr}$ for many reactions (2) are reflected in changes in $\Delta G_{tr}(Y^-)$. Indeed an acceptable extrathermodynamic assumption is that $\Delta G_{tr}(RX) = \Delta G_{tr}(YRX^{\neq -})$, especially for reaction 1,[8] so that even if each of these terms is large, they cancel in eq 4. This is confirmed in Table IV, where $\Delta G_{tr}(RX) - \Delta G_{tr}(YRX^{\neq -})$ is recorded.

Haberfield, *et al.*,[5] feel that this observation on free energies does not extend to enthalpies of transfer from methanol, *i.e.*, that large changes in $\Delta H^{\neq}{}_{tr}$ are not reflected in large changes of $\Delta H_{tr}(N_3^-)$, but rather in changes in the enthalpy of transfer of the transition-state anion $\Delta H_{tr}(\neq^-)$. To test this feeling, one must accept an extrathermodynamic assumption to estimate $\Delta H_{tr}(\neq^-)$ and $\Delta H_{tr}(N_3^-)$. For consistency and for other reasons that need not concern us here, we have chosen the same assumption for free energies and enthalpies of transfer of single ions that $\Delta H_{tr}(Ph_4As^+) = \Delta H_{tr}(Ph_4B^-)$ and $\Delta G_{tr}(Ph_4As^+) = \Delta G_{tr}(Ph_4B^-)$. We have confidence in these assumptions.[1]

According to transition-state theory, $\Delta G^{\neq}{}_{tr}$ and $\Delta H^{\neq}{}_{tr}$ for reaction 1 are given by eq 5 and 6,[4] respectively.

$$\Delta G_{tr}{}^{\neq} = \Delta G_{tr}(\neq^-) - \Delta G_{tr}(N_3^-) - \Delta G_{tr}(ArF) \quad (5)$$

$$\Delta H_{tr}{}^{\neq} = \Delta H_{tr}(\neq^-) - \Delta H_{tr}(N_3^-) - \Delta H_{tr}(ArF) \quad (6)$$

Reaction 1 is analyzed in terms of eq 5 and 6 in Table IV using free energies and enthalpies of transfer of azide ion derived from the Ph_4AsBPh_4 assumption, the enthalpies of transfer of 4-fluoronitrobenzene are from Table II and the activation parameters are recorded in Table III. Values of ΔS_{tr} follow from relationship 7.

$$\Delta G_{tr} = \Delta H_{tr} - T\Delta S_{tr} \quad (7)$$

The free energy differences in Table IV are already understood,[4] and it can now be seen that the *decrease in enthalpy of activation of reaction 1 on transfer from methanol to dipolar aprotic solvents is made up of (a) a strongly exothermic enthalpy of transfer of the transition state anion, i.e., it is well solvated, "enthalpywise," by the dipolar aprotic solvent, (b) an endothermic enthalpy of transfer of azide ions, which however lowers $\Delta H^{\neq}{}_{tr}$ less than does (a), and (c) an exothermic enthalpy of transfer of 4-fluoronitrobenzene which tends to increase $\Delta H^{\neq}{}_{tr}$.* The magnitude of effect a is fairly constant for a variety of dipolar aprotic solvents, *i.e.*, $\Delta H_{tr}(\neq^-)$ is about 5 kcal mol^{-1} exothermic (transfer to HMPT from methanol is an exception, in which $\Delta H_{tr}(\neq^-)$ is exothermic by about 9 kcal mol^{-1}). Clearly the behavior of the free energy terms in eq 5 does not parallel the behavior of the enthalpy terms in eq 6.

It seems that large polarizable transition-state anions such as those used by reaction 1 have enthalpies of transfer from methanol to dipolar aprotic solvents which are substantially exothermic. This enthalpy term will always be an important factor in general equations like (6), especially for transfer to "super polariz-

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(9) E. M. Arnett, W. G. Bentrude, J. J. Burke, and P. McC. Duggelby, *J. Amer. Chem. Soc.*, 87, 1541 (1965).

(10) A. J. Parker and R. Alexander, *ibid.*, 90, 3313 (1968), and references therein.

Table IV. Analysis of Reaction 1 by Eq 5 and 6, Based on the Tetraphenylarsonium–Tetraphenylboride Assumption. Transfer from Methanol to Other Solvents[a]

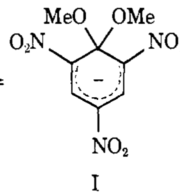
Solvent	$\Delta G^{\ddagger}_{tr}$[d]	$\Delta G_{tr}(N_3^-)$[c]	$\Delta H_{tr}^{\ddagger}$[d]	$\Delta H_{tr}(\ddagger^-)$[f]	$\Delta H_{tr}(N_3^-)$[c]	$\Delta H_{tr}(ArF)$[b]
DMSO	−5.7	+4.2	−4.8	−6.5	−1.0	−0.6
CH_3CN	−5.7	+5.1	−6.5	−5.3[i]	+1.8[j]	−0.6
DMF	−6.4	+6.2	−5.1	−4.5	+2.0	−1.4
H_2O	+0.6	−1.9	+0.5	+0.2	−0.2	−0.1
MeOH	0.0	0.0	0.0	0.0	0.0	0.0
TMS	−6.4	+7.8	−7.7	−5.3	+3.4	−1.0
PC	−5.8	+5.8	−7.9	−4.0	+4.7	−0.8
$MeNO_2$	−5.5	+4.5	−5.0	−4.6[j]	+0.8[j]	−0.4
HMPT	−8.6	+8.2[g]	−8.8	−9.0	+3.0[h]	−3.2

Solvent	$-298\Delta S^{\ddagger}_{tr}$	$-298\Delta S_{tr}(N_3^-)$[i]	$\Delta G_{tr}(\ddagger^-) - \Delta G_{tr}(ArF)$[e]	$\Delta H_{tr}(\ddagger^-) - \Delta H_{tr}(ArF)$[f]	$-298(\Delta S_{tr}(\ddagger^-) - \Delta S_{tr}(ArF)$[i]
DMSO	−0.8	+5.2	−1.5	−5.9	+4.4
CH_3CN	+0.8	+3.8[j]	−0.6	−4.7	+4.6[j]
DMF	−1.3	+4.2	−0.2	−3.1	+2.9
H_2O	+0.1	−1.7	−1.3	+0.3	−1.6
MeOH	0.0	0.0	0.0	0.0	0.0
TMS	+1.3	+4.4	+1.4	−4.3	+5.7
PC	+2.1	+1.1	0.0	−3.2	+3.2
$MeNO_2$	−0.5	+3.7[j]	−1.0	−4.2	+3.2[j]
HMPT	+0.2	+5.2	−0.4	−5.8	+5.3

[a] Values in kcal mol^{-1}. [b] Data from Table II. [c] Calculated from data recorded in ref 1 unless stated otherwise. [d] Data from Table III. [e] Calculated from eq 5. [f] Calculated from eq 6. [g] From data in ref 8. [h] This work using procedures described in ref 1 for other solvents. [i] Calculated from eq 7. [j] Based on the mean value from the ferrocene and negligible E_{lj} assumption (*cf.* ref 1).

able" polar solvents like HMPT. However, the question of whether $\Delta H_{tr}(\ddagger^-)$ is always the major term in the expression corresponding to (6) for the general case of SNAr reactions of anions other than N_3^- will depend very much on the anion. Thus for anions like SCN^-, I^-, and $4\text{-}NO_2C_6H_4S^-$, or for uncharged nucleophiles which do not have large endothermic enthalpies of transfer from methanol to dipolar aprotics, the enthalpy of transfer of the transition state will be the major factor in changing $\Delta H^{\ddagger}$ on solvent transfer; for anions Y^-, like Cl^- and 4-nitrophenoxide which have moderately positive values of $\Delta H_{tr}(Y^-)$, both $\Delta H_{tr}(Y^-)$ and $\Delta H_{tr}(\ddagger^-)$ will be of comparable magnitude; and for SNAr reactions of anions like methoxide ion, which have a very endothermic enthalpy of transfer, $\Delta H_{tr}(Y^-)$ will become the dominant term in the general equation like (6). No matter what the variation in $\Delta H_{tr}(Y^-)$, it seems that, for SNAr reactions, an enthalpy of transfer of the transition-state anion from methanol to dipolar aprotic solvents of about 5 kcal mol^{-1} can be expected. This will always have a rate-enhancing effect on the reaction, for such a solvent transfer, irrespective of the behavior of the reactants.

We use the data of Larson, Amin, and Fendler[11] on the reaction (8) between methoxide ion and 2,4,6-tri-

NaOMe + 2,4,6-$(NO_2)_3C_6H_2OMe$ $\rightleftharpoons$  (8)

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nitroanisole to form the Meisenheimer complex I in DMSO–methanol mixtures to illustrate the above argument. Reaction 8 is thought to closely resemble the hypothetical equilibrium between the same reactants and the transition-state anion for the SNAr exchange of methoxide ion. Larson, Amin, and Fendler[11] studied the enthalpies involved in reaction 8 in DMSO–methanol mixtures. We have extrapolated their data to pure DMSO to derive the numbers given in Table V.

Table V. Enthalpies of Transfer from Methanol to DMSO for Reactions 1 and 8

Solute[a]	OMe^-	TNA	Complex I^-	
ΔH_{tr}, kcal mol^{-1} [b]	+13.7[c]	−1.8[c]	−7.5[c]	
Solute[a]	N_3^-	ArF	$\ddagger^-$	Pic^-
ΔH_{tr}, kcal mol^{-1} [b]	−0.7[d]	−0.6[d]	−6.2[d]	+0.1[c]

[a] Abbreviations: TNA is 2,4,6-trinitroanisole, Ar is 4-nitrophenyl, $\ddagger^-$ is the transition state anion in reaction 1, and Pic^- is the picrate anion. [b] The numbers are based on $\Delta^M H^{DMSO}(Na^+) = 1.6$ (ref 6). [c] Extrapolated from data in ref 11. [d] This work.

The difference of 5.7 kcal mol^{-1} which exists between the heat of transfer from methanol to DMSO of 2,4,6-trinitroanisole and the Meisenheimer complex anion I is very similar to the difference of 5.6 kcal mol^{-1} between 4-fluoronitrobenzene and the transition-state anion of reaction 1. The much greater exothermic behavior of the Meisenheimer complex anion I relative to its structurally related reactant, on protic–dipolar aprotic transfer, is thus very similar to that of the transition-state anion, for reaction 1 relative to 4-fluoronitrobenzene. The transition-state anion for reaction 1 does not behave like the picrate anion, contrary to our suggestion in part I.[3] Apparently cyclohexadienide-like anions respond more strongly on transfer to dipolar aprotic solvents than do benzenoid-like anions. We note that the Meisenheimer type complexes absorb at longer wavelengths than the picrate ion in dipolar aprotic solvents; *i.e.*, they are more delocalized oscillators.[12]

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(11) J. W. Larson, K. Amin, and J. H. Fendler, *J. Amer. Chem. Soc.*, **93**, 2910 (1971).

(12) E. Grunwald and E. Price, *ibid.*, **86**, 4517 (1964).