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Thermodynamic Basis of Hydrogen Bonding Effects on Reactivity of Nucleophiles with Retinyl and Triarylmethyl Carbenium Ions[†]

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Abstract: The enthalpies and free energies for hydrogen bonding have been determined between a series of acceptors (anionic and neutral nucleophiles) and donors (water, 2,2,2-trifluoroethanol, and 4-nitrophenol) in dipolar aprotic solvents (acetonitrile, dimethylformamide, acetone, and dimethyl sulfoxide). The calorimetric measurements correspond to conditions under which the rates of coordination between carbenium ions and the nucleophiles were collected. The relationship between the free energy of nucleophile hydrogen bonding, ΔG_{HB}, and the change in free energy of activation in the absence and presence of nucleophile hydrogen bonding, $\Delta\Delta G_{\mathrm{rxn}}$, depends on the nature of the carbocations. Poor electrophiles like those that adhere to Ritchie's N^+ scale (e.g., crystal violet, malachite green, and trianisyl cation) show a $\Delta\Delta G_{\mathrm{rxn}}$ that exactly matches the hydrogen bonding free energy. Cations like trityl or retinyl are less sensitive to the degree that the nucleophiles are complexed with the hydrolytic solvents. Plots of the rates of reaction between the cations and nucleophiles (as log k_{NU}) versus Swain-Scott/Pearson n values are linear and provide a selectivity measure for the group of cations more reactive than those that adhere to the N^+ scale and can be used to show that the two groups of carbenium ions have different rate determining steps. These observations appear to be general for all carbocations and are discussed in terms of S_N1 mechanistic reactivity and selectivity.

Introduction

The study of solvent effects has played an important part in the development of our understanding of the details of nucleophilic substitution reactions. In particular, the distinction between the roles of polar aprotic and protic solvents has given rise to an abundance of data and to the dilemma of trying to ascribe mechanistic significance to the resulting, extensive literature.[1–15] In the case of S_N1 reactions, comprehensive evaluations yield different models even when the role of solvent is ignored. Thus, Raber, Harris, Hall, and Schleyer[16] found conformance to the reactivity–selectivity principle, Richey[17] proposed an invariant nucleophilicity scale (N^+ values), and TaShma and Rappaport[18] categorized four or five different "classes" of carbenium ions. The use of the data reviewed in those studies to evaluate solvent effects (in addition to carbenium ion electrophilicity) does not appear to be a particularly productive approach.

That the solvent must play critical functions in the S_N1 mechanism is obvious. It must do so through its effects on the ionization of the carbon–nucleofuge bond and the solvation of the resulting anion/cation pair, the nucleophile, and the product. In spite of such apparent complexity, the matter can be somewhat simplified by looking at an individual step in the mechanism and can be accomplished experimentally by measuring the rates of coordination (i.e., combination) of a carbenium ion with various nucleophiles. Thus, direct measurement of rate constants has given rise to orders of relative and absolute nucleophilicities that are free from concerns about competing S_N1 and S_N2 mechanisms and independent of the ionization of the carbon–nucleofuge bond. Furthermore, these studies are amenable to techniques like laser flash photolysis[19–21] that are excellent methods for collecting kinetic information over a broad range of absolute rates.

We have reported a systematic study of the retinyl cation (generated by laser flash photolysis of retinyl acetate) in the presence of anionic and neutral nucleophiles in acetonitrile ACN and in that solvent with 1, 11, and 36 M water.[22] The critical role of water as a hydrogen bond donor with nucleophiles as

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[†] Dedicated to E. M. Arnett on the occasion of the beginning of the "Emeritus" half of his science career.

(1) The popularity of this area over the last four decades is manifested in the massive collection of information available. Various aspects of specific solvent effects have been discussed, and the reader is referred to excellent monographs,[2,3] books,[4–9] and reviews.[10–15]

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acceptors has been demonstrated unequivocally and quantitatively. For example, the second-order rate constant for coordination of retinyl cation with fluoride changes by four orders of magnitude in going from acetonitrile to 11 M water in acetonitrile, while the corresponding rate for iodide decreases by ca. 40. These data encouraged us to seek more information about the thermodynamic basis for these effects. The results contained herein attempt to relate calorimetrically-obtained enthalpies of hydrogen bonding (between a number of hydrogen bond donors and the nucleophiles in acetonitrile) with changes in the free energy of activation for the reactions of various cations with nucleophiles in the presence and absence of the protic cosolvents (i.e., water, 2,2,2-trifluoroethanol, 4-nitrophenol).

Experimental Section

General Methods. Freshly opened bottles of acetonitrile ACN (Mallinckrodt ChromAR HPLC grade), acetone (EM Science), and dimethylformamide DMF (EM Science) were used as obtained; the water content was checked periodically by Karl-Fisher titration. 2,2,2-Trifluoroethanol (Aldrich) was used as obtained. 4-Nitrophenol was recrystallized from hot water, dried *in vacuo* (for 4–6 days), and stored in a vacuum desiccator. Tetrabutylammonium salts (except the azide and phenoxides) were obtained commercially (Aldrich), recrystallized from ethanol/hexane solutions, dried *in vacuo* for several days, and stored in a vacuum desiccator.[23] The preparation of the azide has been reported.[22,24] The phenoxides were prepared from the corresponding phenol by adding an equivalent of tetrabutylammonium hydroxide (Aldrich, 40% in methanol), removing the solvent, recrystallizing, drying, and storing *in vacuo*.[23]

Calorimetry. Titration calorimetry was performed using a Tronac 450 instrument used in the isoperibol mode. The instrument is interfaced to an IBM-PC computer which collects and plots the voltage from the thermistor bridge and can turn the buret and calibration heater on and off. Thus, the voltage from the standard instrument thermistor bridge is amplified by a factor of ca. 12 and digitized by a 12-bit A/D converter. Control is based on a BASIC program written in-house. The sampling rate used was 0.2 Hz.

The instrument bath was set at 25.0 ± 0.1 °C and was maintained at ±0.002 °C by the instrument controller. In a typical experiment, the reaction dewar was charged with 50.0 mL of a solution (protic and/or aprotic solvent) and placed in the bath until the thermistor bridge signified temperature equilibration between the dewar contents and the bath. Likewise, the Gilford high precision buret was filled with ACN or a nucleophile/ACN solution (in the latter case at 0.20 M) and equilibrated for 1–2 h. The delivery rate (6.65×10^{-3} mL/s) of the buret in the automated, motor-driven mode was calibrated by titrating distilled water into a vessel on an analytical balance. The heat capacity of the reaction dewar and contents was determined using the calibration heater. The operation of the system was checked periodically using the neutralization reaction of HCl and THAM.[25]

The titrations normally involved the addition of 0.332 mL (50 s at 6.65 10^{-3} mL/s) of titrant into the dewar and could be repeated 6–8 times for each time the buret was filled (ca 2.6 mL total volume). Each enthalpy reported is the average of 2–3 independent runs of this type. Each mixture of ACN and protic solvent was first titrated with the dry ACN in a separate series of experiments. These data (presented as a plot of heat absorbed versus the total volume of the reaction dewar in Figure 1) were used to correct data from subsequent titrations using the nucleophile/ACN solutions. In other words, addition of 0.332 mL of ACN into 50.0 mL of 11 M water in ACN produces a thermogram that indicates a temperature decrease sensed by the thermistor bridge (i.e., observed as a decrease in voltage) of a certain magnitude. If 0.332 mL of a 0.200 M solution of acetate in dry ACN is titrated into 50.0 mL of 11 M water in ACN, another thermogram is collected but in this case with a much smaller decrease in temperature sensed by the thermistor bridge. The difference is a positive temperature change (i.e., exothermic interaction) due to the transfer of acetate from dry ACN to 11 M water. Alternatively, addition of 0.200 M $TBA^+BF_4^-$ to 11 M water in ACN was used to correct for the dilution of water in the presence of ions. The 0.200 M $TBA^+BF_4^-$ in dry ACN produces a more endothermic outcome than just dry ACN (by 1.31 ± 0.04 kcal/mol based on the amount of salt added). These titrations were quite reproducible over the range employed (i.e., a 4–6% increase in the contents of the reaction dewar).

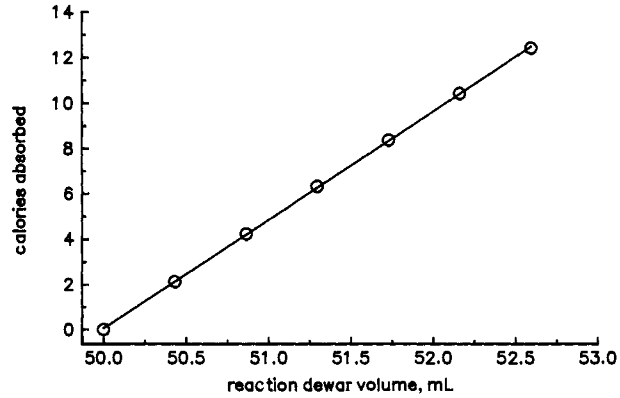

Figure 1. Cumulative heat absorbed by the solution (in cal) vs the total volume of the reaction dewar when dry ACN was added to 11.1 M water in ACN. The line is the least-squares fit.

Nucleophile solutions (0.200 M in ACN) were freshly prepared under dry conditions, charged into the buret, equilibrated, and titrated into the appropriate solutions. Each run (buret total volume = ca. 2.6 mL, 0.332 mL/titration) produced 6–8 points, which were reproducible (±3%) and independent of the amount of the nucleophile already in the dewar (over ca. 0–0.01 M). The values in the tables are the result of 2–3 such runs each.

Kinetics. The rates of reaction of crystal violet and malachite green with water were measured with a Hewlett Packard 8452A diode array spectrophotometer using the change in absorbance at λ_{max} of the cation. Thus, microliter quantities of a solution of the appropriate cation dissolved in dry ACN were added to stirred, distilled water at pH 7.00 in a cuvette so that the OD = ca. 1. The instrument was operated in the kinetics mode with the OD being measured and recorded at regular intervals. The rate constants (k, s^{-1}) were determined after ca. 4–5 half-lives and are derived from 300–500 points, were converted to a second-order rate (k, M^{-1} s^{-1}), and are reported in Table III (as an average of five determinations).

Fast kinetics were determined using data obtained by laser flash photolysis; experimental details have been reported previously.[22] The rates (k, s^{-1}) were measured at various nucleophile concentrations, and the slope of the Stern–Volmer plots gives the second-order rates that are averaged and reported in Table III.

Results

Calorimetry. Titration of dry acetonitrile ACN into the same solvent containing water (or other protic molecules) produces an endothermic response that is reproducible and linear over relatively small changes (ca. 5%) in the total volume of the reaction dewar. Typical results are shown graphically in Figure 1, a plot of heat absorbed from the solution versus the total volume of solution in the reaction dewar. (Data in the example are taken from the addition of ACN into 11 M water in ACN.) These plots provide an easy and convenient method to correct the data when solutions containing the nucleophiles are titrated into the protic/aprotic solvent mixtures. For a given concentration of protic solvent, titration of dry ACN into water solutions produces larger endothermic responses than trifluoroethanol or nitrophenol.

Figure 2 shows typical data obtained when tetrabutylammonium acetate TBA^+OAc^- (0.20 M in ACN) is titrated into 11 M water. The plot shows total heat produced vesus the total amount of acetate added and has been corrected for the effect of adding dry ACN into the same solution (see Experimental Section for details). These data represent the effect that water

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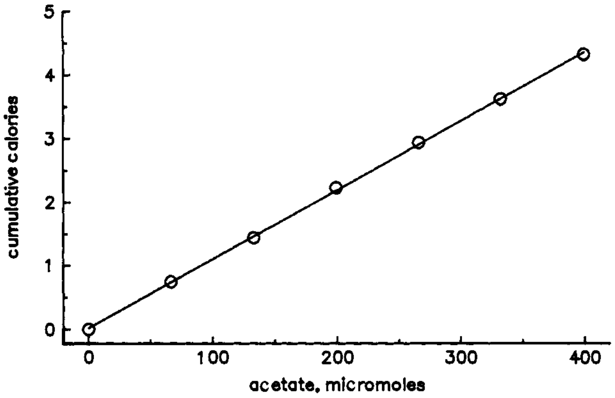


Figure 2. Cumulative heat evolved (in cal) vs the total amount of acetate in the reaction dewar when 0.20 M TBA^+OAc^- in ACN was added to 11.1 M water in ACN. Corrected for the endothermic heat of dilution when 0.20 M $TBA^+BF_4^-$ in ACN was added to 11.1 M water in ACN. The line is the least-squares fit.

Table I. ΔH_{HB} for Acetate in Protic/Aprotic Solvent Mixtures at Various Compositions

	$-\Delta H_{HB}$[b] (kcal/mol)					
[HBD][a] (M)	W/ ACN[c]	TFE/ ACN[c,d]	NPL/ ACN[c,d]	W/ DMF[c]	W/ ACE[c]	W/ DMSO[c]
0.006		1.7				
0.01			3.8			
0.03		3.2	4.5			
0.10	0.96	5.0	6.3		2.4	
0.30	3.1					
0.50	5.0				4.0	
1.00	6.3	7.6	8.5			
2.00			9.8		6.1	
5.00	8.1			1.2	5.5	1.1
6.85		9.9				
11.10	9.6			1.7	5.8	1.6
27.7	11.7			3.9		
37.0	12.2					

[a] TBA^+OAc^- in dry dipolar aprotic solvent was added to a solution of HBD (water, trifluoroethanol, or nitrophenol) at this concentration in the same aprotic solvent. The values are corrected for the heat of dilution that results when dry aprotic solvent is titrated into the same solvent mixture. [b] ΔH_{HB} is defined in the results section. [c] The mixed solvent pairs are made up of the following components: W = water, TFE = trifluoroethanol, NPL = 4-nitrophenol, ACN = acetonitrile, DMF = dimethylformamide, ACE = acetone, DMSO = dimethyl sulfoxide. [d] Neat water is 55.5 M and neat trifluoroethanol is 13.7 M.

has on both ions of the salt and is meant to show the method by which the values were collected and the goodness of the fits. That the TBA^+ cation has a minor or negligible contribution will be discussed later. The slope of the least-squares regression line through the points in Figure 2 gives the enthalpy for the transfer of the nucleophile from dry acetonitrile to ACN/protic solvent mixtures, is ascribed to hydrogen bonding processes (*vide infra*), and is called ΔH_{HB} henceforth. As can be seen from the fit to the line, these titrations are quite reproducible, generally to ±3%.

Data obtained from the titrations are contained in Tables I–II. Table I lists the ΔH_{HB} values measured from the addition of TBA^+OAc^- to mixed solvents comprised of an aprotic component and either water, 2,2,2-trifluoroethanol, or 4-nitrophenol at various concentrations and are corrected for the endothermic effect of adding dry apolar solvent into the same solvent mixture. Figure 3 is a plot of ΔH_{HB} versus the log of the total hydrogen bond donor, HBD, concentration. The log scale enables one to look over a large concentration range. Although some of the data in each respective set appears to fit a linear relationship, this may be fortuitous and will be discussed later.

Table II. ΔH_{HB}, ΔH_{tr}, and $\Delta G_t°$ for Various Solutes in 11 M Water in Acetonitrile and $\Delta\Delta G_{rxn}$ for the Coordination Reaction of Carbenium Ions with the Nucleophiles

				retinyl	trityl	most stable[e]	
solute[a]	$-\Delta H_{HB}$[b]	ΔH_{tr}[c]	$\Delta G_t°$[d]	$\Delta\Delta G_{rxn}$[f]	$\Delta\Delta G_{rxn}$[f]	N^+[g]	$\Delta\Delta G_{rxn}$[h]
water	(15)			8.51	5.42	0.00	14.2
F^-	11.8		17	6.04	4.36	2.70	10.5
$CH_3CO_2^-$	10.9		14.6	4.89	4.82	2.95	10.1
NO_2PhO^-	10.0					4.05	8.66
CN^-	8.7		8.4		3.21	3.67	9.18
PhO^-	7.8					5.60	6.58
Cl^-	6.0	8.9	10.1	3.90			
piperidine	(6)				2.81	6.11	5.90
DABCO	5.8				4.41	5.30	6.98
Br^-	5.4	6.2	7.5	3.90	3.26		
azide	3.9	6.4	8.8	2.84		7.54	3.98
tosylate	3.9					3.67[i]	
Et_3N	3.2			2.71			
SCN^-	2.5		3.4	2.46			
Ph_3P	1.7			2.19			
I^-	1.5	2.5	4.0	1.49		8.8[j]	2.33[j]
NO_3^-	1.1		5.0		3.04	10.1	
BPh_4^-	0.4	1.8	−7.8				
ClO_4^-	0.2	−0.3	0.5				
PhS^-	0.1			0		10.5	0
BF_4^-	0.0						
pentyl-OAc	−0.8						
pentyl-F	−1.2						

[a] Anionic nucleophiles are added as tetrabutylammonium salts. Tosylate = *p*-toluenesulfonate, pentyl-OAc = 1-acetoxypentane, pentyl-F = 1-fluoropentane. [b] Enthalpy of transfer from dry ACN to 11 M water in ACN. $TBA^+BF_4^-$ in ACN is used at the heat of dilution reference for all anionic nucleophiles, while dry ACN is used for the neutral nucleophiles. The values in parentheses are estimates (see text). [c] ΔH_{tr} is the sum of single ion enthalpies of transfer: $\Delta H_t°$ (water → ACN) for both TBA^+ (i.e., 4.32 kcal/mol) and for each A^- using single ion values from ref 26. [d] $\Delta G_t°$ (water → ACN) is the single ion free energy of transfer for each A^- from ref 26. [e] Highly resonance stabilized cations including members of trityl, xanthylium, and tropylium families. [f] $\Delta\Delta G_{rxn} = 2.3RT \log(k_{in\ water}/k_{dry})$, see text. [g] N^+ values from refs 17 and 29. [h] $\Delta\Delta G_{rxn} = -2.3RT[N^+(\text{nucleophile}) - N^+(PhS^-)]$. [i] Data from benzene sulfonate in methanol. [j] Based on the ratio of rates for water and the indicated nucleophile using values for crystal violet **5**.

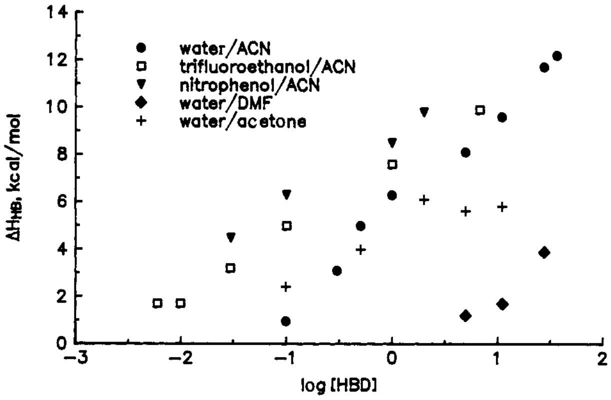


Figure 3. ΔH_{HB} for acetate (in kcal/mol) vs log of the total concentration of HBD in the reaction dewar for various mixtures of protic and aprotic solvents.

Table II (second column) includes ΔH_{HB} values from a wide variety of nucleophiles in 11 M water in ACN. The heats for neutral nucleophiles are corrected using dry ACN titrated into 11 M water in ACN. Alternatively, tetrabutylammonium tetrafluoroborate $TBA^+BF_4^-$ in ACN has been used to correct for the dilution of 11 M water with the anionic nucleophiles, since BF_4^- has been shown to be a very poor hydrogen bond acceptor.[23a] Thus, $TBA^+BF_4^-$ provides an excellent reference for titrations using anionic nucleophiles since it corrects for the role of ionic strength, the solvation of the cation (common to all systems), and the effect of ions on the structure of the protic and aprotic solvent components.

The third and fourth columns in Table II contain enthalpies and free energies of transfer from compilations of single ion values based on the $(phenyl)_4As^+B(phenyl)_4^-$ assumption.[26] In general,

Table III. Log (k_{NU}, M^{-1} s^{-1}) from the reaction of Various Cation and Nucleophiles at High Water Concentrations

		log k_{NU}[c]				
Nu =[a]	*n* value[b]	**1**[d]	**2**[e]	**3**[f]	**4**[g]	**5**[g]
water	(−1)	2	3.61	−2.54[h]	−6.48	−5.42
CH_3OH	0.0	3.04				
tosylate	(1.6)	4.34				
nitrate	1.5	4.61				
F^-	2.7	4.78	5.93			
acetate	4.3	5.58	5.6	2.07[h]	−2.4	
Cl^-	4.37	6.28	6.34	2.18[h]		
imidazole	4.97		6.45	2.75		
HO^-	(6)		6.72	3.91	−0.69	0.34
NH_3	5.5			3.2		
PhO^-	5.75			5.02		
Br^-	5.79	6.28	6.7		−1.62	
azide	5.78	7.04	9.61	6.7	0.15	
CH_3O^-	6.29				1.81	3.1
NH_2OH	6.6		7.11	4.3		0.8
NH_2NH_2	6.61		7.32	5.51		1.6
SCN^-	6.7	7.28				
Et_3N	6.66	7.48				
CN^-	(5.9)[i]		6.74	3.43	−1.27	−0.26
$PrNH_2$	7		7.11	3.7		0.88
Ph_3P	7	7.87				
piperidine	7.3		7.02	5.81		
I^-	7.42	7.96			2.28	
HOO^-	7.8					4.4
SO_3^{2-}	8.53	9.4[h]	8.38	6.8	1.97	3.6
$S_2O_3^{2-}$	8.95	9.2[h]				
RS^-	9		8.48	7.85		4.49
PhS^-	9.92	9.6[h]				6.01

[a] Nucleophiles: tosylate = *p*-toluenesulfonate, PhO^- = phenoxide, Et_3N = triethylamine, $PrNH_2$ = *n*-propylamine, RS^- = alkyl thiolate (i.e., *n*-butyl-S^-, $CH_3CH_2O_2CCH_2CH_2S^-$). [b] For a complete list of *n* values, see ref 46. The values in parentheses are estimates based on analogues or the fit of the data to the straight lines in Figure 5 (see text). [c] Log of the second-order rate constant for the reaction of the indicated cations and anions. [d] 11 M water in ACN as solvent, ref 22. [e] 36 M water in ACN as solvent, ref 20b. [f] Water as solvent, ref 28. [g] Water as solvent, ref 29. [h] Values from this work. [i] The *n* value of 6.7 (ref 46) for cyanide has been adjusted based on plots like those in Figure 5 for 35 resonance stabilized cations (ref 50).

these data are obtained from the difference of the heats of solution of the ions in the two respective, pure solvents. The enthalpy ΔH_{tr} is the sum of $\Delta H_t°$ (water → ACN) for both TBA^+ (i.e., 4.32 kcal/mol) and for each A^-, where A^- is any anion in the first column. The entry for free energy is the $\Delta G_t°$ (water → ACN) for each A^-. ($\Delta H_t°$ and $\Delta G_t°$ are single ion values from Marcus.[26])

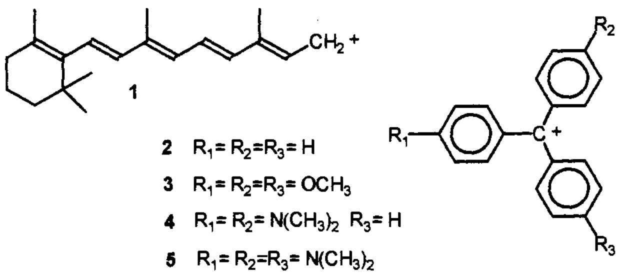
Table II also contains three sets of data corresponding to the retinyl cation, the trityl cation, and the group of the highly resonance stabilized cations described by N^+. The first two columns contain $\Delta\Delta G_{rxn}$ data based on the reaction of the cation with the corresponding nucleophile in 11 M water in ACN for retinyl,[22] in 36 M water in ACN for trityl,[20b] and in water for the most stable cations.[3,4,17] For retinyl and trityl cations, $\Delta\Delta G_{rxn}$ values are determined from the expression $\Delta\Delta G_{rxn} = 2.3RT\log(k_{\text{in water}}/k_{dry})$ where log ($k_{\text{in water}}$) is the log *k* value in Table III and $\log(k_{dry})$ is the rate in dry ACN. Measured, diffusion-controlled rates for retinyl in dry ACN have been reported[22] and are in the range, $\log(k_{dry}) = 9.2–9.7$. We have used the value $\log(k_{dry}) = 9.5$ for the calculations. Although higher values might be expected (i.e., $\log(k_{dry})$ = ca. 10),[20] we have used the lower value based on the expected effect of water as a cosolvent on the diffusion controlled limit.[27] The last two columns contain data for the most stable cations in the form of N^+ values and $\Delta\Delta G_{rxn}$. N^+ is defined as $\log(k_{NU}/k_{water})$ where k_{NU} and k_{water} are the rate constants for any nucleophile and for water, respectively. $\Delta\Delta G_{rxn}$ is calculated from the expression $\Delta\Delta G_{rxn} = 2.3RT[N^+(\text{nucleophile}) - N^+(PhS^-)]$ where the difference of the N^+ values is equal to $\log(k_{NU}/k_{PhS})$ and is equivalent to $\log(k_{\text{in water}}/k_{dry})$.

Table IV. E_T Values and Enthalpies of Transfer for Water/Acetonitrile Mixtures

[water]	E_T[a]	ΔG_{ET}[b] (kcal/mol)	$-\Delta H_{HB}$ (E_T)[c] (kcal/mol)
11.1	53.5	8.3	7.7
5.55	51.9	6.7	6.1
1.0	48.9	3.7	4.0
0	45.2	0	0

[a] E_T values from ref 31 and this work. [b] ΔG_{ET} = E_T in water/ACN mixture − E_T in dry ACN. [c] ΔH_{HB} (E_T) is the enthalpy of transfer of the E_T dye from ACN to the indicated solvent mixture.

Kinetics. Rates of reaction of a variety of nucleophiles with the retinyl **1**, trityl **2**, trianisyl **3**, malachite green **4** (i.e., 4,4′-bis[dimethylamino]triphenylmethyl), crystal violet **5** (i.e., 4,4′,4″-tris[dimethylamino]triphenylmethyl) cations are given as log (k_{NU}) in Table III. The values for **1** were measured in 11.1 M water in ACN and most have been previously reported.[22] The values for **2** were measured in 36 M water in ACN by McClelland and co-workers.[20b] The rates in water as solvent were determined by Bunton *et al.* for **3**[28] and Ritchie *et al.* for **4** and **5**.[29] Some new rates for **1** and **3**–**5** are reported herein.



Bunton and Huang report the rate of disappearance of trianisyl **3** as 15.2 s^{-1} in 0.1 M HCl and 11.8 s^{-1} in 0.1 M sodium acetate and then assign those rate values (k = 0.27 and 0.21 M^{-1} s^{-1}, respectively) to the reaction of **3** with water.[28c] We have measured the reaction with water to be much slower, $k_{NU} = 2.9 \times 10^{-3}$ M^{-1} s^{-1} (see Experimental Section for details). As a result, we have assigned Bunton's values to the rates for chloride and acetate ions, respectively.

Estimation of Entropies of Hydrogen Bonding. The E_T scale is a measure of solvent polarity that uses a pyridinium–phenoxide betaine dye.[30] Table IV contains the E_T values for some water/ACN mixtures[31] and the corresponding enthalpies (i.e., ΔH_{HB} (E_T)) when 0.03 M E_T dye is titrated into the various solvents (all corrected using the $TBA^+BF_4^-$ in ACN reference). The middle column is defined as ΔG_{ET}, where $\Delta G_{ET} = E_T$(in water/ACN mixture) − E_T(in dry ACN). Since the E_T values are the peak maxima in units of kcal/mol, ΔG_{ET} is the free energy of transfer from dry ACN into water/ACN mixtures. Linear regression analysis of the data in Table IV yields the following relationship: $\Delta H_{HB}(E_T) = 0.93\Delta G_{ET} + 0.20$ (in units of kcal/mol; $r^2 = 0.996$).

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Discussion

In the process of trying to understand the nature of hydroxylic solvent effects on the rates observed during the reaction of retinyl cation with nucleophiles,[22] a number of questions can be posed: (1) Is the origin of the solvent effect due to a simple change in the microscopic polarity of the reaction medium, a specific interaction like hydrogen bonding, or some combination of both? (2) Is that solvent effect operating on the cations, the nucleophiles, or both? (3) Is this a general phenomenon that can be extended to the entire class of carbocations? We will show that the solvent effect is primarily one operating on the anions but that the consequences of that anion solvation include a profound and general effect on the reactivity of all cations.

Since preliminary evidence suggested hydrogen bonding to nucleophiles as the primary factor, the energetics of the interaction between the nucleophiles and various hydrogen bond donors HBD[32] were sought under the experimental conditions of the rate measurements. Hydrogen bonding energetics of solutes by protic solvents generally have appeared from two different kinds of experiments. In the first type, the free energies, enthalpies, and entropies of transfer for single ions from water to dipolar aprotic solvents (e.g., DMSO, DMF, and ACN) and to other protic solvents (e.g., water, alcohol, formamide) are compiled.[26] Those data come primarily from experiments in which the ions are dissolved in *single* solvents. The second type of data comes from measurements that were most often conducted in nonpolar solvents at low hydrogen bond donor concentrations.[33] In other words, direct measurement of the magnitude of a single interaction (i.e., HBA···HBD) was sought, and those experiments are conducted in nonpolar solvents (e.g., CCl_4) where the interactions are maximized. In contrast, the data in this study are novel since ionic and nonionic hydrogen bond acceptors are used, various concentrations of hydrogen bond donors (including very large ones) are reported, and the studies were conducted in a number of polar solvents including ones where the aprotic solvent can serve as a hydrogen bond acceptor.

Specific Solvation of Anions and Cations. The effect of protic solvents on S_N reactions has led to many investigations on the origin of solvent effects.[1-15] Protic solvents play a particularly important role in solvating anions, with an inverse relationship between the size and the degree of association.[10a] Thus, small anions like F^-, Cl^-, and HO^- are much more strongly hydrogen bonded than I^-, ClO_4^-, or picrate. This is substantiated clearly in gas-phase results[34] and in data for the free energy, enthalpy, and entropy of transfer of single ions from water to dipolar aprotic or hydroxylic solvents.[26] Representative values of the latter are given as ΔH_{tr} and ΔG_t° in Table II.

ΔH_{tr} is the enthalpy for the transfer of any tetrabutylammonium salt, TBA^+A^-, from water to acetonitrile and is comprised of the single ion values of *both* the cation and anion. The enthalpy values appear to be consistent with the ones reported herein (i.e., ΔH_{HB}, Table II, column 2). It is tempting to use ΔH_{tr} in Table I or Figure 3 for the enthalpy at $[H_2O] = 55.5$ M. However, it should be noted that ΔH_{HB} and ΔH_{tr} are not directly comparable. The enthalpies in this study, ΔH_{HB}, are always measured in mixed solvents where selective solvation of the ions can and presumably does occur. Thus, the anion and cation could be interacting with different components of the binary mixture. The single ion enthalpy, ΔH_t° (water → ACN), for TBA^+ is 4.33 kcal/mol, a value indicating that the cation actually favors water. However, the single ion entropy, ΔS_t° (water → ACN), for TBA^+ is +37 eu, and the resulting ΔG_t° (water → ACN) is −7.4 kcal/mol at 25 °C. Tetrabutylammonium cation strongly prefers the solvent microenvironment in acetonitrile to that of water. The free energy is a clear indication that TBA^+ must remain solvated by acetonitrile even when it is transferred from dry ACN to 11 M water in ACN, the conditions under which the ΔH_{HB} values in Table II are collected.

The single ion transfer data for TBA^+ suggest that it experiences only minimal changes in solvation under the conditions of the calorimetric experiments described herein. The situation for a typical small anion is quite the opposite. The single ion enthalpy, ΔH_t° (water → ACN), for Cl^- is 4.61 kcal/mol, a value indicating that the anion favors water. In addition, the single ion entropy, ΔS_t° (water → ACN), for Cl^- is −18 eu, and the resulting ΔG_t° (water → ACN) is 10.1 kcal/mol. Chloride ion greatly favors the solvation in water to that experienced in acetonitrile. Chloride is therefore predicted to be preferentially solvated by water in 11 M water solutions. In contrast, BPh_4^- will prefer acetonitrile because ΔG_t° (water → ACN) = −7.8 kcal/mol for BPh_4^-. In the calorimetric titrations reported here, the preference of BPh_4^- for acetonitrile solvation is manifested as $\Delta H_{HB} \approx 0$. The ΔG_t° values in Table II are the free energies of transfer of the anion and are left in this form to enable comparison with our data ΔH_{HB} (first column in Table II), which also reflect specific solvation of the anion.

Other measures of the specific effect of solvents on single ions appear in earlier reports by Parker and co-workers.[35] Solvent activity coefficients, ${}^{water}\gamma_i^{ACN}$, for the transfer of single ions from water to acetonitrile are based on formal solubility product data and also use the tetraphenylarsenium tetraphenylboride assumption.[26,35,36] The solvent activity coefficients are defined in eq 1:

$$\log({}^{water}\gamma_i^{ACN}\ \text{cation})({}^{water}\gamma_i^{ACN}\ \text{anion}) = pK_S(\text{ACN}) - pK_S(\text{water}) \quad (1)$$

The values of $\log({}^{water}\gamma_i^{ACN})$ for chloride, bromide, and iodide are 8.4, 5.9, and 3.5, respectively, and these serve to confirm that small densely charged anions are strongly solvated by HBD solvents. The value for the TBA^+ cation $\{\log({}^{water}\gamma_i^{ACN}) = -2.1\}$ shows the preference of the tetrabutylammonium cation for the dipolar aprotic solvent, consistent with the discussion above.

Calorimetric Determination of Enthalpies. Titration of acetonitrile solutions of nucleophiles into that solvent containing various hydrogen bond donors, HBD, are exothermic processes and yield enthalpies of transfer from the aprotic solvent to the protic/aprotic mixture. In order to match the conditions under which kinetics were measured in our previous studies (and those mimicking the ones in which typical S_N1 reactions have been performed), large concentrations of water were used.

Figure 1 shows the results of a typical control experiment that these reaction conditions necessitate. Thus, addition of dry ACN into the protic solvent/ACN mixture produces an endothermic heat change, a heat of dilution. Water is highly ordered and even when diluted by polar solvents is expected to be aggregated.[37] This is confirmed by experiments[23a,38] and calculations.[39,40] The magnitude of water–water interactions is greater than water–

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[32] The labels HBD (hydrogen bond donor) and HBA (hydrogen bond acceptor) were defined: Kamlet, M. J.; Taft, R. W. *J. Am. Chem. Soc.* **1976**, *98*, 377, 2886.

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acetonitrile ones, and therefore dilution of an aqueous solution is endothermic. The size of this heat change decreases as the original concentration of the protic solvent is decreased (see data in ref 41), although it is not possible to determine molar enthalpies (i.e., kcal/mol) because the exact number of water molecules undergoing change in a particular titration is indeterminate. Nonetheless, the heat absorbed during the dilution is reproducible and linear over small changes in total volume of the reaction dewar and thus can be used as a correction factor in subsequent studies.

In order to correct for the effect of ions on the heat of dilution, acetonitrile solutions of $TBA^+BF_4^-$ were titrated into the solvent mixtures. The interaction of BF_4^- with water has been measured in nitrobenzene and dichlorobenzene by an isopiestic method and found to be negligible (i.e., ΔH = ca. 0.1 kcal/mol).[23a] In the present study, the addition of $TBA^+BF_4^-$ (0.20 M in ACN) to 11 M water is more endothermic than the heat of dilution produced by acetonitrile with no additives (by 1.31 ± 0.04 kcal/mol). In the discussion above, we suggested that the TBA^+ undergoes a very minimal change in solvation in the transfer from dry ACN to 11 M water in that solvent. If one assumes that the interaction of the water and BF_4^- is also negligible, then the observed heat must be due to an ionic effect on the solvent structure in the water/ACN solution. It is also likely that both the anion and cation in $TBA^+BF_4^-$ have a small but nonzero contribution due to the change in solvent microenvironment. Irrespective of which factor(s) it is due to, the heat of dilution caused by 0.2 M $TBA^+BF_4^-$ is a correction factor for the anionic nucleophiles in Table II. Since it is used in the same concentration as the nucleophiles, it provides the same ionic strength, and because the TBA^+ cation is common, it is an excellent model in this regard. The titration with $TBA^+BF_4^-$ appears to be linear over the entire series of 7–8 titrations conducted each time (i.e., final concentration of 0–0.01 M $TBA^+BF_4^-$ in the reaction dewar), an observation that argues against a strong ionic strength effect. Further studies are underway on the effect of non-hydrogen bonding salts (i.e., ionic strength) on the hydrogen bonding energetics.

Heats from a typical titration with a nucleophile (in which TBA^+OAc^- is added to 11 M water) are shown in Figure 2. Within the experimental error and under the conditions employed, there appears to be no effect of the cumulative amount of acetate in the reaction dewar. This is not surprising because the large enthalpy (see Table I) assures that the equilibrium greatly favors the complexed form(s), $(HBD)_n\cdots OAc^-$ and is consistent with the linearity in the $TBA^+BF_4^-$ control data. The enthalpies from TBA^+OAc^- with different hydrogen bond donors and at different concentrations of them are in Table I, while enthalpies from various solutes with 11 M water are in Table II. The ΔH_{HB} values in Table I, shown graphically in Figure 3, are compelling evidence that this is a hydrogen bonding effect and not a bulk solvent polarity change. A comparison of the enthalpies at a single concentration consistently shows the order 4-nitrophenol > trifluoroethanol > water, one that follows hydrogen bonding ability and not dielectric constant.[2,42]

The technique that we have employed to measure ΔH_{HB} cannot be used for all nucleophiles. The enthalpy of transfer for nucleophiles that are also hydrogen bond donors (i.e. alcohols, phenols, primary and secondary amines, carboxylic acids) cannot be determined. All of these molecules self-associate to some extent in ACN. Thus, titration of solutions of them into protic/aprotic mixtures contains an enthalpic term equivalent to the heat necessary to break up the self-association. These values would have to be determined or estimated before these nucleophiles can be included in the present analysis.

An estimate of the value of ΔH_{HB} for water is given in Table II. This number corresponds to the enthalpic term for taking a monomeric water in ACN and producing a complex in 11 M water. Best estimates suggest 3–5 nearest neighbors in water itself.[43] Thus, the value in the table, ΔH_{HB} = 15 kcal/mol, ascribes 3–5 kcal/mol to each of these interactions. The validity of this assumption is tested later.

Enthalpies vs Free Energies of Hydrogen Bonding. The goal of comparing rates (or changes in free energies of activation) for cation–nucleophile coordination reactions necessitates the use of free energies of hydrogen bonding. The ready access to ΔH_{HB} values from calorimetric studies already described encouraged us to seek methods to measure or determine the missing entropic term. Based on first principles, one could imagine that the entropy change for a water molecule being hydrogen bonded to a nucleophile versus another water molecule would be very minimal. The following system confirms that this hypothesis is true by using experimental measurements of both the free energy and the enthalpy on a single zwitterionic species.

The E_T scale is a measure of solvent polarity based on the solvatochromic dye, 2,6-diphenyl-4-(2,4,6-triphenylpyridinio)-phenolate.[30] The solvatochromic band is a charge-transfer transition of the electron from the p-orbital of the oxygen on the phenoxide portion to the π^* orbitals of the pyridinium system. The E_T values of protic solvents are among the highest ones, and a recent study by Murray and Coleman[42] reports equilibrium constants for the first and second equilibria between the dye and water, alcohols, and phenols. Their data also follow the expected order based on hydrogen bonding and not bulk polarity. Table IV contains the E_T values for various water/ACN mixtures and the enthalpies obtained when 0.03 M dye was titrated into these mixed solvents. Note that the values of ΔH_{HB} for the E_T dye are consistent with the values of the other phenoxides in Table II.

The E_T value is simply the location of the charge-transfer band expressed in energy units (i.e., kcal/mol). The ΔG_{ET} values in Table IV represent the free energy of transfer of the dye from dry ACN to the water solutions. It assumes that the differential solvation occurs in the zwitterionic ground state at the phenoxide and not in the excited state at the pyridinium π system. Linear regression analysis of the data in Table IV yields the following relationship: $\Delta H_{HB}(E_T) = 0.93\Delta G_{ET} + 0.20$ (in units of kcal/mol; $r^2 = 0.996$). The slope of near unity and the small *y*-intercept confirm the minor role of the change in entropy under these conditions. Therefore, in succeeding discussions, ΔG_{HB} will be used in place in ΔH_{HB} with the caveat that this may not be strictly true under all circumstances or conditions. Further corroboration for this assumption (i.e., $\Delta G_{HB} = \Delta H_{HB}$ ± ca. 0.5 kcal/mol) appears later.

The Concentration Dependence of ΔH_{HB}. Much of the data in Table I or Figure 3 appear to show a linear relationship between ΔH_{HB} and log[HBD], an apparent coincidence that results from the conditions and concentrations. Closer inspection of the data for water/acetonitrile mixtures suggests that the enthalpies begin to plateau at the highest water concentrations. One would also expect that the enthalpies would slowly approach zero at very low water concentrations. A plateau at high water concentrations is obvious in the data from water/acetone mixtures.

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(41) Addition of 0.332 mL of dry ACN into 50.0 mL of various water solutions in ACN produced the following heats (concentration of water in dewar, heat absorbed in cal): 0.1 M, 0.017; 0.5 M, 0.064; 1.0 M, 0.093; 5.0 M, 0.79; 11.1 M, 1.59; 27.7 M, 3.36; 37 M, 4.49; 55.5 M, 7.16. Each such titration represents a ca. 0.66% dilution of the water in the dewar.

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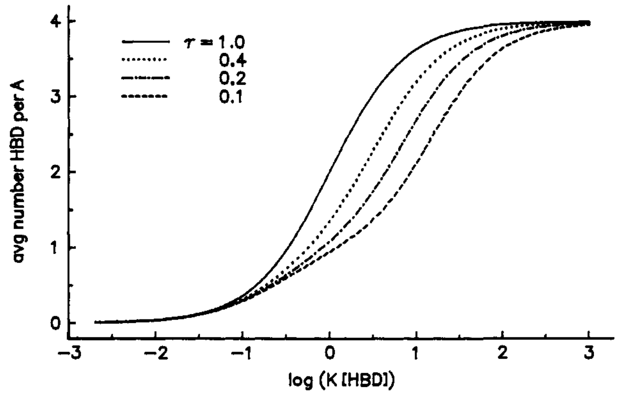

Figure 4. Modified Ising model: a plot of the average number of HBD molecules (out of a maximum of four) bound per nucleophile A vs the log of the concentration of HBD molecules that are not hydrogen bonded. The value of τ indicates the degree to which the binding of a subsequent HBD is decreased by the presence of one HBD that is already bound. A value of $\tau = 1$ indicates no interaction; the smaller the value of τ, the smaller the value of the subsequent equilibrium constant.

The interaction of acetate with an HBD molecule or many of them is quite complex and is expected to involve multiple sequential equilibria. Some simple models can be generated to represent multiple bindings of a species at a particular site, including the case where each sequential HBD binds less strongly than the previous one. Such "anticooperative" binding is apparent from the sequential addition of water to the halide ions in the gas phase.[34] In the absence of sufficient data to accurately determine the various equilibrium constants, a modified version of the Ising model can provide a semiquantitative picture for the concentration data.[44] In this model, the first equilibrium constant is K, and each successive one is multiplied by a parameter τ that accounts for the diminution due to the interaction. The equilibria are shown in eqs 2–5 where the statistical weights or concentrations of A-HBD$_n$ are given after the equilibria and in which $S = K$[HBD]:

$$\text{HBD} + \text{A} \rightleftharpoons \text{A-HBD} \qquad S \tag{2}$$

$$2\text{HBD} + \text{A} \rightleftharpoons \text{A-HBD}_2 \qquad \tau S^2 \tag{3}$$

$$3\text{HBD} + \text{A} \rightleftharpoons \text{A-HBD}_3 \qquad \tau^2 S^3 \tag{4}$$

$$4\text{HBD} + \text{A} \rightleftharpoons \text{A-HBD}_4 \qquad \tau^3 S^4 \tag{5}$$

The average number of HBD per A is defined as ν and is given by the following equation (see derivation in the supplementary material):

$$\nu = \frac{4S + 12\tau S^2 + 12\tau^2 S^3 + 4\tau^3 S^4}{1 + 4S + 6\tau S^2 + 4\tau^2 S^3 + \tau^3 S^4} \tag{6}$$

A plot of ν versus log S (i.e., log K[HBD]) is shown in Figure 4 for a series of τ values. K is the equilibrium constant above and [HBD] is the concentration of free HBD in the solution. A value of $\tau = 1$ would indicate no anticooperative effect. The smaller the value of τ is, the larger the effect an HBD molecule has on preventing the next HBD from being bound. We suggest that the data in Figure 3 represents the middle, linear portion of the kind of plot shown in Figure 4 and for water/acetonitrile data the plateau is being approached at high water concentration. However, in order to match them quantitatively, the value of K must be known, the unbound HBD concentration in solution measured, and ΔH_{HB} values converted to ν. Even in the qualitative picture, one can see that the τ value is related to the hydrogen bonding ability of the protic additive.

Reactivity–Selectivity Relationships for Carbenium Ions. The most general model for the relationship between reactivity and selectivity of carbenium ions is that given by Rappaport and TaShma.[18] That study suggested the presence of at least four different selectivity regions based on the electrophilicity of the cations: (1) a region of constant selectivity given by Ritchie's N$^+$ values;[17] (2) a region of adherence to the reactivity–selectivity principle, proposed by Raber, Harris, Hall, and Schleyer;[16] (3) a constant selectivity region apparently due to reactivity of contact ion pairs; and (4) an inverted region, apparently due to a competing S$_N$2 mechanism, based on the work of Jencks and Richard.[45] It is appropriate to reexamine these models and hypotheses in the context of the solvent effects being examined here.

Kinetic data for five cations **1–5** have been included in Table III, and all of these values represent second-order rate constants for the disappearance of the cations. This eliminates concern about contributions from the breaking of the carbon–nucleofuge bond and from competition from an S$_N$2 mechanism. The retinyl cation **1** is the one for which we have the most systematic data as a function of solvent. The remaining four carbenium ions are structurally very similar to each other, but cations **2** and **3** appear in region 2 while **4** and **5** are in region 1 of the Rappaport/TaShma model. Based on our earlier report, **1** would also appear in region 1, but it should be more selective than **2**.

Cation Reactions in the Absence of Hydrogen Bonding. Information about reactions in the absence of hydrogen bonding effects can come from two sources: rates measured in dry aprotic solvents or rates from those nucleophiles which show very little propensity to hydrogen bond. The fastest rates for **1** and **2** are $>10^9$ M^{-1} s^{-1} in dry ACN.[20,22] However, rates at or near diffusion-controlled are also observed for **1–3** in solutions containing high concentrations of water (i.e., >11 M) *but only for those nucleophiles which are poor hydrogen bond acceptors* (i.e., ΔH_{HB} < ca. 1 kcal/mol). Thus, thiolates (e.g., PhS$^-$, $CH_3OCH_2CH_2S^-$, $CH_3O_2CCH_2S^-$, and $^-O_2CCH_2S^-$) are among the "fastest" nucleophiles. This can be seen from the data in Figure 5, a plot of log(k_{NU}) versus Swain-Scott/Pearson n values[46] for the cations at high concentrations of water or in water. We define k_{lim} as the maximum rate observed for a cation (i.e., the rate of the most reactive nucleophiles or, in other words, those with an n value of ca. 10). Note that thiophenoxide has an n value of 9.92 and a ΔH_{HB} of ca. 0.1 kcal/mol.

Cations **1–3** have k_{lim} values greater than ca. 10^9 M^{-1} s^{-1}. We interpret this to mean that the reactions of **1–3** have a rate determining step that is at or near diffusion-controlled in the absence of hydrogen bonding. Scheme I shows a typical mechanism for carbenium ion reactivity in which C$^+$ is the cation, A$^-$ is the nucleophile, SSIP is a solvent-separated ion pair, CIP is a contact ion pair, S is an aprotic solvent, and HBD is a hydrogen bond donor solvent. The steps in which free ions are converted into a contact ion pair are in fact the ones that should be controlled by diffusion and apparently are also the rate determining step in the case of **1–3**.

The fastest reactions of malachite green **4** and crystal violet **5** are not so well characterized or consistent. In dry aprotic solvents, only a few rates have been reported, and they are considerably slower than the diffusional limit and not self-

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(44) (a) Tinoco, I., Jr.; Sauer, K.; Wang, J. C. *Physical Chemistry—Principles and Applications in Biological Sciences*, 2nd ed.; Prentice-Hall: Englewood Cliffs, NJ, 1985; pp 559–627. (b) Cantor, C. R.; Schimmel, P. R. *Biophysical Chemistry, Part III: The Behavior of Biological Macromolecules*; W. H. Freeman: San Francisco, 1980. (c) Tanford, C. *Physical Chemistry of Macromolecules*; Wiley: New York, 1961.

(45) (a) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361. (b) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373, 1383.

(46) The reactivity of nucleophiles with methyl iodide in methanol solution by an S$_N$2 mechanism is given by n, where $n = \log(k_{\text{nucleophile}}/k_{\text{methanol}})$. For an extensive compilation of n values, see: Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319–26.

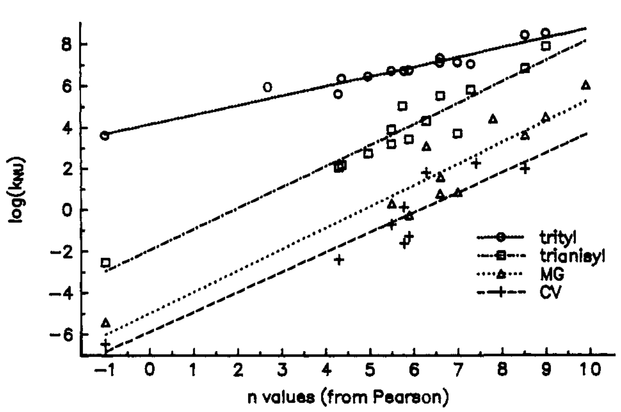
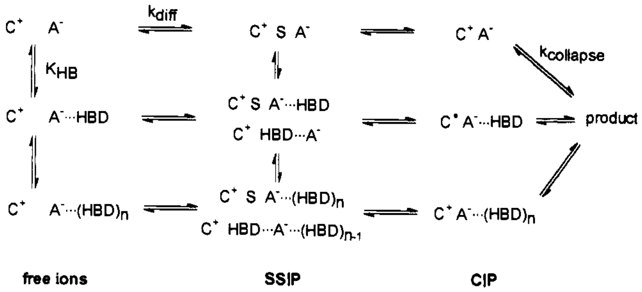


Figure 5. Log k_{NU} (second-order rate constants from reaction of carbenium ions with nucleophiles) vs Pearson *n* values. Rates from **2** in 36 M water in ACN and from **3–5** in water.

Scheme I. Mechanism for Cation Coordination with Nucleophiles



consistent.[47] The k_{lim} values from Figure 5 are ca. 2 × 10^5 for **4** and 5 × 10^3 M^{-1} s^{-1} for **5**. These values are much slower than the ones above for **1–3**, even though the formation of the contact ion pair from free ions still involves diffusional processes. The k_{lim} rates suggest that *malachite green and crystal violet have a different rate determining step than cations* **1–3**. For these highly resonance stabilized cations, the collapse of the contact ion pair to form the covalent product must be the slow step in the absence of significant hydrogen bonding. This suggests that the collapse of the contact ion pairs CIP of **1–3** in Scheme I, $k_{collapse}$, must be slower than k_{diff} × [nucleophile].

Cation Reactions in Hydrogen Bonding Solvent Mixtures. Figure 5 contains plots of log k_{NU} versus *n* values, measures of nucleophilicity toward CH_3I in methanol. The data for cations **1–5** and the least-squares lines through them confirm a linear relationship,[48] an observation that is not surprising considering the solvent for the S_N2 reaction is methanol. The scatter in the values for malachite green and crystal violet is considerable due in large part to the difficulty of these measurements. The covalent product is in equilibrium with the cation even at relatively large concentrations of nucleophile; this situation results in measurements of a small change in a large absorbance in the stopped–flow experiment.

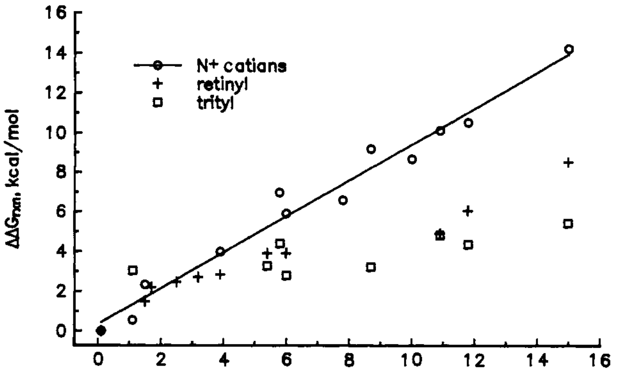


Figure 6. $\Delta\Delta G_{rxn}$ (free energy difference calculated from rates in the presence and absence of water) vs ΔG_{HB} (free energy of hydrogen bonding of the indicated nucleophile in 11.1 M water in ACN).

The k_{lim} values taken from Figure 5 proved valuable for predicting the maximum rates for the "best" nucleophiles even at high concentrations of water. The slopes of the lines in Figure 5 are a quantitative measure of selectivity, one considerably more dependable than the ratios of k_{azide}/k_{water} that have been widely used. The slopes[48] are 0.65, 0.33, 1.01, 0.96, and 1.04 for **1–5**, respectively. Note that **3–5** have unit slopes within experimental error. This is simply another manifestation of the phenomenon that led Ritchie to propose the N^+ values; the selectivity of these cations toward a nucleophile is constant, irrespective of the structure of the cation. This relationship also holds true for a number of other substrates (e.g., aryl diazonium ions) reacting with nucleophiles under these conditions.[17,29]

The rate diminution on going from dry apolar solvents to mixtures containing high concentrations of HBD solvents is due to the hydrogen bonding of the protic solvent with the nucleophiles, an observation that is further apparent after an inspection of Figure 6. That figure is a series of plots of $\Delta\Delta G_{rxn}$ (for cations **1**, **2**, and for the collection of cations described by N^+ values) versus ΔG_{HB} (or more correctly ΔH_{HB}). The plot is linear for the N^+ cations and has a unit slope and a zero *y*-intercept. The change in the activation barrier for the reaction of **3–5** exactly matches the energy that is required to free the nucleophiles from the water. We conclude that the reactions of **3–5** in water or in high concentrations of it and the S_N2 reactions of CH_3I in methanol reach a limiting selectivity that is a direct measure of the energy required to break (or counteract) the hydrogen-bonding forces experienced by the nucleophiles. That the plots for **3–5** in Figure 5 have unit slope is not surprising if one thinks of CH_3I as a poorer Lewis acid (i.e., electrophile) than the cations **3–5**. That is also true for the other types of reactions that Ritchie reports as fitting his N^+ parameters.

Several other matters warrant discussion. The presence of hydrogen bonding solvents can lead to interactions between them and the cations and/or nucleophiles. Cations **3–5** have oxygen or nitrogen atoms in their structure which could serve as hydrogen bond acceptor sites. If these cations formed a hydrogen bonded complex with protic solvents, they could diffuse much slower in the protic solvents as hydrogen bonds to the ions (or to the solvents already attached to the ions) interacted with the protic solvent as the ion moved through it. This is also true for the anions. For example, complexed acetate [$(H_2O)_4\cdots{}^-OAc$] is not only much larger than acetate but it is also "stickier" if those four waters interact with the surrounding water as the complex diffuses through solution. However, such interactions cannot be the sole factor for the observed rate changes; if the rate diminutions were due to "sticky" complexes of the nucleophiles alone, the selectivity would have to be the same for all cations not just **3–5**. It seems likely that large changes in the diffusional rate of the cations is also not the dominant factor; the anions are better at hydrogen

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(47) The rate constants (ref 29g) in dry apolar solvents are as follows (nucleophile, log k_{NU}, solvent): For **4**: propyl amine, 3.46, DMSO; cyanide, 4.23, DMSO; cyanide, 5.04, DMF; azide, >7, DMSO or DMF; $CH_3OCH_2CH_2S^-$ or $CH_3O_2CCH_2S^-$, 8.3, DMSO: For **5**: propyl amine, 2.3, DMSO; cyanide, 3.08, DMSO; cyanide, 3.86, DMF; azide, >7, DMF; $CH_3OCH_2CH_2S^-$ or $CH_3O_2CCH_2S^-$, 7.4, DMSO.

(48) Least-squares linear regression of the data in Table III yields the relationship log(k_{NU}) = (slope × *n* value) + intercept where the following values have been obtained (cation, slope, intercept, *r*, number of points): **1**, 0.70, 2.82, 0.99, 14; **2**, 0.46, 4.22, 0.97, 14; **3**, 1.01, –1.98, 0.96, 14; **4**, 0.96, –5.90, 0.93, 9; **5**, 1.03, –5.04, 0.94, 11. Azide was omitted from the fits for **2** and **3**. A referee suggested that we consider the influence of the data for water as a nucleophile on the fits. Clearly, the water point has a major impact on the fits for **3–5** since its *n* value is so much less than the others. The following values have been obtained when water is excluded (cation, slope, intercept, *r*, number of points): **3**, 1.14, –2.85, 0.93, 13; **4**, 1.20, –7.48, 0.83, 8; **5**, 1.35, –7.47, 0.89, 10.

bonding so the number of HBD atoms complexed to the cations should be smaller, and the effect should be less than that of the anions.

The linear relationships between $\Delta\Delta G_{rxn}$ and ΔG_{HB} in Figure 6 confirms an earlier hypothesis that ΔH_{HB} approximates ΔG_{HB} under the conditions prescribed. The slope is near unity, and the intercept is small (<0.5 kcal/mol). We would anticipate the fit to be even better if we had ΔH_{HB} data at higher concentrations of water since the N^+ rates were measured in water itself. The $\Delta G_t°$ values in Table II could also be used to compare with $\Delta\Delta G_{rxn}$ after a correction is applied. The $\Delta G_t°$ values need an adjustment due to the cation used; unfortunately, the cation is an organic one TBA^+ in measurements in dry DMSO or DMF, while inorganic cations were used in water. Nonetheless, a plot of $\Delta\Delta G_{rxn}$ (for N^+ cations) versus $\Delta G_t°$ values from Table II could be interpreted as being linear (slope = 0.61, y-intercept = 0.77, and $r^2 = 0.84$ for five pairs of values). The intercept is nonzero because of the uncertain correction factor for the cation.

Cations **1** and **2** react slower in the presence of hydrogen bond donors than in pure dipolar aprotic solvents; the magnitude of $\Delta\Delta G_{rxn}$ appears to be proportional to ΔG_{HB} (or ΔH_{HB}) but not equal to it. It also appears that a good estimate for the proportionality constant α in eq 7 is the slope from the plots of log k_{NU} versus n values in Figure 5:

$$\Delta\Delta G_{rxn} = \alpha \Delta G_{HB} \qquad (7)$$

There is not sufficient data from only two cations **1** and **2** to validate such a hypothesis, but the idea is being pursued with a larger collection of cations.[50] At values of ΔH_{HB} < ca. 3 kcal/mol, $\Delta\Delta G_{rxn}$ values for **1** and **2** approach those for **3–5**. The entire magnitude of the hydrogen bonding effect is reflected in the rates for those nucleophiles, although the effect is small because they are poor hydrogen bond acceptors. Nonetheless, a $\Delta\Delta G_{rxn}$ of ca. 3 kcal/mol represents a change in rates by a factor of ca. 150.

The rates or n values in Table III are a useful measure of nucleophile selectivity for reactions that occur by either an S_N1 and S_N2 mechanism. Pearson has demonstrated the use of n values for organic and inorganic substrates via S_N2 pathways,[46] and the correlation for carbenium ions is shown here and in the previous report on the retinyl system.[22] These relationships hold true only in the presence of high concentrations of water or methanol, although a good case can be made for a similar response in the presence of other hydrogen bond donor molecules (e.g., trifluoroethanol, nitrophenol) or even a Lewis acid (like Li^+). Nucleophile selectivity in the absence of such strong, solvent interactions is clearly a different case that will require another complete, systematic analysis. Selectivity data in dry apolar solvents can be seen in the reports from Parker[10] who has addressed this problem for a handful of nucleophiles. Cations **1** and **2** are not good candidates for such a complete study since most of the rates measured in dry solvents are at the diffusion controlled limit. There are a few notable exceptions from the reactivity of the retinyl cation **1**; the rates for nitrate and tosylate with **1** in dry ACN are 1.8×10^7 and 1.2×10^8 M^{-1} s^{-1}, respectively.[22] Those two nucleophiles are clearly much poorer than fluoride, chloride, bromide, iodide, and acetate, which all react at or near the diffusion controlled limit. Of course, these rates in dry acetonitrile will not correlate with n values and should not even be expected to correlate with nucleophile selectivities from S_N2 reactions in HBD-free solvents. The electronic requirements for a nucleophile reacting with a cation versus an S_N2 substrate are clearly different. This can be seen even in data for the relative reactivity of halide ions in various dry apolar solvents.[10] A more universal picture of selectivity in dry apolar solvents awaits a complete, systematic set of data.

Table I and Figure 3 include ΔH_{HB} values for acetate in a variety of binary solvents comprised of a protic and aprotic component. The data involving acetonitrile and three protic solvents demonstrate the relative ability of these three to hydrogen bond. The behavior of water in a few aprotic solvents demonstrates an important consequence of their structures. Two types of aprotic solvents are represented: (1) those like acetone, dimethyl sulfoxide (DMSO), and dimethylformamide (DMF) which are hydrogen bond acceptors and (2) ACN, which is not a very good one. There is a marked difference that a particular water concentration has on acetate hydrogen bonding in the two different types of solvents. In solutions containing 11.1 M water, the concentrations of water and dipolar solvent are quite similar (virtually the same to a first approximation).[51] However, at those concentrations the effect of the water on acetate is profoundly different. The relative effect of aprotic solvent on the water/acetate complex formation ($n H_2O \cdots OAc^-$) follows the order ACN ≪ acetone ≪ DMF, DMSO. This order tracks the ability of these solvents to accept hydrogen bonds and correlates very well with quantitative measures of this property.[52] In turn, this suggests that even larger values of ΔH_{HB} would be expected in less polar solvents that were also poorer hydrogen bond acceptors than acetonitrile. These data emphasize the potential hazards of comparing rate data obtained under widely differing conditions; even the comparison of binary mixtures in which the water concentration is the same can be misleading. On the other hand, using slightly "wet" DMSO or DMF is not likely to have much of an influence on the rates (based on the reactivity of the nucleophile).

The hydrogen bond donor α and hydrogen bond acceptor β scales of Kamlet and Taft[52] can also be used to interpret the ΔH_{HB} data from water, trifluoroethanol, and nitrophenol in ACN (see Table I, Figure 3). Trifluoroethanol (TFE) is both a better hydrogen bond donor and poorer hydrogen bond acceptor than water. The former property means stronger hydrogen bonds to acetate, while the latter means that TFE will virtually not self-associate. Both factors contribute to larger ΔH_{HB} values for TFE than water (at the same concentration of the protic solvent dissolved in an aprotic one). Nitrophenol must be a substantially better hydrogen bond donor than TFE on the α scale. The Kamlet–Taft HBD and HBA scales (i.e., α and β) are based on regression analysis of many different indicator dyes,[52] and the difficulty in obtaining additional, accurate values precludes their use in an extensive, systematic study using protic/aprotic solvents.

Although the value of ΔH_{HB} for water in Table II is only an estimate, its fit in the plot in Figure 6 lends credence to the choice of ca. 15 kcal/mol. The immense energy barrier produced by water self-association (in water or at high concentrations of it in aprotic cosolvents) warrants an evaluation of it as a nucleophile. The difference in n values for water and hydroxide is ca. 7 (see estimated values in Table III). In other words, hydroxide is at least seven orders of magnitude more reactive than water. Autoprotolysis in water produces a hydroxide concentration that is somewhat greater than eight orders of magnitude less than that of water (i.e., a factor 5.55×10^{-8}), if the activity of water in itself is 1! It is quite possible that hydroxide and not water

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(49) McClelland, R. A., personal communication.

(50) Rates for ca. 35 resonance stabilized carbenium ions (including substituted triphenylmethyl, diphenylmethyl, xanthyl, tropilium, and phenethyl) have been correlated to n values to yield the k_{lim} and slope values, and those values have been fit to a linear free energy relationship with pK_{R^+}: Pienta, N. J.; Kessler, R. J., unpublished.

(51) The concentration of a solvent in itself is as follows (solvent, molar concentration): ACN, 19.0 M; DMF, 12.9 M; acetone, 13.5 M; and DMSO, 14.0 M. At 20% by volume of water (i.e., 11.1 M), the solvent concentrations in the mixture are ACN, 15.2 M; DMF, 10.3 M; acetone, 10.8 M; and DMSO, 11.2 M.

(52) For scales of solvent hydrogen bond acceptor basicity (called β), hydrogen bond donor acidity (called α), and dipolarity/polarizability (called π^*), see: (a) Kamlet, M. J.; Taft, R. W. *J. Am. Chem. Soc.* **1976**, *98*, 377, 2886. (b) Kamlet, M. J.; Abboud, J. L.; Taft, R. W.; *J. Am. Chem. Soc.* **1977**, *99*, 6027. 8325. The values of β for trifluoroethanol, water, ACN, acetone, DMF, and DMSO are 0, 0.18, 0.31, 0.48, 0.69, and 0.76, respectively. The α donor values for trifluoroethanol, water, ACN, acetone, DMF, and DMSO are 1.51, 1.17, 0.19, 0.08, 0 and 0, respectively.

is the reacting nucleophile even at neutral pH for cations that adhere to the N^+ scale and for S_N2 reactions. The *n* value of −1 in Table III is based on observed pseudo-first-order rates that are then converted to second-order rate constants by dividing by the water concentration. As such, they can only approximate the *upper limit* for the true second-order rates; the difference in hydroxide and water reactivity may actually be separated by 8–9 orders of magnitude. Although the points for water fit on the lines in Figure 5, they would also fit if the rates were 2–3 orders of magnitude slower and the *n* values were decreased by 2–3 units. Careful experiments using various water concentrations in acetonitrile with a variety of aryl cations has led McClelland to question whether water reacts in the traditional way ascribed to it.[20,49] This is further evidence that supports abandoning water rates for use in selectivity measures like k_{azide}/k_{water}. This situation also emphasizes the need for extremely precise determination and control of pH in cases where the rates for "water" are being evaluated. The use of buffers does not entirely solve the problem, since it may also introduce additional nucleophiles that would further complicate the issue (*vide infra*, rate data for trianisyl cation **3**).

Mechanistic Models for Hydrogen-Bonding Effects. The diminished availability of lone pair electrons on a variably hydrogen bonded anion is evident from the pioneering work by Kolthoff and Chantooni.[53] They qualitatively and quantitatively demonstrated a large change in a standard potential at an electrode as a function of the number of HBD molecules bound to an organic anion. Thus, a difference of 1.6 V is observed for the anion, 3,5-dinitrobenzoate, when it is complexed with either one or two HBD molecules in ACN. (The HBD used in that study was the phenol, resorcinol.)

It is reasonable to account for the rate decreases in the data presented in this study as being due to electronic factors. The nucleophilicity of the Lewis base lone pair is diminished by charge dispersal among the constituent molecules involved in the hydrogen bonding interactions. The complex $[(H_2O)_4\cdots{}^-OAc]$ is a softer base (or is less nucleophilic) than acetate itself. Apparently, only the more electrophilic cations like **1** and **2** are not as sensitive to the diminished Lewis basicity.

Another model for envisioning the diminished nucleophilicity of anions in HBD solvents is one in which the approach of the anion and cation is blocked by the presence of a tightly bound solvent molecule. A solvent-separated ion pair intermediate in which the intervening solvent molecule is hydrogen bonded to the anion has been proposed previously[54] and such species are included in Scheme I. An extensive steric blocking of the anion is a physical model that is satisfactory in accounting for the difference in rate due to a change from an aprotic to an HBD solvent. The less electrophilic carbenium ions would require very close approach or actual "collision" with the orbitals of the nucleophile. For more electrophilic cations, the degree of attraction apparently enables the cation to "move" the intervening solvent to allow coupling. From a more realistic perspective than the physical picture presented above, an electron transfer or quantum mechanical tunnelling can occur over a greater anion/cation separation for the more electrophilic cations.

Comprehensive models of reactivity/selectivity relationships for carbenium ions and nucleophiles have led to various conventions for those two features. Measurement of carbenium ion selectivity based on ratios of rate constant for azide and water no longer appears to be satisfactory because of the change in rate determining step that occurs as the electrophilicity of the carbocation decreases. Questions concerning inconsistencies in the rates for azide[55] and the validity of using the observed first-order rate for water support this suggestion.. The optimal measure of reactivity of all cations would be the rate at which the contact ion pair collapses to covalent product ($k_{collapse}$ in Scheme I). These can only be determined for the most stable cations (i.e., those that adhere to Ritchie's N^+ scale), and they correspond to the k_{lim} value (from Figure 5). We suggest the use of k_{lim} values based on a plot of many data points. Alternatively, the slopes of the plots in Figure 5 are the only measure of reactivity available for the more electrophilic cations. We suggest the use of the slopes in place of the ratio of two rate constants. A linear free energy relationship that includes these two parameters (i.e., k_{lim} and the slope) and pK_{R^+} has been developed for ca. 15 cations and appears to be quite satisfactory.[50]

Conclusions

A series of calorimetric measurements has determined the enthalpy and free energy for hydrogen bonding between various donors (i.e., water, trifluoroethanol, and 4-nitrophenol) and acceptors (i.e., anionic and neutral nucleophiles and other solutes) in acetonitrile, DMF, acetone, and DMSO. Calorimetric and spectroscopic measurements with the solvatochromic E_T dye suggest that there is only a very small entropic contribution to the transfer of tetrabutylammonium salts from acetonitrile to that solvent containing high concentrations of water.

The change in free energy due to anion hydrogen bonding provides the entire barrier to reactivity changes (i.e., rates) when the medium is changed from a dipolar aprotic to a hydrogen bond donor solvent. Thus, the highly resonance stabilized carbenium ions (and other substrates) that fit Ritchie's N^+ criteria are such poor Lewis acids (i.e., electrophiles) that they can only react with a Lewis base (i.e., nucleophile) that is unencumbered by the solvent hydrogen bonding that diminishes the nucleophile's basicity. More electrophilic cations are only sensitive to the decreased Lewis basicity in hydrogen bonded anions to a degree that depends on their own Lewis acidity.

Plots of log k_{NU} versus *n* values are linear and give rise to two useful values: the slope of the line and k_{lim} (i.e., the rate constant at $n = 10$). The slopes are measures of selectivity and are highly preferred to ones based on a ratio of two rates (although a constant can be used to convert from one to the other). The k_{lim} rates indicate a change in rate determining step. Thus, cations that can be described by N^+ (or have slopes equal to one in the plots of log k_{NU} versus *n* values) react at the rate that the contact ion pair collapses to product in the absence of hydrogen bonding solvents. On the other hand, the cations whose slope is less than 1 react at the diffusion controlled limit without hydrogen bond donors.

Acknowledgment. We are grateful to E. M. Arnett (Duke), R. A. McClelland (Toronto), and C. J. Murray (Arkansas) for comments and suggestions.

Supplementary Material Available: Modified Ising model for the binding of molecules at interacting sites (i.e., derivation of eq 6) (2 pages). Ordering information is given on any current masthead page.

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(53) Kolthoff, I. M.; Chantooni, M. K. *J. Am. Chem. Soc.* **1963**, *85*, 426, 2195.

(54) For a review on the effects of HBD solvents on ion-pairing, see: Davis, M. M. *Acid-Base Behavior in Aprotic Organic Solvents*, Monograph *105*; National Bureau of Standards Washington, DC, 1968; pp 88–112.

(55) In plots of log(k_{NU}) vs *n* values like those shown in Figure 5, the values for azide are orders of magnitude faster than the best fit line predicts but only for certain carbenium ions. Deviations of azide from N^+ behavior were previously reported by Ritchie in ref 17. In the present context this could be due to a problem with the *n* value for azide or with the appearance of another reaction pathway for certain cations. This question may be resolved by a systematic examination.