Does Dissociation of Amine–Water Complexes Depend upon Amine Basicity? Proton Exchange between Quinuclidinium Ions and Solvent

Ulf Berg*,† and William P. Jencks*

Contribution No. 1726 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02254. Received January 17, 1991

Abstract: The rate of proton exchange between 3-X-quinuclidinium ions (X = H, OH, Cl, and CN) and solvent water was studied by dynamic ^{1}H NMR techniques. The rate constants show a pH dependence expected for the Swain–Grunwald mechanism, with a pH-independent region above pH ≈ 1 and the characteristic inhibition at lower pH values. The rate constants for breaking the $R_3N\cdot HOH$ hydrogen bond, k_H, range from 1.9×10^9 s^{-1} for X = H to 1.2×10^{10} s^{-1} for X = CN, and show a dependence on the base strength of R_3N with a Brønsted plot slope of $\beta_{diss} = -0.25 \pm 0.04$. A molecular mechanics computation on complexes of representative model compounds and solvent molecules of different sizes indicates that the London dispersion contribution to the interaction enthalpy only accounts for a minor fraction of the dissociation barrier, at variance with earlier findings of Grunwald and co-workers. It is suggested that the rate of dissociation of amine–water or amine–alcohol complexes is primarily determined by the Gibbs free energy contributions from the pK_a-dependent hydrogen-bond breaking, dispersion forces between acceptor and donor, and the energy required to create a cavity prior to dissociation.

Proton transfer from protonated amines to water frequently occurs through a hydrogen-bonded amine–water complex according to the Swain–Grunwald mechanism.[1] This is experimentally manifested by the retardation of the rate of proton exchange between ammonium ions and water by the addition of acid. The reason for this inhibition is that the proton that has been transferred to a water molecule may be transferred back to the amine before it undergoes diffusional separation. The mechanism is shown in Scheme I.

According to this mechanism, the initial product is the amine–water hydrogen-bonded complex in which the proton transferred makes up the hydrogen bond. For proton exchange to occur the amine–water complex must dissociate. The rate law for the proton exchange in acidic solutions is given in eq 1. The

$$k_{ex} = v/[\text{BH}^+] = k_a k_H/(k_H + k_{-a}[\text{H}^+]) + k_2[\text{B}] \quad (1)$$

second term is the direct deprotonation by free amine through a water molecule, a reaction that is not significant at low pH. The factor $k_H/(k_H + k_{-a}[\text{H}^+])$ signifies the probability that the amine–water complex is dissociated before the hydrated amine returns to BH$^+$. The measurement of the observed rate of exchange, k_{ex}, at various pH values enables the derivation of all the rate constants, k_a, k_{-a}, k_H, and at higher pH, k_2 provided that the pK_a is known.

In a series of papers, Grunwald and his co-workers[2-9] examined various amines in water and other protic solvents, and made several important observations. (1) Surprisingly, k_H showed no obvious dependence on the base strength. This conclusion was, however, drawn from the results of only a few compounds. It might have been expected that the strongest base forms the strongest hydrogen bond, and thus the least readily dissociated complex. (2) The dissociation rate constant, k_H, varies as the reciprocal of the viscosity of the medium. (3) For nonpolar substituents, k_H depends on the molar volume of the amine, such that a complex of a larger amine dissociates more slowly. (4) A decrease of k_H was also observed for an increase in the size of the hydrogen-bond-donating solvent in the series H$_2$O, CH$_3$OH, and (CH$_3$)$_3$COH.[9] In order to account for these observations, Grunwald and co-workers treated the breaking of the hydrogen bond as a diffusional dissociation process with a stabilized ground state owing to London dispersion interactions, which were assumed to be negligible in the transition state.[1,9] This hypothesis was supported by calculation of the London dispersion energies for complexes between *N,N*-diethyl-*m*-toluidine and water, methanol, and *tert*-butyl alcohol.

Scheme I
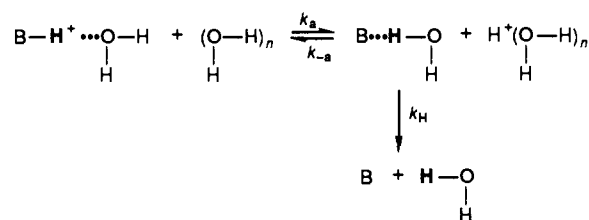
Thus, the enthalpy difference in dispersion interactions for the *tert*-butyl alcohol was calculated to be 6.7–7.9 kcal mol^{-1} larger relative to the hydrate, while the experimental difference in $-RT \ln k_H$ is 6.0 kcal mol^{-1}.

In an investigation of the rate of phosphoryl transfer to substituted quinuclidines from various substrates, one of us (W.P.J.) found that a plot of log k against pK_a for the ammonium ions gave slopes of $\beta_{nuc} \approx -0.1$.[10] This decreasing reactivity with increasing nucleophile basicity was attributed to a requirement for desolvation of the amine before nucleophilic attack, and a β_{diss} of -0.2 for desolvation was suggested. This result raises some questions regarding the conclusions of Grunwald and co-workers.

We report here a ^{1}H NMR investigation of the rate of proton transfer of some substituted quinuclidines (1-azabicyclo[2.2.2]-octane) in aqueous solutions. The amines were chosen so as to eliminate, as much as possible, other parameters than basicity that may influence the rate, and also to eliminate other mechanisms for the dissociation of the complex, such as Walden inversion about nitrogen rather than removal of the water molecule by diffusion. Differences in size and London dispersion forces for the various quinuclidines were considered negligible as well. We also carried out computations of the van der Waals interactions between

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†Present address: Organic Chemistry 3, Chemical Center, University of Lund, P.O. Box 124, S-221 00 Lund, Sweden.

representative models of N,N-diethyl-m-toluidine complexes with water, methanol, and *tert*-butyl alcohol utilizing a modern force field (MM2-85) and including an energy-minimizing procedure. This force field has been tested to reproduce both intra- and intermolecular interactions dominated by London dispersion forces. A reinvestigation of trimethylamine was also performed for comparison with earlier results.

Experimental Section

Commercial substituted quinuclidine hydrochlorides were recrystallized twice, dried, and stored in vacuo. 3-Cyanoquinuclidine was prepared according to Grob et al.[11] from 3-quinuclidone hydrochloride (2.5 g), (p-tolylsulfonyl)methyl isocyanide (TosMIC, 4.0 g), and absolute ethanol (1.6 mL) in dry dimethoxyethane (60 mL) by addition of potassium *tert*-butoxide (6.2 g) at 5–10 °C. After heating at 40 °C for 1 h, cooling, and filtration, the amine hydrochloride was precipitated by an HCl–ether solution. The precipitate was made basic by aqueous K_2CO_3 solution and the amine was extracted by ether. Evaporation gave ca. 2 g of an oil, which was distilled at reduced pressure. The distillate was dissolved in a small amount of absolute ethanol and the hydrochloride was precipitated by concentrated HCl. Recrystallization from absolute ethanol gave 0.9 g of white crystals, mp 211–13 °C (lit. mp 212–13 °C).[12]

Solutions for Kinetic Measurements. Stock solutions of amine hydrochlorides (1 M) were freshly prepared before each experiment. Samples were 0.1 M in amine hydrochloride and 10% in D_2O. The pH was measured with an Orion Research Model 701A pH meter with a Radiometer GK2321C combination electrode standardized at pHs 7.0 and 4.0. Pasteur pipets and NMR tubes were rinsed with the solutions to reduce drift in pH. The pH was measured at room temperature both before and after NMR experiments and agreed within 0.1 pH unit. The pH value was used without correction for the effect of D_2O (the correction in pH is 0.04 unit for 10% D_2O).[13]

Solutions in strong acids were prepared according to ref 14 and the H_0 acidity function[15,16] was used, but it was verified that the same results within the experimental error were obtained with the H_0''' function.[17]

pK_a values for quinuclidinium and 3-chloroquinuclidinium ions in 10% D_2O at 25 °C were determined from the pH of dilute buffer solutions and were identical with those given earlier[11] within experimental errors (±0.04 pH unit). Glass-distilled water was used throughout.

NMR measurements were performed on a 500-MHz instrument designed by Redfield.[18] For experiments in H_2O, the solvent signal was suppressed by a "214"[19] or a modification[20] observation pulse sequence. All spectra were recorded in 5-mm nonspinning NMR tubes. Routine ^{1}H and ^{13}C spectra were recorded on a Varian XL-300 NMR spectrometer.

Kinetics for the proton exchange was studied by three different NMR techniques, which made it possible to cover a range of rate constants of ca. 10^6. (1) In the fast exchange rate region ($k_{ex} > 100$ s^{-1}), the band-shape method was applied to the NH signal. These experiments were restricted to exchange rates where the NH signal could be observed and treated by band-shape methods (below coalescence). Rate constants were derived by both band-broadening and total band-shape methods.[21] (2) In the intermediate exchange rate domain ($0.02 < k_{ex} < 100$ s^{-1}), k_{ex} was determined by a combined saturation-recovery and saturation-transfer procedure.[22,23] The NH proton resonance was saturated by a long (0.2 s) weak preirradiation pulse, followed by a 3-ms homospoil pulse (to reduce signals induced by the preirradiation pulse), a 2–4-ms recovery time to allow homogeneity to recover, and a variable delay, τ, before the observation pulse was applied. The free induction decay was stored followed by a restoration time of 0.5–5 s before repeating the cycle four times, after which a Fourier transform was performed. The entire se-
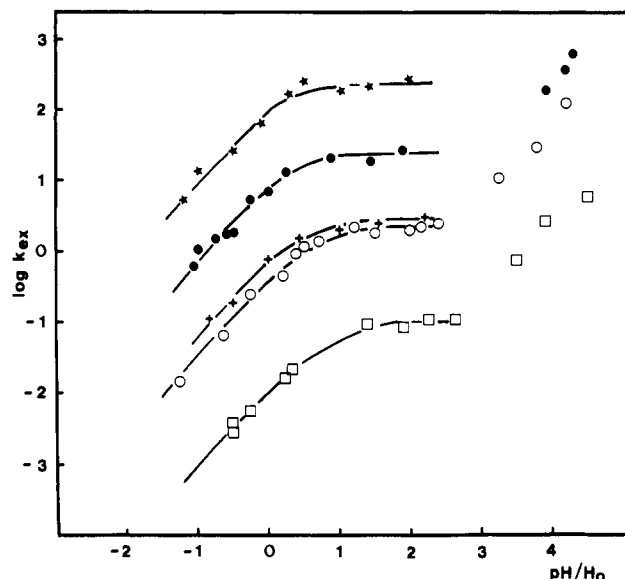
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Figure 1. The pH/H_0 dependence of log k_{ex} for 3-X-quinuclidines (X = CN, ★; Cl, ●; OH, O; H, □) and for $(CH_3)_3N$ (+) at 25 °C in water + 10% D_2O. The curves are calculated from eq 5.

quence was repeated for 8 τ values and the end point was determined by using a τ of about 5–8 times the halftime.

Pseudo-first-order recovery rate constants, k_{rec}, were obtained from semilog plots according to eq 2, where M_z, the magnetization along the z axis, was measured as the height of the signal. The rate constant k_{rec}

$$\log [M_z(\infty) - M_Z(\tau)] = \log [M_z(\infty) - M_z(0)] - k_{rec}\tau \qquad (2)$$

is composed of two terms, the proton exchange constant, k_{ex}, and the magnetic relaxation constant, k_{magn} (= $1/T_1$), such that $k_{rec} = k_{ex} + k_{magn}$. The exchange rate, k_{ex}, was extracted by measuring the saturation transfer from water to NH.[21,24,25] The water signal was completely saturated by a preirradiation pulse of 0.5–8 s, followed by a short delay (1–3 ms) and the observation pulse. This led to reduced intensity of the NH signal due to the transfer of saturated protons from water. The reduction is determined by taking a difference spectrum between preirradiation at a frequency symmetric about the NH frequency and preirradiation at water in order to reduce "spillover" effects. The fraction of saturation transfer, f_{sat}, is defined by eq 3, in which I_{off} and I_{on} are the heights of the NH signal with off and on resonance preirradiation, respectively. The product $f_{sat}k_{rec}$ then gives the rate constant for chemical

$$f_{sat} = (I_{off} - I_{on})/I_{off} = k_{ex}/(k_{ex} + k_{magn}) \qquad (3)$$

exchange, k_{ex}. (3) In the slow exchange region ($k_{ex} < 0.016$ s^{-1}), the rate was determined by classical kinetics. The intensity of the NH signal was followed immediately after the ammonium salt had been dissolved in DCl/D_2O by running the spectrum at suitable intervals and storing the free induction decays over at least 3 half-lives. These rate constants were corrected for the use of D_2O with respect to pH (pD – pH = 0.4 pH unit)[13] and viscosity ($\eta_{D_2O}/\eta_{H_2O} = 1.23$).

Molecular Mechanics Calculations. The computations were performed with utilization of the MM2(1985) force field.[26,27] The newer versions of this force field also include hydrogen bonds that are simulated by adjustment of the van der Waals parameters of the atoms making up the hydrogen bond as well as by electrostatic interactions. This makes the results less straightforward to interpret for our purpose. Therefore, we used two different approaches, which are described in the following section. Input structures for the MM2 calculations were constructed by the molecular modeling program system MIMIC.[28] In the version without hydrogen bonds, the total steric energies of the isolated acceptor and

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Dissociation of Amine-Water Complexes

J. Am. Chem. Soc., Vol. 113, No. 18, 1991 6999

Table I. Rate Constants for Proton Exchange of 0.1 M 3-X-Quinuclidinium and Trimethylammonium Ions in Water with 10% D_2O at 24.7 °C Calculated by Eq 5

amine	$pK_a{}^a$	$k_a{}^0$ (s^{-1})	$10^{-10} k_{-a}{}^0$ (s^{-1} M^{-1})	$10^{-9} k_H{}^0$ (s^{-1})
Q^b	11.29	0.11	2.2	1.9
3-OH-Q	9.91	2.6	2.1	3.1
3-Cl-Q	8.85	25	1.8	6.8
3-CN-Q	7.89	230	1.8	12
$(CH_3)_3N$	9.80	2.72	1.7	5.1

^{a} pK_a values from ref 11. ^{b} Q = quinuclidine.

donor molecules, E_m, and of the geometry-optimized complexes, $E_{complex}$, were calculated. These values are force field dependent and have no physical meaning. The interaction enthalpy was obtained by subtracting the energy of the two isolated molecules from that of the complex, according to eq 4.

$$\delta E_{disp} = E_{complex} - \sum E_m \qquad (4)$$

In the second approach, standard force field parameters were used with the following modification: the hydrogen-bond parameters simulating hydrogen bonds between OH and the aromatic carbon atoms in this force field were replaced with standard van der Waals parameters. These calculations were carried out on the hydrogen-bonded complexes of N,N-diethyl-m-toluidine with water, methanol, and $tert$-butyl alcohol. The dispersion part of the interaction was then extracted by summation of the van der Waals term for all atom–atom pairs in the two molecules.

Results

Kinetic Results. The observed rate constants (k_{ex}) for the proton exchange were determined at 24.7 ± 1.0 °C over the experimentally available pH range by dynamic ^{1}H NMR techniques, and a plot of log k_{ex} versus pH/H_0 is shown in Figure 1. The three domains expected from operation of the Swain–Grunwald mechanism, given as eq 1, were obviously obtained. The curves for the data obtained at pH <3 have been calculated from eq 5, which is obtained from eq 1 in which k_a is replaced according to eq 6 due to inhibition of the rate of ionization of an acid in strong acidic media because of acidity function effects.[14] The rate constants are defined in Scheme I, and superscripts zero mean that the rate constants signify values in dilute aqueous solution. The quotient η_0/η is the viscosity relative to the viscosity in dilute solution,[29] and h_0 = antilog $(-H_0)$.

$$k_{ex} = \frac{K_a k_{-a}^0 \dfrac{\eta_0}{\eta} \dfrac{[H^+]}{h_0} k_H^0 \dfrac{\eta_0}{\eta}}{k_H^0 \dfrac{\eta_0}{\eta} + k_{-a}^0 \dfrac{\eta_0}{\eta}[H^+]} \qquad (5)$$

$$k_a = k_{-a} K_a \frac{[H^+]}{h_0} \qquad (6)$$

The rate constants that match the curves[30] are shown in Table I, including also values for trimethylamine for comparison. A conservative estimate of the accuracy in the rate constants gives errors of the order of 20%. The relative error between the compounds in the series is smaller, however, since systematic errors, such as in temperature and from acidity function, cancel. We estimate the relative error to be of the order of 10% or less. The rate constant k_2 for the catalysis of proton exchange by base, either free amine through water (eq 7) or hydroxide ion, was not evaluated in this work.

$$B-H^+\cdots O-H + B \rightleftharpoons H-O\cdots H^+B \qquad (7)$$
$$\qquad \qquad | \qquad \qquad \qquad \qquad |$$
$$\qquad \qquad H \qquad \qquad \qquad \qquad H$$
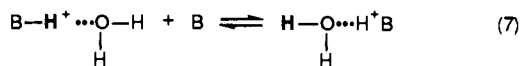
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(30) The rate constants were calculated from linear analyses in two domains: (i) $H_0 \lesssim 0$, in which $k_H^0 \ll k_{-a}^0$ [H$^+$], and eq 5 after logarithmation is reduced to log $k_{ex}/(\eta_0/\eta)$ = log K_a k_H^0 + H_0 and (ii) $1 \lesssim pH \lesssim 3$, where k_{-a}^0 [H$^+$] $\ll k_H^0$, and eq 5 is reduced to $k_{ex} = K_a$ k_{-a}^0 η_0/η. Subsequently, the complete eq 5 with the obtained rate constants was visually checked in the entire region.
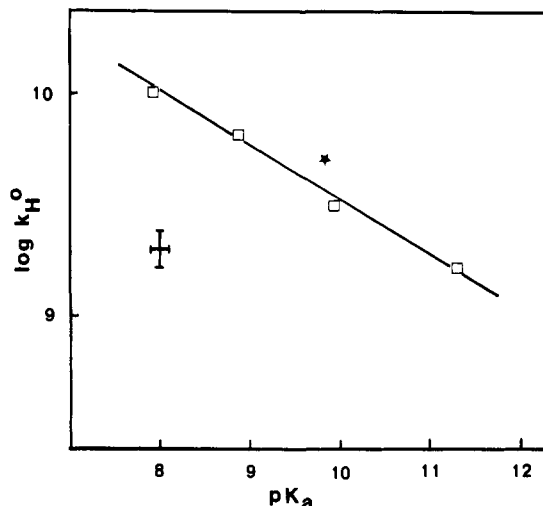
Figure 2. Brønsted type plot for the rate of exchange of substituted quinuclidines at 25 °C in water + 10% D_2O. The value for trimethylamine (★) is not included in the correlation.
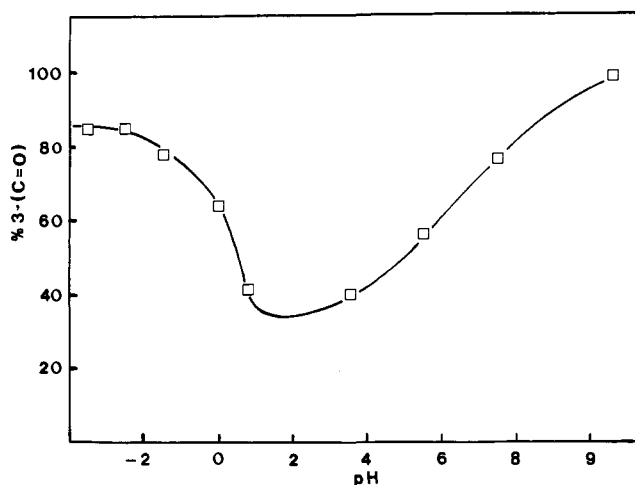

Figure 3. The pH dependence of the equilibrium between keto and hydrated forms of 3-quinuclidone.

Table II. ^{13}C NMR Chemical Shifts of the Two Species of 3-Quinuclidone in D_2O at pD 4.4^a

C atom	D	D
2	58.2	61.8
3	208.9	92.8
4	39.5	34.3
5, 8	22.5	21.4
6, 7	49.4	48.3

^{a} Dioxane (δ 67.0) was used as internal reference.

The effects on the exchange rate of the concentrations of the ammonium ion and of added potassium chloride were investigated for 3-chloroquinuclidinium chloride in the concentration range 0–1 M. A minor decrease in k_{ex} of 30–35% over this range was observed in agreement with observations by Grunwald and coworkers for added electrolytes.[4] Likewise, an increase of the D_2O content from 0 to 50% (v/v) resulted in an 18% decrease in k_{ex}.

The logarithms of the rate constants for dissociation of the amine–water complexes, k_H^0, are plotted against the pK_as of the conjugate acids of the amines in Figure 2. The slope of β_{diss} = −0.25 ± 0.04 indicates that in a series of compounds of minimal structural variation, k_H^0 does indeed depend on pK_a and the slope is close to the value (−0.2) suggested by Jencks et al.[10] The point

7000 *J. Am. Chem. Soc., Vol. 113, No. 18, 1991*

Berg and Jencks

Table III. Steric Energies (in Kilocalories per Mole) of the Isolated Molecules, E_m, and of Complexes, $E_{complex}$, between m-Xylene and Water, Methanol, and *tert*-Butyl Alcohol, Respectively, and the Interaction Energies, δE_{disp}, Calculated by the MM2(1985) Force Field

compd	E_m	$E_{complex}$	δE_{disp}
m-xylene	-1.44		
water	0.0	-3.33	-1.89
methanol	0.05	-3.55	-2.16
tert-butyl alcohol	2.99	-1.87	-3.42

for trimethylamine, also shown in the figure, is not included in the correlation. However, there is a discrepancy between our values for k_a, k_{-a}^0, and k_H^0 compared to those of Grunwald et al.[1,4] for trimethylamine by a factor of 1.5 to 2. The experiments with trimethylamine were repeated on two different instruments and by two different techniques: band-shape analysis and saturation recovery.

Originally, 3-quinuclidone was included in the study, but it was observed that new signals appeared in the NMR spectrum in acidic solution, and ^{1}H and ^{13}C NMR analysis at several pH values revealed that the carbonyl group was partly hydrated in a broad pH range. The evidence comes mainly from the ^{13}C NMR spectra and the chemical shifts of the two species are given in Table II. The pH dependence of the equilibrium is shown in Figure 3. The N-protonated form is the most readily hydrated, giving rise to the curve in the pH range 3–9, whereas the decrease in hydration at low pH is probably caused by the decrease of water activity. Attempts to determine the rate of proton exchange in both species of the equilibrium failed due to the complicated equilibria involved, but an approximate pK_a for NH^+ dissociation of 8.0 ± 0.3 was estimated for the hydrate. The accuracy of this value is, however, uncertain due to the complicated equilibria involved.

We also tried to determine the rate of proton exchange in the dication of diazabicyclooctane. Although a few rate constants could be determined by band-shape analysis in very acidic solutions ($H_0 \approx -3.5$), the calculation of rate constants, k_H, from these data was not considered meaningful.

Molecular Mechanics Calculations. Grunwald and Ralph[1,8,9] presented both experimental and computational evidence in support of their suggestion that London dispersion forces are the dominating factor determining the rate of dissociation of the amine–water complexes. The computational results stem from the application of the methods of London and Linder to complexes constructed from molecular models and did not include forces due to van der Waals repulsion, nor did they include energy minimization. Since we now have in our hands force fields that have been tested to reproduce both structures and energies of conformational equilibria determined primarily by London dispersion interactions as well as for van der Waals complexes[31-34] and efficient programs for energy minimization, we found it worthwhile to apply these to the same systems as those studied by Grunwald and co-workers, i.e. the solvates of N,N-diethyl-m-toluidine and water, methanol, and *tert*-butyl alcohol, respectively.[9] These systems are particularly illustrative because the differences in dispersion forces between water and *tert*-butyl alcohol complexes with N,N-diethyl-m-toluidine are comparatively large. In a first attempt we replaced N,N-diethyl-m-toluidine with m-xylene. The two molecules give very similar dispersion interactions with a molecule above the plane, particularly when the ethyl groups point toward the opposite side as expected in the hydrogen-bonded complex, and furthermore, no manipulations with the force field are needed. Thus, m-xylene was allowed to dock with water, methanol, and *tert*-butyl alcohol, respectively, and the minimum-energy geometries of the complexes were found. The

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Table IV. Results of the MM2 Calculations for Formation of the Hydrogen-Bonded Complexes of N,N-Diethyl-m-toluidine with Water and *tert*-Butyl Alcohol[a]

	δE (kcal mol^{-1})
stretch	-0.104
bend	0.039
stretch-bend	-0.012
torsion	0.215
van der Waals	
1,4	0.094
other	**-3.752**
dipole	0.013
H-bond	-3.113
sum	-6.620

	δE (kcal mol^{-1})
stretch	-0.064
bend	0.022
stretch-bend	-0.007
torsion	0.101
van der Waals	
1,4	0.032
other	**-1.258**
dipole	0.074
H-bond	-3.157
sum	-4.257

[a] δE values are differences between the calculated energies for the complex and the sum of the energies of isolated molecules of acceptor and donor.

tert-butyl alcohol complex was not allowed to assume structures in which all three methyl groups were pointing toward the ring, since this clearly is an unrealistic model for the hydrogen-bonded complex and affects the magnitude of the dispersion interaction considerably. The results are given in Table III. The calculated difference in the enthalpy contribution from dispersion interactions, $\Delta \delta E_{disp}$, between *tert*-butyl alcohol and water complexes with m-xylene is thus 1.53 kcal mol^{-1}.

We then proceeded by constructing hydrogen-bonded models of N,N-diethyl-m-toluidine complexes with water and *tert*-butyl alcohol. The force field had to be slightly modified because the hydrogen bond is partly simulated by van der Waals attraction. Thus, "normal" van der Waals parameters were used for the oxygen-bound hydrogens to $C(sp^2)$ carbons instead of the "hydrogen-bond" parameters. The hydrogen bond was represented by electrostatic interactions (dipole–dipole) and by the van der Waals attraction between the oxygen-bound hydrogen and the nitrogen atom. In this case, the dispersion part of the interaction energy had to be extracted from the van der Waals forces between the two molecules in the complex. The results of these calculations are shown in Table IV.

The calculated dispersion enthalpies differ, not surprisingly, somewhat in the two models. Nevertheless, a comparison with the experimentally obtained *difference* in dissociation barrier of the complexes between N,N-diethyl-m-toluidine with *tert*-butyl alcohol and with water, 6.0 kcal mol^{-1},[1,9] should be compared with the *difference* in calculated dispersion forces, 1.5–2.5 kcal mol^{-1}, depending on the model used.

These results suggest that the dispersion contribution to the interaction enthalpy only accounts for a minor part of the sub-

stituent effect on the dissociation barrier.

Discussion

The rate constants of the proton exchange reactions of quinuclidinium ions with water were found to decrease in acidic solutions according to the Swain–Grunwald mechanism, as shown in Figure 1. The rate constants for proton transfer as well as for the dissociation of the amine solvates (Scheme I) were calculated by the rate law in eq 1, after correction for acidity function and viscosity effects according to eq 5, and are given in Table I. The Brønsted plot in Figure 2 shows the dependence of the rate constants for dissociation of the water–amine complexes on the pK_a of the protonated amines. There is a decrease in the rate of dissociation as the quinuclidine becomes more basic. The slope of $\beta_{diss} = -0.25 \pm 0.04$ is consistent with the value proposed earlier,[10] and helps in understanding the surprising effect of basicity change on the rate of phosphoryl transfer reactions[10] and other reactions with small intrinsic values of β_{nuc}.

Amines are less strongly solvated than oxygen anions, for example, but there is evidence for a substantial solvation energy of amines in water. The Gibbs free energy for breaking the hydrogen bond between water and pyridine in water solution has been estimated to be as large as 4.3 kcal mol^{-1}.[35] The value in CCl$_4$ has been measured as 4.1 kcal mol^{-1}.[36] If the recombination rates of water and amine were known, our k_H values could be used to estimate the strength of the hydrogen bond of the quinuclidines in water solution. Although we have no direct access to the value of this rate constant, an approximate estimate should be the dielectric relaxation rate of water, which is 1.06×10^{11} s^{-1}.[37] This value leads to equilibrium constants $K_{diss} = k_H/k_{relax}$ giving Gibbs free energies for breaking the hydrogen bond at 25 °C for 3-X-quinuclidines of 2.4 (X = H), 2.1 (X = OH), 1.6 (X = Cl), and 1.3 (X = CN) kcal mol^{-1}. The difference between the extreme values ($\Delta pK_a = 3.4$) is 1.1 kcal mol^{-1}. This difference may be compared to the difference in the free energies for hydration from the gas phase between 4-methylpyridine and 3-chloropyridine ($\Delta pK_a = 3.2$), which is 0.87 kcal mol^{-1}.[38]

Although our results indicate that basicity indeed has an effect on the rate of dissociation of the amine–water complex, it is obvious that there are also other contributions to the dissociation barrier.[1] Analogous to the work of Krishnan and Friedman[39-42] for the thermodynamics of solutions of amines, we consider these predominant terms: hydrogen-bond breaking between water and amine (E_{HB}); van der Waals dispersion forces between water and the amine molecule (E_{DISP}); and formation of a cavity (E_{CAV}) prior to dissociation. Other minor factors may also contribute, such as variation in solvent structure. We believe that the E_{HB} term is dominating for the substituent effect in the quinuclidine series, because the 3-substituents are far away from the hydrogen-bonding water molecule and are small compared to the rest of the amine molecule.

In other cases, such as the series studied by Grunwald and his co-workers; methyl-, dimethyl-, trimethyl-, and triethylamine, E_{DISP} contributes and even seems to dominate the substituent effect. Quantitatively, E_{DISP} and E_{CAV} are best considered by comparing the complexes of N,N-diethyl-m-toluidine with water and with $tert$-butyl alcohol, respectively.[9] $tert$-Butyl alcohol is less acidic than water and thus, if anything, should be expected to give a weaker hydrogen bond. Still the amine–water complex dissociates 2.5×10^4 times faster than the $tert$-butyl alcohol complex. We calculated that about 40% of that difference could

Table V. Values for the Calculation of E_{CAV}

compd	V_m (cm^3 mol^{-1})	P_i (cal cm^{-3})^a	P_i (mixture)^b	E_{CAV} (kcal mol^{-1})
H$_2$O	18	36	41	0.74
$tert$-butyl alcohol	74	80	41	3.85

^{a}From ref 45. ^{b}11.47 mol % $tert$-butyl alcohol–88.53 mol % water.

Table VI. Comparison Between Gibbs Free Energy of Activation for Dissociation, $\Delta G^{\ddagger}$, of N,N-Diethyl-m-toluidine (DEMT) Complexes with Water or $tert$-Butyl Alcohol, and for Trimethylamine with Water, and Calculated Values for E_{HB}, E_{DISP}, and E_{CAV} (Energies in Kilocalories per Mole)

system	$\Delta G^{\ddagger}$	$E_{HB}{}^a$	E_{DISP}	E_{CAV}	ΣE
DEMT/H$_2$O	4.1^b	3.2	1.3	0.7	5.2
DEMT/t-BuOH	10.1^b	3.1	3.8	3.8	10.7
(CH$_3$)$_3$N/H$_2$O	3.8^c	3.2	1.3	0.6	5.1

^{a}From molecular mechanics calculations. ^{b}From ref 9. Temperature 25 °C. ^{c}The observed enthalpy and entropy of activation for dissociation of the trimethylamine–water complex are $\Delta H^{\ddagger} = 2.3$ kcal mol^{-1} and $\Delta S^{\ddagger} = -5.0 \pm 4.0$ eu, respectively.[4]

be ascribed to the E_{DISP} term.

Is it possible, then, to estimate E_{CAV}? In the example mentioned, cavities to hold a water or a $tert$-butyl alcohol molecule must be created before these molecules can jump. There are various methods to estimate E_{CAV}.[43,44] Since the experiments considered here are performed in a solvent mixture, which complicates such calculations, we decided to try a very simple estimate of E_{CAV}. By this method, E_{CAV} is given by eq 8, in which P_i is the internal pressure of the solvent and V_m is the molar volume of the jumping molecule. Internal pressures, P_i, defined by eq 9, have been tabulated for various solvents, and solvent mixtures have also been studied.[45] We simply used a linear interpolation of the P_i for the individual solvents, an assumption that is probably not seriously erroneous.[45] The results are given in Table V. The

$$E_{CAV} = P_i V_m \tag{8}$$

$$P_i = \left(\frac{\partial U}{\partial V}\right)_T \tag{9}$$

difference, $\Delta E_{CAV} = 3.1$ kcal mol^{-1}, thus represents the calculated enthalpy contribution to the difference in activation energy of 6.0 kcal mol^{-1}. So far we have concentrated on differences between water and $tert$-butyl alcohol complexes. Table VI shows a comparison of experimental Gibbs free energies of activation and the theoretically derived components. It should be noted that E_{CAV} is constant as long as water complexes in water solution are considered, and the small difference in E_{CAV} between DEMT/H$_2$O and (CH$_3$)$_3$N/H$_2$O comes from the fact that slightly different solvents were used in the experiments.

Obviously, the experimental and calculated values are not directly comparable, since the former refer to Gibbs free energies and the latter to enthalpies. The only available experimental data on the entropy of activation is the value of $\Delta S^{\ddagger} = -5 \pm 4$ eu for trimethylamine/water.[4] It seems likely that this small negative value is the consequence of large and nearly compensatory contributions from hydrogen-bond breaking, hydrophobic effect differences, and cavity formation. Taking this into account and considering the approximate character of the calculated values in Table VI, the agreement might be considered undeserved, but at least it does not contradict our approach.

Conclusions

The experimental and computational results presented here indicate that the effect of the structure on the rate of desolvation of amines has a more diverse origin than was originally proposed

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by Grunwald and his co-workers. The substituent effect of 3-X-quinuclidines shows that a complex of a more basic amine dissociates more slowly, and the slope of a Brønsted type plot is β_{diss} = −0.25 ± 0.04. Molecular mechanics calculations indicate that dispersion forces represent at most 40% of the activation energy for dissociation of the *N,N*-diethyl-*m*-toluidine–*tert*-butyl alcohol complex, and simple calculation of the cavity term suggests that this may be as important as the dispersion term for this complex. These results help in understanding the surprising effect of basicity change on the rate of phosphoryl transfer reactions[10] and other reactions with small intrinsic β_{nuc} values, as well as the effect of solvation in protic solvents in general.

Free-Radical Telomerization of Chiral Acrylamides: Control of Stereochemistry in Additions and Halogen-Atom Transfer

Ned A. Porter,* Robert Breyer, Elizabeth Swann, James Nally, Jyotsna Pradhan, Timothy Allen, and Andrew T. McPhail

Contribution from the Department of Chemistry, Duke University, Durham, North Carolina 27706. Received April 1, 1991

Abstract: The free-radical reactions of carbon radicals substituted α to a chiral pyrrolidine amide have been studied. The pyrrolidine used was 2,5-dimethylpyrrolidine, available as either the *R,R* or *S,S* enantiomer from D- or L-alanine, and the radicals were generated (1) by tin radical abstraction of the halogen from the 2-iodobutyramide of the pyrrolidine, (2) by decomposition of a pyrrolidine amide substituted Barton ester **4**, and (3) by radical addition to the acrylamide of the pyrrolidine **3**. Addition of chiral α amide radicals to alkenes occurs with a selectivity of ∼15:1 at room temperature, while bromine- and iodine-atom transfer to these radicals occurs with a selectivity of 10:1 at room temperature. Telomerization of the acrylamide **3** is achieved by photolysis of BrCCl₃ in the presence of acrylamide. Telomers are readily formed and the lower telomers, *n* = 1 to 5, were isolated and characterized. Halogens were removed from the telomers by reduction with tributyltin hydride and in this way, the major diastereomers of the *n* = 2 and *n* = 3 telomers were converted to known compounds. Chain-transfer constants for the BrCCl₃ telomerization were determined and they range from 0.3 to 0.5 for $C_n = C_2$ to C_5. An analysis of the chiral amide auxiliary is presented that may prove useful in the consideration of other auxiliary groups.

Control of stereochemistry in the free-radical addition reactions of vinyl monomers has been of interest since 1929 when Staudinger[1,2] pointed out that the tertiary carbons formed in vinyl polymerizations are asymmetric and can assume both the *meso* (isotactic) and *racemic* (syndiotactic) arrangements. Significant stereoregulation in free-radical addition to vinyl monomers has not been observed, atactic polymers generally resulting from free-radical polymerization.[3] The ratio of rate constants that determines the selectivity for methyl acrylate (R = COOMe) is k_i/k_s = 1.1 at 0 °C, for example, and the polymers that result are atactic. In an authoritative review of stereoregulation in polymerization, Pino and Suter suggest that "the perspectives for stereocontrol in free radical polymerization are not very promising" outside of work in "polymerization of monomers included in solid matrices which seem to be today (1976) the only way to obtain highly stereoregular polymers with radical polymerization."[4]

In the polymerization of achiral vinyl monomers, the important stereocontrol element for consideration is the stereogenic center nearest to the radical terminus of the growing chain. If this nearest "R" group were to control the face of the prochiral radical to which addition occurred, stereoregulation would be achieved. This

nearest center effect on stereoselection, which is essentially a 1,3 steric interaction, is apparently small due to the conformational mobility of the chain, which does not "fix" the stereogenic center relative to the radical.

nearest chain stereogenic center control
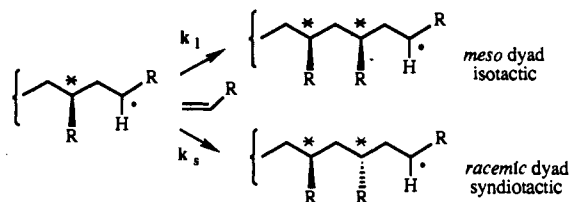
The use of chiral monomers that have an auxiliary group that exerts a biasing effect on the radical face selected for addition is an alternate approach to control polymer tacticity. In this strategy, the chirality of the auxiliary group, R*, would define the stereochemistry of the stereogenic center formed during each addition. If a monomer was chosen that carried with it the auxiliary, a controlling effect would be exerted in the radical addition and a controlling group would also be introduced at the growing radical terminus in each addition step, assuring control at the next step of chain growth in the serial addition sequence.

The use of an auxiliary to control the stereochemistry in the addition reactions of acyclic radicals like those in a growing vinyl free-radical polymer chain is a problem that has not been previously solved, and therefore advances in control of polymer

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