Proton Cryptates. Kinetics and Thermodynamics of Protonation of the [1.1.1] Macrobicyclic Cryptand

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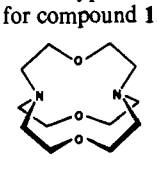
Abstract: The [1.1.1] macrobicyclic cryptand, **1**, binds one or two protons either outside or inside its intramolecular cavity. The structures of the different mono- and diprotonated forms thus produced have been assigned on the basis of their spectral properties and their proton transfer rates. Five forms have been identified, io^+, o^+o^+, i^+i, i^+o^+, and i^+i^+, and the thermodynamics and kinetics of their interconversion have been studied. External mono- and diprotonation or deuteration were studied in D_2O, acetone-d_6, and methanol-d_4. The protonation equilibrium with trifluoroacetic acid in acetone-d_6 was slow enough at 270 K to yield separate ^1H NMR signals for the four sets of nonequivalent protons of the externally monoprotonated species, **[1]**·H^+. In H_2O and D_2O, the pK_{a1} value for the externally monoprotonated species io^+ is 7.1 ± 0.2, while pK_{a2} for the externally diprotonated species o^+o^+ is ≃1. The rates of proton transfer into and out of the cavity are very slow. The internally monoprotonated species, i^+i, cannot be deprotonated unless the cryptand is destroyed. One of the two protons of the internally diprotonated species, i^+i^+, may be removed by base, but only under rigorous conditions. The rates of formation of $[i^+i]$ and $[i^+i^+]$ in D_2O are very slow, with activation energies of about 110 kJ mol^{-1} for each of the processes. The rate of the first process varies with pH in a way which can be correlated with the pH dependence of the equilibria involving the externally protonated forms of **1**. The simplest interpretation is that internal protonation depends on the concentrations of the $[io^+]$ and $[o^+o^+]$ species which protonate internally with the rate constants at 299 K of 2.3 ± 0.3 × 10^{-4} s^{-1} and 3.8 ± 0.6 × 10^{-3} s^{-1}, respectively. The rates for the second internal protonation and the removal of the second internal proton have been studied as a function of temperature. The rate of deprotonation of $[i^+i^+]$ depends on the hydroxide ion concentration and also has an activation energy of about 110 kJ mol^{-1}. The rate data provide a means for estimating the thermodynamic stability of the various protonated species. The pK_b values for the first and second internal protonations of **[1]** at 298 K are respectively $pK_{b1} \geq -4$ ($\Delta G° \leq -20$ kJ mol^{-1}; $pK_{a1} \geq 18$), and $pK_{b2} \simeq 6$ ($\Delta G° \simeq +35$ kJ mol^{-1}; $pK_{a2} \simeq 8$). The results are summarized in Figure 4. Cryptand [1.1.1] is thus a thermodynamically very strong and kinetically extremely slow base. The possible mechanisms for proton transfer into and out of the cavity are discussed.

Proton transfer is one of the simplest, yet one of the most fundamental, chemical reactions, involved in such diverse processes as molecular and enzymatic catalysis, ionic conduction, membrane potentials, and of course all protonation–deprotonation processes occurring in acid–base reactions between chemical compounds of any type. Its kinetics and thermodynamics determine a great number of chemical processes and have been subject to extensive investigation.[1-3]

Proton transfer is usually very fast, but may be markedly affected by structural factors. The study of the influence of structure on proton transfer rates is of interest both as a means of studying the transfer reaction itself and, conversely, for characterizing structural features (steric hindrance, strain, hydrogen binding, etc.). Of special interest, in view of their scarcity and the information which they may provide, are systems which display highly repressed rates. Slow proton transfer has been found in N-alkylated derivatives of 1,8-diaminonaphthalene ("proton sponge")[4,5] where the proton is held in a particularly tight hydrogen bond.[6,7] Even slower rates occur in substances where the proton is contained inside an intramolecular cavity and where transfer involves exchange into and out of the cavity. Such is the case for protonation–deprotonation at the bridgehead amino groups in macrobicyclic diamines[8] and cryptands.[9-11] By far the slowest rates have been reported for compound **1**, the [1.1.1] cryptand[12,13]



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(following the usual cryptand nomenclature).[14] It forms proton cryptates, in which the protons are very efficiently concealed inside a tight molecular cavity strongly hindering the approach of the transfer agent.[12,13] An even tighter inside protonated structure is formed by 1,6-diazabicyclo[4.4.4]tetradecane, where, however, the proton can neither be inserted nor removed by simple proton transfer.[15,16]

We now describe a detailed study of the kinetics and thermodynamics of the genuine proton transfer processes which interconvert the [1.1.1] cryptand and its various proton cryptates.

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Chemical and spectroscopic studies[12,13] have demonstrated the remarkable nature of proton binding to the amine nitrogens of cryptand **1**. Protonation of the nitrogen sites in the exo (or out, *o*) configuration gives a monoprotonated [**1**]·H^+ and a diprotonated [**1**]·$2H^+$ species, in which the protons are outside the cryptand. Since protonation may occur inside (*i*) as well as outside the molecular cavity depending on the orientation of the nitrogen sites, it is necessary to specify more precisely the structure of the protonated species. With use of the symbols *i* or *o* and i^+ or o^+ for inside or outside configurations of the free amines and their protonated forms, [**1**]·H^+ may be either io^+ or oo^+, while [**1**]·$2H^+$ is o^+o^+. The lifetimes of these externally bound protons are short on the ^1H NMR time scale as for normal tertiary amines whereas the rates of conversion to the internaly mono- and diprotonated forms [$H^+\subset$**1**] and [$2H^+\subset$**1**] (where $\subset$ is the inclusion symbol) are very slow.[17] [$H^+\subset$**1**] may exist in principle in two forms, i^+i and i^+o, while [$2H^+\subset$**1**] is i^+i^+. Conversion of [$2H^+\subset$**1**] into [$H^+\subset$**1**] is very slow even in 5 M KOH at 330 K, and the latter is not deprotonated under these conditions even after several days. Finally, the additional species [$H^+\subset$**1**]·H^+, i^+o^+, which is protonated both externally and internally, can be detected in acidic solutions of [$H^+\subset$**1**]. The pH of a solution of the free amine [**1**], and the absence of N···$DCCl_3$ hydrogen bonding as shown by its IR spectrum, were used as evidence favoring predominantly the *ii* configuration at the bridgehead nitrogens.[13] The pH titrations described in this paper confirm this assumption and, together with the ^1H NMR spectra, provide information about the thermodynamics of external protonation and the thermodynamics and kinetics of internal protonation.[18]

On the basis of temperature-dependent ^1H and ^{13}C NMR studies, Cheney, Kintzinger, and Lehn[13] concluded that the effective D_{3h} symmetry on the NMR time scale at 298 K results from rapid interconversion of two conformers, each with C_{3h} or D_3 symmetry. Interconversion occurs by torsional motions about the single bonds in the three bridges. the motion could occur either simultaneously or consecutively and has the rather high free energy of activtion of 41.0 ± 0.4 kJ mol^{-1} at the coalescence temperature of 208 K in CHF_2Cl. Similar conformational changes which occur for the protonated species will be described in a separate paper.

Experimental Section

Cryptand [1.1.1] was synthesized as previously described[13] and purified by passing a diethyl ether solution through an alumina column. The deuterated solvents, methanol-d_4 (MSD Isotopes, Inc.), and acetone-d_6 (Stohler Isotopic Chemicals, Inc.) were dried by refluxing over BaO followed by vacuum distillation onto freshly dried type 4A molecular sieves (Linde, Union Carbide). Samples were prepared by distilling the solvent from the molecular sieves into NMR tubes which contained the solute. D_2O (99.85% D) from Norell Chemical Co., Inc. was used without purification.

The pD values of the buffers used in the rate studies were measured with a calibrated radiometer and were shifted upwards by 0.4 unit to correct for the deuterium isotope effect.[19] Temperatures were measured with a calibrated digital thermocouple. All ^1H and ^{13}C NMR spectra were obtained with a Bruker WH-180 NMR spectrometer operating in the pulsed Fourier-transform mode. Care was taken to ensure the absence of significant effects due to saturation and filter or delay time attenuation so that the spectra could be used for quantitative analysis of the various species. The largest analysis errors resulted from overlapping lines, but even in the worst case, rate constants with standard deviations below 20% were obtained. In most cases the standard deviations were less than 10% as estimated by a fit of the data with a nonlinear least-squares program.[20] All uncertainties given in this paper are statistical estimates of the marginal standard deviations based upon the least-squares analysis.

(17) The studies described in this paper involve both deuteration (in D_2O and methanol-d_4) and protonation (in acetone-d_6). To simplify the notation, we will generally refer to "protonation" and "deprotonation" processes and to pH rather than pD.

(18) Although small amounts of other configurations may be present, we will frequently use the notation *ii* for [**1**], io^+ for [**1**]·H^+ and i^+i for [$H^+\subset$**1**]. The notations o^+o^+, i^+o^+, and i^+i^+ are unambiguous.

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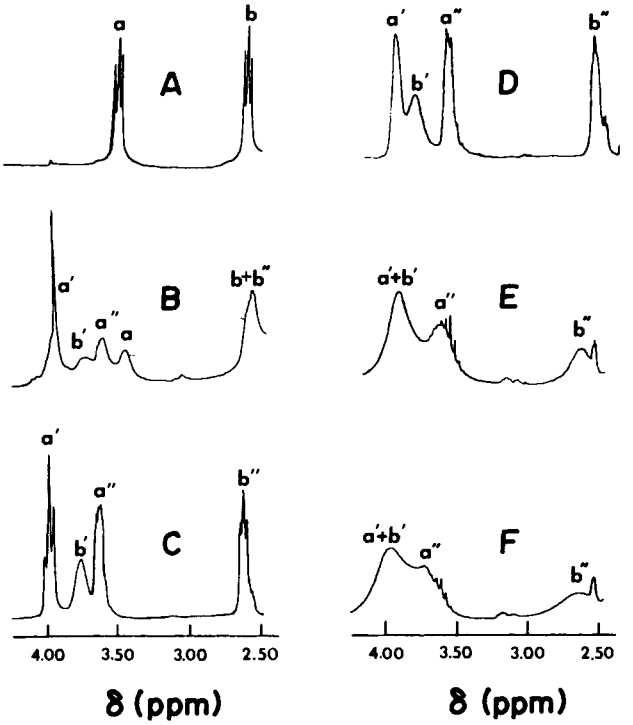
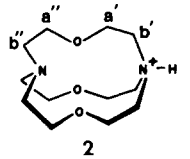


Figure 1. ^1H NMR spectra of [**1**] in acetone-d_6 at 270 K in the presence of various concentrations of trifloroacetic acid (TFAA). Approximate mole ratios, (TFAA)/**1** are: A, 0.0, B, 0.7; C, 1.4; D, 1.7; E, 8.4; F, 29. For signal assignments see text and structure **2**.

Results

External Protonation of 1. The [1]·H^+ and [1]·$2H^+$ Species and Their Deuterio Analogues.[19] Proton NMR spectra at 298 K of [**1**] in $CDCl_3$ and of i^+i and i^+i^+ in D_2O have been previously reported.[12,13] Because internal protonation is slow at low temperatures, it was also possible to obtain the ^1H NMR spectra of the *externally* monodeuterated species io^+ and approximate spectra of o^+o^+ as well as the mixed species i^+o^+.

When trifluoroacetic acid (TFAA) was added to a solution of [**1**] in acetone-d_6 at 270 K the ^1H NMR spectra changed as shown in Figure 1. The triplets of $-CH_2O$ and $-CH_2N$ at δ 3.47 and 2.56, respectively (a and b), diminished as the amount of TFAA increased with the introduction of four new well-defined peaks of the externally monoprotonated species. The chemical shifts (relative to Me_4Si) were 4.01 (a′, triplet), 3.88 (b′, broad singlet), 3.65 (a″, broad multiplet), and 2.68 (b″, triplet). The similarity of the NMR spectrum to that of the endo–exo monoborane adduct of C111, (*io*-BH_3)[13] is consistent with the assignments given for [**1**]·H^+ as the io^+ structure **2**. This result shows that the proton-exchange reaction between TFAA and [**1**] is slow on the NMR time scale at 270 K. Upon addition of excess TFAA, all signals broaden and the peaks of a″ and b″ decrease in intensity until at 50/1 mole ratio most of the area is contained within a single broad peak at δ = 3.9–4.0 ppm.



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When dichloroacetic acid (DCAA) is used, the exchange in acetone-d_6 is fast enough at 270 K to yield only broad, exchange-averaged peaks at 3.79 ppm and ~3 ppm for the $-CH_2O$ and $-CH_2N$ protons, respectively. The corresponding average shifts calculated from the results with TFAA are 3.83 and 3.28 ppm. The full widths at half-height are ~25 and ~94 Hz, respectively.

The difference in proton exchange rates with trifluoroacetic acid and dichloroacetic acid probably results from the difference

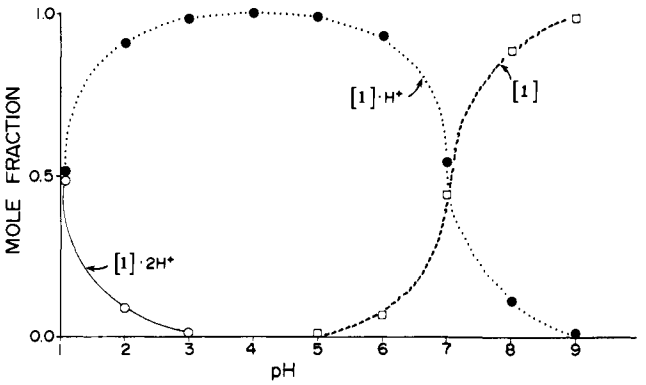

Figure 2. Relative concentrations of [1] and the externally protonated species as a functioin of pH, calculated by using $pK_{a1} = 7.1$, $pK_{a2} = 1.0$.

in their acidities. According to Eigen's theory of proton exchange rates[21] we can expect slow exchange on the ^1H NMR time scale when the pK_a values of the donor and acceptor differ by ~6–7 units. While the pK values are not known in acetone, the values for TFAA,[21] DCAA,[21] and [1]·H^+ in water are 0.23, 1.25, and 7.1, respectively. Therefore we would expect exchange times in the millisecond region for TFAA while the exchange rate with DCAA should be an order of magnitude faster.

The ^1H NMR spectra in D_2O vary with pH upon external deuteration. In particular, the signal from the $-CH_2N$ protons shifts from 2.53 ppm at a pD value of 9.0 to 3.20 ± 0.04 ppm (relative to TMPS) at the break in the titration curve (pH 4–6). The shift of the $-CH_2O$ proton signals from 3.57–3.82 ppm is less pronounced. Both peaks broaden, attaining widths of ~15 and ~45 Hz for the $-CH_2O$ and $-CH_2N$ protons, respectively. As the acidity is further increased, a second proton can be added externally as indicated by a further increase in δ for the protons at pH 1.1. If we assume that δ for these protons on o^+o^+ is 3.9–4.0 ppm, as in acetone-d_6, a pK_a value of 0.5–1 is obtained for the externally diprotonated species. A pH titration of [1] with HCl yields $pK_{a1} = 7.1 \pm 0.2$ for io^+ and shows no second break, indicating that the value of pK_{a2} is less than 1.5 for the o^+o^+ species. The pH titrations and NMR spectra permit calculations of the relative amounts of *ii*, io^+, and o^+o^+ present at various pH values. By using $pK_{a1} = 7.1$ and $pK_{a2} = 1.0$, we obtain the results shown in Figure 2.

External Protonation of the Internally Monoprotonated Species i^+i. As reported previously,[12,13] both the $-CH_2O$ and $-CH_2N$ proton NMR signals of i^+i in D_2O shift downfield with increasing acidity, indicating the formation of i^+o^+. Exchange is rapid on the NMR time scale. The signal of the internal proton shifts upfield from 9.67 ppm in i^+i to 8.8 ppm in 1 M DCl, i.e., toward the value of 7.34 ppm in i^+i^+.[13] The results suggest that i^+i is 40–50% externally protonated in 1 M HCl so that $pK_a \approx 0$ for this species.

Titration of i^+i bromide in MeOH-d_4 with acetyl chloride was monitored by observing the proton NMR signal of the internal proton. The methyl acetate which formed served as an internal indicator of the amount of acid added. At 200 K two lines at 9.2 and 8.6 ppm were observed whose relative areas changed with the amount of acid added. The dissociation constant of i^+o^+ determined in this way was $7 \pm 1 \times 10^{-3}$ M at 200 K. At a mole ratio of $[HCl]/[i^+i]$ of ~0.5, the relative areas of the two peaks varied with temperature indicating more dissociation at higher temperatures.

The temperature dependence of the chemical shifts of the $-CH_2N$ protons and the internal proton in the presence of HCl were used to estimate $\Delta H°$ for the dissociation of i^+o^+ in MeOH-d_4. Limiting chemical shifts of 3.10 and 3.74 ppm were used for the $-CH_2N$ protons of i^+i and i^+o^+, respectively, while the experimentally determined shifts of the internal proton at each temperature were used for i^+i (varying from 9.03 ppm at 300 K to 9.16 ppm at 205 K) and a value of 8.58 ppm was used for the internal proton of i^+o^+. Both sets of data yielded $\Delta H° = 8.4 \pm 0.4$ kJ mol^{-1} which, with the value of K_a at 200 k, gives $\Delta S° \approx 1$ J mol^{-1} deg^{-1} (molar basis). Extrapolation to 298 K gives $pK_a \approx 1$ for the dissociation of i^+o^+ in this solvent.

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Table I. The Dependence of the Rate of Internal Monodeuteration of Cryptand [1.1.1] on pD

pD[a]	buffer comp	ionic strength, M	k,[b] $s^{-1} \times 10^4$
~9	unbuffered		0.043 (3)[c]
8.7	KH_2PO_4–NaOH	0.29	0.157 (3)
7.5	KH_2PO_4–NaOH	0.37	0.87 (3)
7.5	KH_2PO_4–NaOH	0.37	3.7 (1) (T = 310 K)
7.5	KH_2PO_4–NaOH	0.37	12.5 (5) (T = 320 K)
6.5	KH_2PO_4–NaOH	0.33	1.14 (8)
4.9	KH phthalate–NaOH	0.34	1.7 (1)
4.9	KH phthalate–NaOH	0.34	21 (2) (T = 320 K)
4.0	KH tartrate	0.22	2.0 (2)
4.0	KH phthalate–HCl	0.29	2.0 (1)
3.2	KH phthalate–HCl	0.29	2.3 (1)
2.6	KCl–HCl	0.30	4.2 (7)
1.8	KCl–HCl	0.36	6.4 (2)
1.5	KCl–HCl	0.41	8.5 (1)
1.3	KCl–HCl	0.38	9.4 (2)
1.1	KCl–HCl	0.55	10.3 (1)

[a] pD values were measured with a calibrated radiometer and increased by 0.4 units to correct for the deuterium isotope effect. [b] Rate constants at 299 K unless indicated otherwise. Some values were corrected to 299 K by using $E_a = 110$ kJ mol^{-1}. [c] Linear estimate of the marginal standard deviation of the last significant digit.

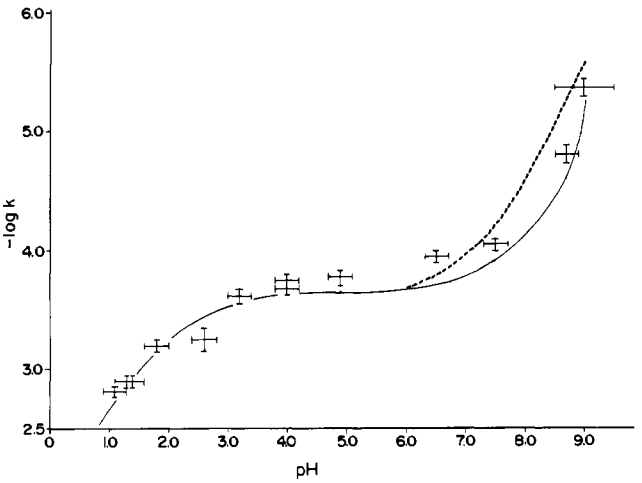

Figure 3. The pH dependence of the rate of internal monoprotonation of [1] in aqueous solution at 299 K. Curves calculated by eq 2 for $pK_{a2} = 1.0$ and $pK_{a1} = 7.1$ (dashed curve) and $pK_{a1} = 7.5$ (solid curve).

Rate of the First Internal Protonation of [1] in D_2O. The rate of the first internal protonation of [1] was studied as a function of pH and temperature in D_2O by using buffers to obtain the desired pH. The compositions and pH values of the buffers are given in Table I. The rates of internal protonation were measured by following the integrated ^1H NMR intensities of the $-CH_2O$ protons for the two forms, [1] and i^+i, at constant temperature and pH. Pseudo-first-order kinetics were observed in all cases. The pseudo-first-order rate constant depended strongly on both pH and temperature as shown in Table I. It should be emphasized that these rates were slow enough to permit low-noise ^1H NMR spectra to be obtained as a function of time.

The temperature dependence of the rate of internal protonation was studied at pH values of 7.5 and 4.9 (Table I), both of which gave similar activation energies (110 ± 8 kJ mol^{-1}). The large activation energy is responsible for the slow rate of internal protonation and is presumably the energy required to distort the face of the ligand, in order to allow the proton carrier access to the cavity.

The state of external protonation of cryptand [1.1.1] is influenced by the pH of the medium, since either one or two protons can be bound externally, with concommitant changes in the exo–endo conformational equilibria (see above). The rate of internal protonation seems to correlate well with the relative amounts of the *ii*, io^+, and o^+o^+ species (Figure 2). Figure 3 shows the dependence of this rate upon pH. The rate does not change appreciably between pH values of 3 and 6 where the externally monoprotonated species is predominant. Below a pH value of 3, the rate increases and approaches a first-order dependence on the hydrogen ion concentration as the relative concentration of the externally diprotonated complex increases. Above a pH value of 7, the rate decreases markedly as the mole ratio of io^+ decreases and the unprotonated species *ii* predominates.

The correlation of the rate of internal protonation with the nature of the species present as a function of pH suggests that the rate increases with the amount of a given species along the sequence $ii < io^+ < o^+o^+$. Protonation of the free ligand is apparently too slow to measure. If we take only the externally protonated species into account, the rate expression becomes

$$\text{rate} = k_1(io^+) + k_2(o^+o^+) = k_{obsd}C_T \quad (1)$$

where C_T is the total concentration of **1** and

$$k_{obsd} = \frac{k_1 + k_2(H^+)/K_{a2}}{1 + K_{a1}/(H^+) + (H^+)/K_{a2}} \quad (2)$$

This equation was used to describe the pH dependence of the rate of internal protonation of [**1**]. A computer fit of eq 2 to the pseudo-first-order rate constant with the nonlinear least-squares program KINFIT4[20] is shown in Figure 3 (dashed line) and yields $k_1 = 2.3 \pm 0.3 \times 10^{-4}$ s^{-1} and $k_2 = 3.8 \pm 0.6 \times 10^{-3}$ s^{-1}. The values of K_{a1} and K_{a2} were taken as 7.9×10^{-8} and 0.1. The experimental points fit the rate expression rather well. If K_{a1} is given a value of 3×10^{-8}, the fit is even better (solid line). However, the values of k_1 and k_2 do not change appreciably when the latter value of K_{a1} is used.

It should be pointed out that several other rate experssions would yield the same form of k_{obsd} as given in eq 2. These include:

$$\text{rate} = k_1'(io^+)(H^+) + k_2'(io^+) \quad (3)$$

$$\text{rate} = k_1''(io^+)(H^+) + k_2''(ii)(H^+) \quad (4)$$

$$\text{rate} = k_1'''(o^+o^+) + k_2'''(ii)(H^+) \quad (5)$$

Therefore, a unique mechanism for internal protonation cannot be determined from the rate data given here. The alternative rate constants can be calculated from the values listed for k_1, k_2, K_{a1}, and K_{a2}.

The Kinetics of the Second Internal Protonation of i^+i in D_2O. The internally monoprotonated species may be internally protonated a second time, but only under more rigorous conditions that those used for the first internal protonation. For example, at a pH value of 1 and room temperature, [**1**] has a half-time of about 7 min for conversion to the internally monoprotonated form, but gives no detectable amount of internally diprotonated species for days. In 1 M HCl, the second internal protonation requires several weeks at room temperature and is accompanied by considerable decomposition of the ligand. At elevated temperatures, the rates are much faster and the effect of decomposition is minimized.

The rate of internal protonation of i^+i was studied by following the time dependence of the ^{1}H NMR intensities in 1 M HCl in D_2O at four temperatures. Just as for the first internal protonation, the rates showed a first-order dependence on the ligand concentration. Table II gives the pseudo-first-order rate constant as a function of temperature. The linear dependence of ln (k) on $1/T$ gives $E_a = 110 \pm 8$ kJ mol^{-1}. This value is the same as that for the first internal protonation and suggests that the same type of ligand deformation is responsible for both processes.

The Kinetics of Deprotonation of the Internally Diprotonated Species i^+i^+. The rate of proton extraction from i^+i^+ was studied as a function of temperature in 5 M KOH in D_2O. The rates were again first order in ligand and were very slow. For example, at room temperature the complex was stable for weeks in 5 M KOH, while at elevated temperatures, the reaction proceded with the extraction of only one of the two internal protons. At the highest temperature (386 K), the reaction was accompanied by considerable decomposition of the ligand. The temperature dependence of the pseudo-first-order rate constant for deprotonation is given in Table II and yields $E_a = 105 \pm 8$ kJ mol^{-1}. Again, the similarity of E_a to that of internal protonation is striking. The deprotonation rate was also determined in 1 M KOH at 372 K. The rate constant (Table II) decreased by a factor of about 3 compared with the interpolated value at 372 K for 5 M KOH.

Table II. Temperature Dependent of the Rate Constant for the Second Internal Protonation of [$2H^+\subset$1] by Acid and for the Removal of a Proton from [$H^+\subset$1] by Base in D_2O

temp, K	acid or base added to D_2O	pseudo-first-order rate constant, $s^{-1} \times 10^4$
333	1 M HCl	0.23 (2)[a]
343	1 M HCl	0.80 (1)
359	1 M HCl	3.7 (1)
361	1 M HCl	5.3 (2)
349	5 M NaOH	0.255 (4)
363	5 M NaOH	1.40 (7)
386	5 M NaOH	10.4 (8)
372	1 M NaOH	0.433 (5)

[a] Linear estimate of the marginal standard deviation of the last significant digit.

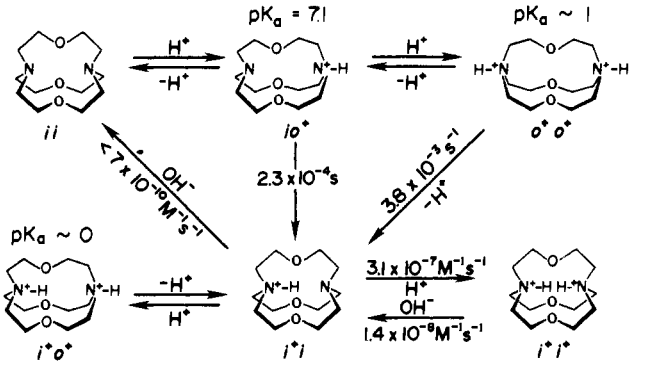

Figure 4. Equilibrium and rate constants for the interconversion of various forms of cryptand [1.1.1], **1**, in aqueous solution at 298 K.

Discussion

Although a unique mechanism for the internal protonation of the cryptand [1.1.1], **1**, cannot be deduced from the rate data, it is possible, with the aid of certain assumptions, to estimate the stabilities of the various protonated forms, and, in some cases, the rate constants for their interconversion. Conversely, these thermodynamic and kinetic results provide a basis for the structural assignment of the various species.

The observed pK_a value of 7.1 ± 0.2 for the first external protonation of [**1**] is much lower than that expected for a tertiary aliphatic amine, as previously noted,[13] and indicates that the *ii* form is more stable than the *io* form.

The pK_a value of ~1 for the second external protonation of [**1**]·H^+ shows that the equilibrium constant for

$$o^+i \rightleftharpoons o^+o \quad (6)$$

is less than 10^{-6} based upon p$K_a > 7$ for an *o*-nitrogen site.[22] Similarly the stability of i^+i is much greater than that of i^+o with $K < 10^{-7}$ for the conversion of i^+i^+ to i^+o. The measured rate and equilibrium constants for the various protonation steps are summarized in Figure 4. The o^+/i^+ assignment for the bridgeheads of the protonated species rests on the observation of fast

(22) Albert, A.; Serjeaut, E. P. "Ionization Constants of Acids and Bases"; Butler and Tanner, Ltd.: London, 1962; p 124.

and very slow proton transfer rates, respectively.

For the first internal protonation,

$$H_2O + [1] \underset{k_{-1}'}{\overset{k_1'}{\rightleftharpoons}} i^+i + OH^- \quad (7)$$

the apparent value of k_1' has been measured in pure D_2O, as 4.3×10^{-6} s^{-1} at 299 K (Table II). The rate constant k_1' may also be estimated by using the following scheme:

$$H_2O + [1] \underset{}{\overset{k_w/K_{a1}}{\rightleftharpoons}} io^+ + OH^- \quad (8)$$

$$\downarrow k_1$$

$$i^+i$$

The value of k_1 obtained from the pH dependence of the rate of internal protonation is 2.3×10^{-4} s^{-1}; k_1' is the overall rate constant for the process described by eq 8 and is given by:

$$k_1' = k_1K_w/[OH^-]K_{a1} \quad (9)$$

At a pH value of 9, where only [1] and the externally monprotonated species are present, eq 9 yields $k_1' = 2.9 \times 10^{-6}$ s^{-1}, in satisfactory agreement with the direct calculation.

The rate constant for dissociation, k_{-1}', is too slow to be observed directly, but an upper limit may be estimated from the measured value of the pseudo-first-order rate constant for the reaction

$$i^+i^+ + OH^- \xrightarrow{k_{-2}} i^+i + H_2O \quad (10)$$

Its value is 4.3×10^{-5} s^{-1} at 372 K for 1 M KOH, which may be extrapolated to 298 K by using $E_a = 105$ kJ mol^{-1} to give $k_{-2} \approx 1.4 \times 10^{-8}$ M^{-1} s^{-1}. If the formation of the free ligand were faster than about 5% of this rate it would be easily detected, so $k_{-1}' \lesssim 7 \times 10^{-10}$ M^{-1} s^{-1}. This gives $K_{b1} = k_1'/k_{-1}' \geq 6 \times 10^3$ M, $pK_b \leq -3.8$, and $pK_a \geq 17.8$. For reaction 7 as written above, $\Delta G^0 \leq -20$ kJ mol^{-1} which indicates that, because of encapsulation, $i^+i{\cdot}OH^-$ is thermodynamically stable to dissociation into **1** and H_2O. Thus we conclude that cryptand [1.1.1] is a *very strong base thermodynamically but a very poor one kinetically.*

For the second internal protonation,

$$i^+i + H_2O \underset{k_{-2}'}{\overset{k_2'}{\rightleftharpoons}} i^+i^+ + OH^- \quad (11)$$

the pseudo-first-order rate constant is 3.1×10^{-7} s^{-1} at 300 K and $[H^+] = 1$ M. If we assume a first-order dependence on $[H^+]$, $k_2' = 3.1 \times 10^{-14}$ s^{-1} in pure water. As calculated above, $k_2' = 1.4 \times 10^{-8}$ M^{-1} s^{-1}. This gives $K_{b2} = k_{11} = k_2'/k_{-2}' \approx 2 \times 10^{-6}$ M, $pK_{b2} \simeq 5.7$, $pK_{a2} \simeq 8.3$, $\Delta G_{11}^0 \simeq +35$ kJ mol^{-1}. Thus, the thermodynamic stability of the second internal protonation is similar to that of "normal" tertiary amines. Its *apparent* stability, as indicated by the slow rates of proton transfer into the out of the cavity, does not originate from a thermodynamic source. Rather, the slow proton transfer processes are due solely to the large activation barrier which must be surmounted in order for the proton to escape from or enter into the cavity.

An approximate *potential energy diagram* may be constructed from the kinetic and thermodynamic parameters which have been accumulated. This diagram, presented in Figure 5, utilizes free energies for consistency, since the ΔH values are generally not known. The direction of various changes, whose $\Delta G^{\ddagger}$ values have been determined experimentally, are indicated by the solid lines, whereas the dashed lines merely join the transition states with the products, and have not been determined experimentally. The diagram is only schematic since the pathway between reactants and the transition state is represented by a smooth curve but intermediates may well form.

With respect to the *structural mechanism* by which a proton enters into the cavity or leaves it, some information may be drawn from the kinetics of the first and second internal protonations and of the deprotonation of the i^+i^+ species. The activation energies for the three processes are very similar (≈110 kJ mol^{-1}). Furthermore, the pH dependence of the rate of the first internal protonation (see above) points to the possible role played by exo oriented nitrogen sites in proton transfer. These results may be adduced to indicate the following: (1) proton transfer requires a similar distortion of the macrobicyclic structure of cryptand [1.1.1] in all these cases; (2) inside protonation might best take place during exo → endo ($o \rightarrow i$) conversion of a nitrogen bridgehead.

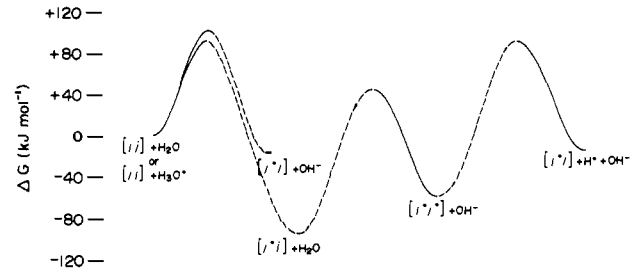

Figure 5. Approximate free energy diagram for the proton transfer reactions of [1] in aqueous solution at 298 K; the ΔG° and $\Delta G^{\ddagger}$ values correspond to the equilibrium and rate constants of Figure 4 for the interconversion of species *ii*, i^+i, and i^+i^+ (see text).

The $o \rightarrow i$ process may occur in two ways: (1) by nitrogen inversion (NI), which opens up the cavity to some extent as the nitrogen site flattens out; and (2) by homeomorphic isomerization (HI), i.e., passage of one bridge of a macrobicyclic through the ring formed by the two other ones.[8,23-25] The latter (HI) route would convert an o^+ site directly into an i^+ site (io^+ (HI) → oi^+; o^+o^+ (HI) → i^+i^+). However, with such a tight system as the [1.1.1] cryptand, the small size of the macrocycle is expected to be hindered by a barrier probably much higher than ~110 kJ mol^{-1} for (HI) processes. The (NI) pathway imples either a deprotonation–protonation sequence (io^+ ($-H^+$) → *io* (H^+, NI) i^+i; o^+o^+ ($-H^+$) → oo^+ (H^+, NI) → i^+o^+, or protonation of an *i* site while the other inverts (*ii* (H^+, NI) → i^+o; *io* (H^+, NI) → i^+i). Of course, if direct protonation of an *i* site is also possible (*ii* (H^+) i^+i; *io* → i^+o), the energy barrier arises from distortion of one face of the macrobicycle to allow approach of the proton carrier. It is possible that the ether oxygen sites participate to some extent in the transfer process, at least by contributing electrostatic stabilization of the proton in the transition state.

Conclusions

Cryptand [1.1.1], **1**, presents very unusual proton transfer properties. With a $pK_a \geq 17.8$, it is at least one order of magnitude more basic than the most basic "proton sponge" type compounds.[5] The i^+i^+ and i^+i species undergo proton transfer respectively about 10^8 and $> 10^{10}$ times more slowly than the slowest rates previously reported.[5] Thus, cryptand [1.1.1] is the thermodynamically strongest and kinetically slowest base known to date.[26]

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(26) The recently reported 1,6-diazabicyclo[4.4.4]tetradecane is probably an even stronger and more sluggish base than [1]. Deprotonation of its i^+i species is also extremely slow. Internal protonation does however not occur by direct proton transfer. Formation of the i^+o^+ form requires 1:1 HSO_3F/SbF_5.[15]