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Bifunctional Proton Transfer and Acid–Base Properties of 1,4,7,10-Tetraazacyclododecane (Cyclen)[1]

K. C. Chang, Ernest Grunwald,* and Lawrence R. Robinson

Contribution from the Department of Chemistry, Brandeis University, Waltham, Massachusetts 02154. *Received September 24, 1976*

Abstract: Stepwise acid dissociation constants of $(H_2NCH_2CH_2)_4{}^{4+}$ (cyclen·4HCl) in water at 25 °C are p$K_1 < 1$; p$K_2 = 1.15$ ($I = 0.6$); p$K_3 = 9.60$ ($I = 0$); p$K_4 = 10.53$ ($I = 0$). For the diprotonated species, the equilibrium ratio [1,7-diprotiocyclen]/[1,4-diprotiocyclen] is estimated as 1/400. Bifunctional proton transfer with water participation is fast. For 1,7-diprotiocyclen → 1,4-diprotiocyclen, $k_1 = 3.3 \times 10^4\ s^{-1}$; for 1-protiocyclen → 4-protiocyclen, $k_{cyclic} = 1.1 \times 10^8\ s^{-1}$. Reactions of 1,7-diprotiocyclen with H_3O^+ or OH^- are diffusion controlled.

The acid-base chemistry of the cation-complexing agent 1,4,7,10-tetraazacyclododecane, $(HNCH_2CH_2)_4$ (cyclen),[2,3] is of interest because of the possibility of fast intramolecular proton transfer. We wish to report the results of a kinetic study by dynamic NMR,[4] which confirms this possibility, as well as acid dissociation constants.

pK_a Measurements. Pure crystalline cyclen tetrahydrochloride[3] served as starting material. The acid dissociation scheme for this substrate in aqueous solution is shown in Figure 1. Values of pK_3 and pK_4, listed in that figure, were obtained by potentiometric titration at 0.017 M substrate concentration and have been corrected to zero ionic strength, using the Debye–Hückel formula: $\log \gamma_i = -0.509 z_i^2 I^{1/2}/(1 + I^{1/2})$ (γ_i = molar activity coefficient and z_i = charge number of ith solute species; I = ionic strength).

pK_2 was determined with a precision of better than 0.1 unit by measurement of the CH_2 vs. H_2O NMR chemical shift as a function of pH in the range 1–3, using the CH_3 proton resonance of either acetone (0.1 M) or t-$BuNH_3{}^+$ (0.1 M) as internal standard.[5] These measurements were made at 0.12 M substrate concentration. Because of the high ionic strength (~0.6 M), it was not deemed practical to correct pK_2 to zero ionic strength.

Electrostatic Repulsions. Our notation for molecular species and sites of protonation is indicated in Figure 1. pK_3 and pK_4 for the acid dissociation steps $A_2 \rightleftarrows A_1 \rightleftarrows B$ are similar in magnitude to the stepwise pK_a values[6a] for $^+H_3N(CH_2)_5NH_3{}^+$, where the nitrogen atoms are likewise separated by a five-atom chain. Electrostatic repulsion between the $NH_3{}^+$ groups lowers pK_{a1} of this compound by about 0.4 pK unit; we would expect a similar electrostatic interaction between positive charges on N_1 and N_7. The much greater electrostatic interaction between positive charges on N_1 and N_4 may be estimated from stepwise pK_a values[6b] for the cyclic diamines piperazine (1,4-diazacyclohexane), where it amounts to 3.6 pK units, or 1,4-diazacycloheptane, where it amounts to 3.0 pK units. Adopting an average value of ~3.3 units, we expect a total electrostatic contribution to pK_2 of 6.6 units (7.0 units in A_3, less 0.4 unit in A_2), compared to an electrostatic contribution to pK_3 of 0.4 unit. Thus pK_2 − pK_3 should be −6.2

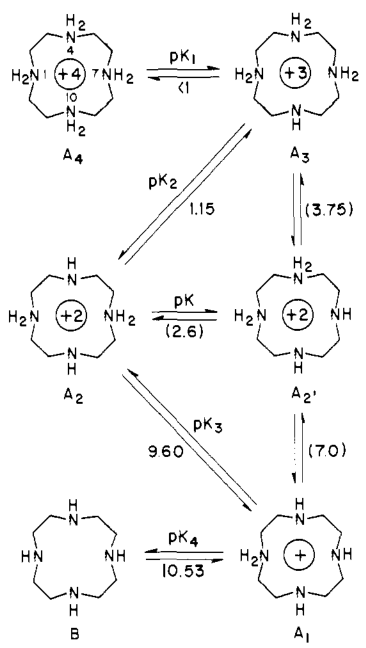


Figure 1. Acid dissociation of 1,4,7,10-tetraazacyclododecane in water.

+ log g, where g is the appropriate statistical factor for the process $2A_2 \rightleftarrows A_3 + A_1$ (Figure 1). Assuming that the A_2 molecules have two equivalent acidic sites and two equivalent basic sites, $g = 1/4$. Hence $pK_2 - pK_3$ should be -5.6, while the experimental value is -8.45. The discrepancy is in the direction which suggests that A_3 is relatively unstable. There are two possible explanations for this. Either the 12-membered ring conformation forces the 1,4,7 sites to be closer together than in the model compounds; or electrostatic repulsion among the three cationic sites forces the 12-membered ring in A_3 to exist in a less stable conformation than in A_2 and A_1.

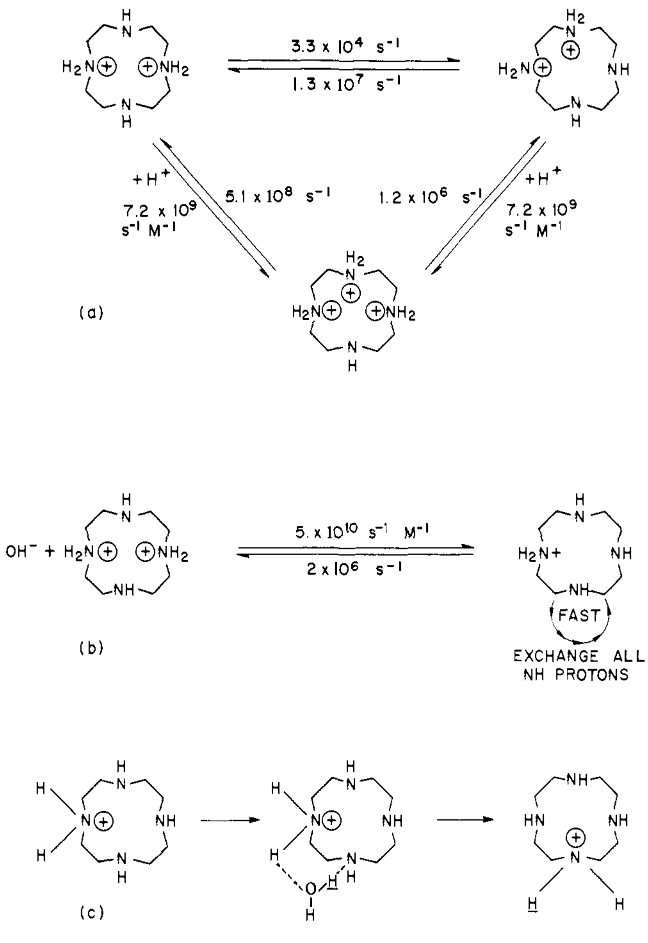
A key species in the mechanism for bifunctional proton transfer is the N_1,N_4-diprotonated isomer A_2'. pK for the equilibrium $A_2 \rightleftarrows A_2'$ may be estimated from electrostatic interactions (3.3 units for A_2' minus 0.4 unit for A_2), and statistical factors (4 for A_2' and 2 for A_2). The result, pK = 2.6, has been entered in Figure 1 and used to estimate other equilibrium constants by completion of thermodynamic cycles.

Proton-Transfer Kinetics. Dynamic NMR experiments[7] have enabled us to infer the rates of bifunctional proton transfer in both A_1 and A_2. In A_1, this process moves the formal positive charge among the nitrogen atoms. In A_2, we visualize that bifunctional proton transfer interconverts A_2 and A_2'. Because we are actually measuring the exchange broadening of the water proton resonance, our results indicate only those processes which proceed with water participation.

In the pH range 7.6-3.0, in which the substrate is essentially all A_2, measurements of NH- to -OH_2- proton exchange lead to the rate law

$$R_{\mathrm{NH\text{-}OH_2}} = k_1[A_2] + k_2[H^+][A_2] + k_3[A_2]/[H^+] \quad (1)$$

At 25 °C, $k_1 = (3.3 \pm 0.3) \times 10^4\ s^{-1}$; $k_2 = (1.8 \pm 0.3) \times 10^7\ s^{-1}\ M^{-1}$; $k_3 = (3.2 \pm 0.4) \times 10^{-3}\ s^{-1}\ M$. Substrate concentrations in these experiments range from 0.04 to 0.13 M. The indicated errors are statistical standard deviations. Further errors may result from our failure to correct for activity coefficients, and from error in the NH- to -OH_2- chemical shift. Measurement of the latter was difficult because of the high exchange rate, which caused the NH and OH_2 protons to be observed as a single exchange-averaged resonance under all accessible conditions. Because of this, the chemical shift was obtained by varying the rf field intensity, as described in the Experimental Section. These experiments also established that the number of exchangeable NH protons in the A_2 molecules, which in principle may be either 2, 4, or 6, is in fact 6. The average chemical shift (relative to H_2O) of the 6 NH protons was found to be 1.56 ppm.



$k_{\mathrm{cyclic}} = 1.1 \times 10^8\ s^{-1}$ FOR TWO STEP SEQUENCE

Figure 2. Summary of reaction mechanisms for proton transfer.

We also measured proton exchange rates between water molecules in ^{17}O enriched water,[4,7] looking for catalysis of this process by our substrate. In the pH range 6.8-7.6, at 0.06-0.13 M substrate concentrations, the rate law was found to be

$$\frac{R_{\mathrm{HOH}}}{2[\mathrm{HOH}]} = \frac{1}{\tau_W} = 2.7 \times 10^9[H^+] + k/[H^+] + \frac{k_{\mathrm{cyclic}}[A_1]}{2[\mathrm{HOH}]} + \frac{[A_2](k_1 + k_2[H^+] + k_3/[H^+])}{2[\mathrm{HOH}]} \quad (2)$$

The first two terms on the right in eq 2 represent H^+-catalyzed and OH^--catalyzed exchange, respectively. We shall show that $k_{\mathrm{cyclic}}[A_1]/2[\mathrm{HOH}]$ represents exchange catalyzed by A_1, proceeding by a bifunctional mechanism. The final term is based on eq 1 and, using the known rate constants, turns out to be quite negligible.

At 25 °C, $k = 3.4 \times 10^{-5}\ s^{-1}\ M$; $k/K_W = k_{OH^-}/\gamma_\pm^2 = 3.4 \times 10^9\ s^{-1}\ M^{-1}$; $k_{\mathrm{cyclic}} = 1.1 \times 10^8\ s^{-1}$.

Reaction Mechanisms. Rate constants for actual reaction steps derived from the kinetic data are summarized in Figure 2. These rate constants were obtained by the following reasoning.

In eq 1, $k_1[A_2]$ probably represents a bifunctional process with water participation, in which the rate-determining reaction is $A_2 \rightarrow A_2'$ (Figure 2a). Judging by the known values of pK_2 and pK_3, k_1 is much too great to represent either acid or base dissociation of A_2. On applying pK of ~2.6, k_{-1} for the reverse process is ~$10^7\ s^{-1}$, greater than k for the analogous bifunctional reaction of imidazole,[8] and comparable to k for the analogous reactions of lysine[9] and $H_2N(CH_2)_6NH_3^+$.[10]

We interpret the term $k_2[A_2][H^+]$ in eq 1 as involving a two-step mechanism, $H^+ + A_2 \rightleftarrows A_3 \rightleftarrows A_2' + H^+$, in which the reaction of either A_2 or A_2' with H^+ is diffusion controlled (Figure 2a). Thus $k_2 = k_d p$, where k_d is the diffusion-controlled rate constant for $A_2 + H^+ \rightarrow A_3$ and p is the probability that $A_3 \rightarrow A_2'$. Assuming that the rate constant for $A_2' + H^+ \rightarrow A_3$ is likewise k_d, $p = K/(1 + K) \approx 1/400$, where $K = [A_2']/[A_2]$. Thus, on introducing $k_2 = 1.8 \times 10^7$, we obtain $k_d \approx 7.2 \times 10^9\ s^{-1}\ M^{-1}$, a plausible value. Other rate constants deduced from this scheme are shown in the figure.

The term $k_3[A_2]/[H^+]$ in eq 1 is probably due to reaction of A_2 with OH^-, whose rate constant k_3' then equals k_3/K_W. Thus $k_3' = 3.2 \times 10^{11}\ s^{-1}\ M^{-1}$. This value is too high for simple diffusion-controlled proton abstraction, and suggests that in each reaction cycle all six NH protons of A_2 exchange with water protons. A sufficient explanation, shown in Figure 2b, is that bifunctional proton transfer in the conjugate base of A_2, i.e., in A_1, is very fast. On that basis, the real rate constant for the proton abstraction step from A_2 is $k_3'/6$, or $5 \times 10^{10}\ s^{-1}\ M^{-1}$. This is a plausible value, especially when considering the opposite electrical charges of the reactants. Calculation shows that, for this mechanism to be valid in the given pH range, the rate constant k_{cyclic} for bifunctional reaction of A_1 must be at least 5×10^7. In support of this, direct measurement of k_{cyclic}, using ^{17}O enriched water, resulted in a value of $1.1 \times 10^8\ s^{-1}$. The proposed reaction mechanism, which necessarily involves participation by water molecules, is shown in Figure 2c.

Experimental Section

Materials. Crystalline cyclen·4HCl was provided by Dr. T. J. Atkins of Du Pont's Experimental Station, Wilmington, Del., and was used without further purification.[3] Other materials were standard reagent grade chemicals.

Dynamic NMR Measurements. Our technique of measuring T_1 and T_2 relaxation times and of obtaining reaction rates therefrom have been described.[7] However, we do wish to describe the measurement of the chemical shift difference δ between the NH protons in A_2 and the water protons.

The exchange rate was so high that, under all accessible conditions, the NH and water-OH protons were observed as a single, more or less exchange broadened, resonance. The chemical shift difference δ was measured by varying the rf field intensity and employing two different values, 56.7 and 100 MHz, for the resonance frequency ω_0. Let $\gamma H_1 = \omega_1$ denote the rf field intensity in radians/second. Let $T_2(\omega_1)$ denote the transverse relaxation time at ω_1. Then, under conditions of exchange narrowing ($\delta^2\tau^2 \ll 1$), $T_2(\omega_1)$ is given by eq 3.[11]

$$\Delta(\omega_1) \equiv T_2(\omega_1)^{-1} - T_1^{-1} = p\delta^2\tau/(1 + \omega_1^2\tau^2) \tag{3}$$

p denotes the proton fraction of exchanging NH solute protons and must be $\ll 1$. p is proportional to the molar concentration of A_2, but the precise value depends on whether there are 2, 4, or 6 exchangeable protons per molecule. By measuring $\Delta(\omega_1)$ as a function of ω_1 at a constant resonance frequency ω_0, eq 3 enables us to evaluate the parameters $p\delta^2$ and τ, but not an absolute value for δ unless p is known. This can be seen by rewriting eq 3 in the linearized form (eq 4), which contains only two adjustable parameters, $(p\delta^2\tau)^{-1}$ and $\tau/p\delta^2$.

$$\frac{1}{\Delta(\omega_1)} = \frac{1}{p\delta^2\tau} + \frac{\omega_1^2\tau}{p\delta^2} \tag{4}$$

Given the value of $p\delta^2$ for a given solution, the proper choice of p, i.e., whether there are 2, 4, or 6 exchangeable NH protons per molecule of A_2, can be made by changing the resonance frequency ω_0 and considering the maximum possible exchange broadening. The theoretical maximum exchange broadening is $p\delta/2$,[7] or $\frac{1}{2}(p\delta^2)^{1/2}p^{1/2}$, in which $(p\delta^2)$ is known for the given ω_0. It was found that at 100 MHz and 4 °C, the experimental exchange broadening was significantly greater than the theoretical maximum assuming the numbers 2 or 4 exchangeable NH protons per A_2 molecule, but could be accommodated by assuming the number 6. On that basis, p was calculated and δ was evaluated from the known $p\delta^2$ as 1.56 ppm.

References and Notes

(1) It is a pleasure to thank the National Science Foundation for financial support, Professor E. K. Ralph for making available his laboratory for some of the NMR experiments, and Professors E. K. Ralph and M. M. Kreevoy for helpful discussions.

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