sodium hydroxide, and 15 mL of methanol was held at 25 °C overnight, then worked up as in A to give 119 mg (65%) of the desired tetramate **16a** whose physical and spectroscopic properties were identical with those of the sample from A above.

***N*-Benzyloxycarbonyl-DL-*threo*-β-methylaspartic Acid (11b).** Employing the same conditions utilized for the preparation of **11a**, 36.0 g (240 mmol) of DL-*threo*-β-methylaspartic acid (**10b**, obtained by recrystallizing a commercial sample of β-methylaspartic acid from water),[9] 30.0 g (750 mmol) of sodium hydroxide, 500 mL of water, and 51.5 g (360 mmol) of benzyl chloroformate gave, after recrystallization from ethyl acetate–hexane, 44.0 g (65%) of **11b**, mp 153–154 °C (lit.[8] 149–150 °C).

***N*-Benzyloxycarbonyl-DL-*threo*-β-methylaspartic Anhydride (12b).** Holding 14.6 g (50 mmol) of **11b** and 125 mL of acetic anhydride at 25 °C for 6 h gave 13.0 g (95%) of the desired anhydride **12b** as an oil: IR ($CHCl_3$) 3460, 1800, 1735, 1270, and 980 cm^{-1}; ^1H NMR (CD_3COCD_3, 100 MHz) 1.41 (d, 3 H, CH_3CH), 3.44 (m, 1 H, $CHCH_3$), 4.65 (m, 1 H, $CHNH$), 5.11 (s, 2 H, $ArCH_2$), 7.22 (bd, 1 H, NH), and 7.30 ppm (s, 5 H, ArH). The anhydride underwent reversion to the acid within 24–36 h in air.

Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.39; H, 5.14; N, 5.14.

***N*-Benzyloxycarbonyl-*N'*-methyl-DL-*threo*-β-methylaspartimide (13b).** Liquid methylamine (15 mL) was added to a cold solution of 13.0 g (49 mmol) of **12b** in 100 mL of anhydrous ether at −20 °C. The solution was warmed to 25 °C and concentrated in vacuo and the oily residue was stirred with acetic anhydride for 48 h, concentrated in vacuo, and chromatographed (3% MeOH in $CHCl_3$) to give 9.0 g (75%) of oily imide: IR ($CHCl_3$) 3440, 1782, and 1710 cm^{-1}; ^1H NMR (CD_3COCD_3) 1.28 (major component) and 1.14 (minor impurity) (d, 3 H, CH_3CH), 2.83 (m, 1 H, $CHCH_3$), 2.83 (s, 3 H, NCH_3), 4.13 (m, 1 H, $CHNH$), 5.02 (s, 2 H, $ArCH_2$), 6.83 (m, 1 H, NH), and 7.29 ppm (s, 5 H, ArH).

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.56; H, 5.70; N, 10.20.

***N'*-Methyl-DL-*threo*-β-methylaspartimide (14b).** Hydrogenolysis of 2.16 g (10 mmol) of **13b** in 500 mL of methanol containing 5% palladium on carbon catalyst gave 1.25 g (90%) of the amine as a yellow oil which was used without purification. A small portion was purified by preparative TLC (silica gel GF_{254}, 5% MeOH in $CHCl_3$) to afford the amine as a white solid: mp ca. 60 °C; IR ($CHCl_3$) 3380, 1780, and 1700 cm^{-1}; ^1H NMR ($CDCl_3$) 1.41 (d, 3 H, CH_3CH), 1.82 (bs, 2 H, NH_2), 2.57 (m, 1 H, $CHCH_3$), 3.00 (s, 3 H, NCH_3), and 3.48 ppm (d, 1 H, $CHNH_2$).

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.54; H, 6.92; N, 19.41.

***N*-Acetoacetyl-*N'*-methyl-DL-*threo*-β-methylaspartimide (9b).** Distilled diketene (760 mg, 9 mmol) and 1.25 g (9 mmol) of **14b** gave 1.90 g of **9b** as a yellow oil. A small sample was purified by chromatography (2% MeOH in $CHCl_3$): IR ($CHCl_3$) 3330, 1782, 1710, and 1675 cm^{-1}; ^1H NMR (CD_3COCD_3, 100 MHz) 1.30 (d, 3 H, CH_3CH), 2.18 (s, 3 H, CH_3CO), 2.82 (m, 1 H, $CHCH_3$), 2.85 (s, 3 H, NCH_3), 3.41 (s, 2 H, $COCH_2CO$), 4.24 (m, 1 H, $CHNH$), and 7.95 ppm (m, 1 H, NH).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.15; H, 6.14; N, 12.28.

3-Acetyl-2,4-pyrrolidione-5-(*N*-methyl-α-propionamide) (15b). A solution of 1.16 g (5 mmol) of **9b** in 26 mL of 0.24 N methanolic sodium methoxide was stirred overnight, then worked up as for **15a** to give a yellow solid which was recrystallized from ethyl acetate–hexane to give 850 mg (75%) of **15b**: mp 166–167 °C; IR (KBr) 3360, 3125, 1700, 1660, and 1602 cm^{-1}; ^1H NMR ($CDCl_3$) 1.07 (d, 3 H, CH_3CH), 2.47 (s, 3 H, CH_3CO), 2.83 (d, 3 H, $NHCH_3$), 2.85 (m, 1 H, $CHCH_3$), 4.09 (m, 1 H, $CHNH$), 5.96 and 6.77 ppm (bs, 2 H, NH).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.00; H, 6.20; N, 12.39.

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The Dynamics of Cryptand Protonation

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Abstract: Proton transfer reactions of the [222] cryptand in aqueous solution have been studied by the conventional (Joule heating) temperature-jump technique at 25 °C and μ = 0.1 M tetramethylammonium chloride. For the reaction H_2O + [222] $\rightleftarrows$ $[222.H]^+ + OH^-$, the rate constants are $k_f \leq 1000\ s^{-1}$ and $k_r \leq 10^8\ M^{-1}\ s^{-1}$. The site which is being protonated is within the ligand cavity. These rate constants represent processes which are at least two orders of magnitude slower than normal proton transfer reactions of tertiary amines. This result permits a determination of the extent to which the ligand imposes dynamic constraints on the complexation process and is significant in understanding previously observed slow rates of metal cryptate formation.

Cryptands[1] are macrobicyclic ligands with structures such as I. This is known as the [222] cryptand. The ligand contains a cavity which is capable of completely enclosing a metal ion to form a complex known as a cryptate.[2,3] One reason for the considerable interest in these ligands is that the formation of inclusive complexes with metal ions is highly specific,[4,5] a property which suggests many uses for these ligands.

Both NMR[6,7] and stopped-flow techniques[8,9,10] have been

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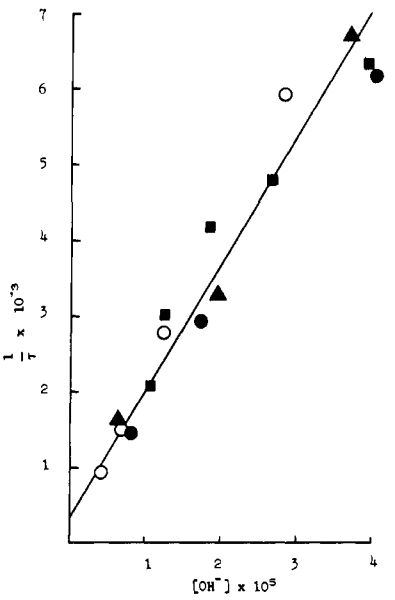
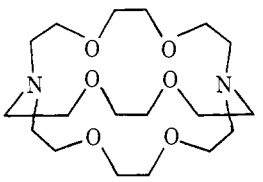


Figure 1. Plot of $1/\tau$ vs. $[OH^-]$ concentration at various cryptand concentrations: ○, $[222]_0 = 6.24 \times 10^{-3}$ M; ■, $[222]_0 = 5.47 \times 10^{-3}$ M; ▲, $[222]_0 = 3.91 \times 10^{-3}$ M; ●, $[222]_0 = 2.35 \times 10^{-3}$ M.



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used to study the kinetics of cryptate formation with metal ions of groups 1A and 2A. In all cases abnormally low formation rates are observed. One explanation we advanced[8,9] for the slow rates of alkaline earth ions complexing with various cryptands centered on the possibility of two ligand conformations, only one of which may be active. The two conformations are the exo-exo (both ligand nitrogens pointing into solution) and the endo-endo (both ligand nitrogens pointing into the ligand cavity).[11] Since the ligand conformation in the metal cryptates is the endo-endo conformation,[2,3] it might be assumed that this is the reactive species. Then, if the cryptand conformational equilibrium favors the unreactive exo-exo form, slow rates of metal cryptate formation will be observed. While this argument is entirely consistent with the results on metal cryptate formation, the inherent reactivity of the endo-endo form has not been measured.

Cryptand protonation provides a way of studying the dynamic constraints imposed by the ligand itself. If protonation of the endo-endo conformation proceeds with a rate constant which is considerably different from the rate constant for the proton transfer reactions of the exo-exo form, then it will be possible to get some idea of the effect of the ligand structure on the rates of reactions which involve direct entry of species into the ligand cavity. The present study concerns the proton transfer reactions of the [222] cryptand by the temperature-jump technique.

Experimental Section

The [222] cryptand and the [22] macrocyclic analogue were obtained from E. Merck Laboratories. Their purity was checked by pH titration with standard acid. In all experiments, the ionic strength was maintained at 0.1 M with tetramethylammonium chloride (Eastman). (Metal ions of groups 1A and 2A must be excluded since they form stable complexes with the cryptand.) Adjustment of solution pH for the kinetic experiments was achieved by addition of HCl or NMe_4OH (Eastman) as required. Distilled, deionized water was used throughout. All experiments were carried out at 25 °C.

Ligand pK_as were determined by pH titration in a N_2 atmosphere using a Corning Model 12 pH meter. The activity coefficient of H^+ was determined from the Davies equation.[12] ΔH for the reactions was determined by titration calorimetry with standard HCl using an LKB 8700 calorimeter.

The conventional (Joule heating) temperature-jump method was used in the kinetic experiments. The apparatus is described elsewhere.[13] Reported relaxation times are the average of at least three traces and the error in the relaxation times is at most ±15%. Solution pH was checked before and after the temperature-jump experiments. The change in pH of a particular solution was at most ±0.03 pH units. Phenolphthalein was used to monitor the reactions (λ 540 nm).

Results

The pK_as of the [222] cryptand are $pK_{a_1} = 7.3$ and $pK_{a_2} = 9.6$. The reactions are

$$CH_2^{2+} \rightleftarrows CH^+ + H^+ \qquad K_{a_1}$$

$$CH^+ \rightleftarrows C + H^+ \qquad K_{a_2}$$

where C is the unprotonated [222] cryptand. The reaction enthalpies were determined by titration calorimetry and found to be $\Delta H_1 = 4.4$ and $\Delta H_2 = 11.3$ kcal/mol for the reactions as written. Both sets of results are in good agreement with those of Anderegg,[14] which were also determined at 25 °C and μ = 0.1 M tetramethylammonium chloride ($pK_{a_1} = 7.31$, $pK_{a_2} = 9.71$, and $\Delta H_1 = 4.5$, $\Delta H_2 = 10.8$ kcal/mol).

The kinetic experiments were carried out at pHs slightly below pK_{a_2}. The predominant species present in solution in all cases are the unprotonated and monoprotonated forms of the cryptand. At both higher and lower pHs, the amplitudes of the observed effects were too small to measure. The kinetic results are presented in Figure 1. The reciprocal of the relaxation time depends *only* on hydroxide ion and is independent of the concentrations of [222] and indicator.

The concentration of hydrogen ion is determined by use of the Davies equation. Determination of the concentration of hydroxide requires a knowledge of K_w in 0.1 M NME_4Cl. K_w in 0.1 M ionic media depends on the particular salt.[15] The value taken for K_w will affect the slope in Figure 1, but the linear dependence of $1/\tau$ on $[OH^-]$ is unaffected. Although Figure 1 was prepared taking K_w to be 1×10^{-14}, a different value for K_w only affects the scale of the abscissa, not the mechanistic arguments.

Discussion

Cryptands exist in at least two conformations in solution. These are the exo-exo and the endo-endo.[11] Despite extensive studies of the cryptands[11,16] and cryptate formation[6,7] by NMR techniques, the equilibrium constant for the exo-exo/endo-endo reaction has not been reported. However, it has been pointed out that the interconversion is rapid.[11,17]

The striking result of the present temperature-jump experiment is that the reciprocal of the relaxation time for the proton transfer process depends *only* on the concentration of the hydroxide ion. The following mechanism is consistent with this result where the exo-exo form of the ligand is designated species A and the endo-endo form of the ligand is designated species B.

$$A \rightleftarrows B \qquad K = B/A \qquad (1)$$

$$H_2O + A \rightleftarrows HA^+ + OH^- \qquad K_b^A \qquad (2)$$

$$H_2O + B \rightleftarrows HB^+ + OH^- \qquad K_b^B \qquad (3)$$

Assuming that the protonated species are similar to the analogous macrobicyclic diamines,[17,18] the protonation of the exo-exo form (HA^+) results in the proton's being outside the ligand cavity; the protonated endo-endo form (HB^+) contains

the proton within the ligand cavity. The proton transfer reactions involving the endo-endo form therefore directly involve the entry into and exit from the ligand cavity of water and hydroxide ion. Since step 2 is simply the protonation of a tertiary amine, it is expected[19] that $k_2 \simeq 10^5 \rightarrow 10^6\ s^{-1}$ and $k_{-2} \simeq 10^{10}\ M^{-1}\ s^{-1}$.

Similarly, if the inversion frequency inferred[18] for macrobicyclic diamines ($\sim 10^6\ s^{-1}$) is any indication of the rate of the same process in cryptands, the relaxation time characteristic of cryptand inversion is expected to be about two orders of magnitude faster than the relaxation times observed in these experiments. For these reasons, both processes 1 and 2 are assumed to be in rapid equilibrium compared with the slower step 3.

Analysis of this mechanism leads to an explicit expression for the relaxation time

$$\frac{1}{\tau} = k_3 \times \left\{ \frac{[\overline{OH^-}]}{(\gamma[\overline{OH^-}] + [\overline{HA^+}])\left(\frac{1}{K}+1\right)\left(\frac{1}{\gamma}\right) + \frac{K_b^A}{K}} \right\} + k_{-3}[\overline{OH^-}] \times \left\{ 1 + \frac{[\overline{HB^+}]\left(\frac{1}{K}+1\right)\left(\frac{1}{\gamma}\right)}{(\gamma[\overline{OH^-}] + [\overline{HA^+}])\left(\frac{1}{K}+1\right)\left(\frac{1}{\gamma}\right) + \frac{K_b^A}{K}} \right\} \quad (4)$$

where

$$\gamma = 1 + \left(\frac{[\overline{In^-}]}{K_{HIn^+}[\overline{H^+}]}\right)\left(\frac{[\overline{H^+}]}{[\overline{OH^-}]}\right)$$

The value of γ in all cases is near unity.

The second term in the relaxation expression is dominant under the conditions of the experiments and a linear dependence of $1/\tau$ on hydroxide is observed. This is made readily apparent if the expression is simplified by making an assumption. Since the concentration of cryptand is greater than 10^{-3} M in all experiments, it is likely that $[\overline{HA^+}]$ is greater than either K_b^A or $[\overline{OH^-}]$ by about two orders of magnitude.[20] Under these conditions, the term K_b^A/K can be neglected and $[\overline{HA^+}] > \gamma[\overline{OH^-}]$. The second term in the relaxation expression then reduces to $k_{-3}[\overline{OH^-}]\ (1 + [\overline{HB^+}]/[\overline{HA^+}])$. From the expression for the equilibrium constants, $[\overline{HB^+}]/[\overline{HA^+}] = KK_b^B/K_b^A$.

Applying the same approximation to the first term as well leads to the final expression for the relaxation time

$$\frac{1}{\tau} = \frac{k_3}{S} + k_{-3}[\overline{OH^-}](1 + KK_b^B/K_b^A)$$

where $S = ([\overline{HA^+}]/[\overline{OH^-}])(1/K + 1)(1/\gamma)$. S is a pH-dependent term which, over the pH and cryptand concentration ranges examined, is at least 10^2. (S cannot be determined exactly since K has not been measured as discussed above. If K is small, S will always be large.) However, since S increases as the pH decreases, the observed intercept should be small. The uncertainty in the value of the intercept and the fact that S cannot be calculated make it impossible to determine k_3 from the observed small intercept.

What is more significant concerning the value of k_3 is that a linear dependence of $1/\tau$ on $[OH^-]$ is observed throughout the pH range examined. This would certainly not be the case if k_3 were the normal ($\sim 10^5\ s^{-1}$) rate constant characteristic of tertiary amines. This consideration and the small intercept leads to a maximum value of $k_3 \leq 1000\ s^{-1}$. The slope of Figure 1 leads to a *maximum* value for $k_{-3} \simeq 10^8\ M^{-1}\ s^{-1}$.

It is important to note that other mechanisms have been assumed, but that each predicts a different functional dependence of $1/\tau$. For example, this is the case if it is assumed that step 1 is slow and the proton transfer reactions are fast or if it is assumed that only one protonated form of the ligand exists. The experimental result therefore supports the contentions that both exo-exo and endo-endo conformations of the ligand exist in solution in rapid equilibrium[11] and that both forms participate in proton transfer reactions.[18]

The values of both k_3 and k_{-3} are at least two orders of magnitude smaller than rate constants normally observed for proton transfer reactions of tertiary amines. This may be a direct consequence of the fact that water and hydroxide enter the ligand cavity in order to effect proton transfer. Further support for the idea that the slowness of the reactions is related to the dynamic constraints imposed by the ligand comes from the examination of the proton transfer reactions of the same ligand with one bridge entirely removed. The proton transfer reactions of the resultant [22] macrocyclic ligand occur with a rate too fast to measure by temperature jump.

Since the cryptand imposes dynamic constraints on the proton transfer reactions, it is probable that similar constraints may be imposed on other entering species. This factor may account in part for the slow rates of metal cryptate formation. It may also be expected that the various cryptands will react with different proton transfer rate constants.[21] The continued study of these proton transfer reactions should prove to be of great interest in itself and will elucidate further the dynamics of the metal cryptation process.

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