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Kinetics of Interaction of Metal Ions with Two Tetraaza Tetraacetate Macrocycles

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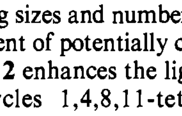
The kinetics of formation of metal complexes of the macrocyclic ligands 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetate (DOTA) and 1,4,8,11-tetraazacyclotetradecane-*N,N′,N″,N‴*-tetraacetate (TETA) have been measured by stopped-flow spectrophotometry. Observations were made at 25 °C and $I = 0.25$ M over a wide range of pH, and the reactive species was characterized as the monoprotonated form of the ligand. Metal ions examined were Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Zn^{2+}, Ni^{2+}, and Cu^{2+}. With a number of systems, plots of the pseudo-first-order rate constant k_{obsd} vs. $[M^{2+}]$ in excess were hyperbolic conforming to the expression $k_{obsd} = (A[M^{2+}])(1 + K[M^{2+}])^{-1}$. K is considered a constant for formation of a preassociation complex. This may then proceed to a final complex (first-order rate constant AK^{-1}) or be a "dead-end" complex, with reactants reacting by a second-order process, rate constant A. With the remaining systems, k_{obsd} vs. $[M^{2+}]$ was linear as required for a second-order reaction.

Introduction

The mechanisms of formation of labile metal complexes have attracted a good deal of attention. The dissociative mechanism dominates the reaction of the labile bivalent metal ions. Although many subtle features are still not understood, one can make a reasonably accurate assessment of the rate constant for the reaction of a particular metal ion–ligand system.[1,2] Attention has therefore more recently been directed to the more unusual ligands. Included are the macrocycles[3,4] and cryptands,[5] where the absence of twisting and folding possibilities, as well as steric restrictions, is likely to slow down the "normal" rates and introduce mechanistic novelties. Undoubtedly, interest in this area has been stimulated by the biological overtones.[6,7] Some of the earliest studies revealed interesting differences between the complexing of copper ion with the macrocycle **1** (R = H, cyclam) and the linear polyamines.[8,9] Recently Kaden and his co-workers,[10] as well as Kodama and Kimura,[11] have carried out a series of kinetic studies of a number of transition-metal ions reacting with **1** (R = H) and **2** (R = H, cyclen) as well as macrocycles with other ring sizes and numbers of nitrogen donor atoms.[12,13] The attachment of potentially coordinating groups on the nitrogens of **1** and **2** enhances the ligation possibilities of the ring. The macrocycles 1,4,8,11-tetraazacyclotetradecane-*N,N′,N″,N‴*-tetraacetate (**1**, R = CH_2COO^-, TETA) and 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetate (**2**, R = CH_2COO^-, DOTA) form strong complexes with a variety of metal ions, including those of group 2A as well as the transition-metal ions.[14-16] Thus using this type of ligand, it is possible to investigate the ring interaction with the alkaline-earth ions, which do not complex well with macrocycles containing only nitrogen donors.



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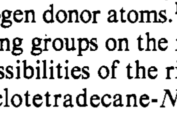

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A comparison can therefore be made with the alkaline-earth ion–cryptand systems which have been intensively studied in recent years.[17-19] Are the slow rates for the latter duplicated by the tetraaza tetraacetate macrocycles? This paper reports then the kinetics of interaction of Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Zn^{2+}, Ni^{2+}, and Cu^{2+} with DOTA and Ca^{2+}, Zn^{2+}, and Ni^{2+} with TETA at 25 °C and over a wide range of pH.

Experimental Section

Reagents. cyclen·4HCl (**2**, R = H) was synthesized according to the method of Richman and Atkins.[20] The derived ligand DOTA (**2**, R = CH_2COOH) was prepared as described by Desreux.[15] Anal. Calcd for $C_{16}H_{28}N_4O_8 \cdot H_2O$: C, 45.5; H, 7.1; N, 13.3. Found: C, 45.2; H, 7.4; N, 13.3. Cyclam (**1**, R = H) (Strem Chemical Co.) was converted into TETA (**1**, R = CH_2COOH) in a manner analogous to that used for DOTA. Anal. Calcd for $C_{18}H_{32}N_4O_8$: C, 50.0; H, 7.4; N, 12.9. Found: C, 49.9; H, 7.3; N, 12.7. The NMR of DOTA and TETA agreed with that described by Desreux.[16] All buffers were obtained from Sigma. Other reagents were CP grade.

Kinetic Measurements. All studies were carried out at 25 °C and an ionic strength of 0.25 M with NaCl as added electrolyte. Most of the reactions were studied by monitoring with indicators the attendant pH decreases (~0.1 unit) that occurred when excess metal ion (0.5–40 mM) and buffer were treated with ligand (0.1–1.0 mM), indicator (5–40 μM), and buffer at the appropriate pH. Lightly buffered solutions ensured a small pH change and an indicator change of 0.05–0.10 absorbance unit. Buffers used were acetate (pH <5), 2-(*N*-morpholino)ethanesulfonic acid (Mes, pH 5–6), *N*-(2-hydroxyethyl)piperazine-*N′*-2-ethanesulfonic acid (Hepes, pH 6–7), piperazine-*N,N′*-bis(2-ethanesulfonic acid) (Pipes, pH 6–7), tris(hydroxymethyl)aminomethane (Tris, pH 7–9), and 3-(cyclohexylamino)-1-propanesulfonic acid (Caps, pH >9). In one or two runs where it was possible to use two different buffer systems, the same result was obtained. Indicators[21] used were (pH and examination wavelength in parentheses) bromocresol green (4.6–5.0, 615 nm),

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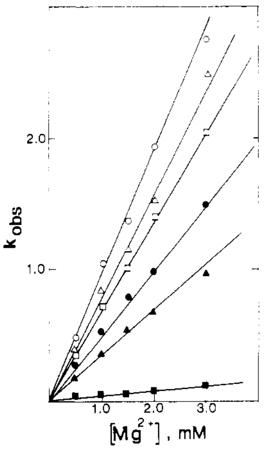

Figure 1. Plots of k_{obsd} vs. excess $[Mg^{2+}]$ for reaction with DOTA at various pHs, at 25 °C and $I = 0.25$ M: (○) pH 9.9; (△) 9.0; (□) 8.8; (●) 8.6; (▲) 8.4; (■) 7.6. Results at some pHs plotted in Figure 3 have been omitted for clarity.

phenol red (7.4–7.6, 560 nm), chlorophenol red (5.8, 575 nm), bromothymol blue (6.8, 620 nm), thymol blue (8.5, 600 nm), and phenolphthalein (8.4–9.5, 552 nm). No interaction of indicator with metal ion, ligand, or buffer over the reaction times was observed, and the use of two different indicators at the same pH gave consistent results. The reactions of Ca^{2+} with TETA at higher pH (>10.3) were studied with use of murexide to monitor $[Ca^{2+}]$ changes at 505 nm.[17] Most reactions of Cu^{2+} and Ni^{2+} were studied by monitoring the formation of complex directly at 375 and 675 nm (Cu) and 570 nm (Ni). The data agreed well with some duplicate runs using the indicator method. For conservation of ligand and because of the limited solubility of TETA, most runs were carried out with excess metal ion. Using excess ligand in two systems gave identical results. The kinetics were carried out in a Gibson-Dionex stopped-flow apparatus interfaced with an OLIS data collection system.

Results

The reaction of metal ion M^{2+} with ligand L can be generalized as

$$M^{2+} + LH_n^{(4-n)-} \rightleftharpoons ML^{2-} + nH^+ \tag{1}$$

and in the majority of studies, pH 5–9, LH_2^{2-} is the predominant ligand species in solution.[22] The rate of the reaction was monitored by using an appropriate indicator to register the pH change, which was kept small by moderate buffering of the solution. Using an excess of M^{2+} gave pseudo-first-order kinetics and drove the reaction to completion.[23]

Two types of behavior were observed when the first-order rate constant k_{obsd} was plotted against $[M^{2+}]$. Over the complete range of metal ion concentration used for $M^{2+} = Mg^{2+}$, Zn^{2+}, and Ba^{2+}, k_{obsd} was a linear function of M^{2+} (illustrated in Figure 1 for the reaction of Mg^{2+} with DOTA). For all other systems (Sr^{2+} only at the highest pH, 9.5), k_{obsd} vs. $[M^{2+}]$ was curved ("saturation kinetics"), and this is shown in Figure 2 for the reaction of Ca^{2+} with DOTA. These findings can be rationalized in terms of eq 2–4 (with omission, for the present, of the location of protons).

$$M^{2+} + L \rightleftharpoons (M^{2+}{\cdot}L)_I \quad \text{fast, } K_2 \tag{2}$$

$$(M^{2+}{\cdot}L)_I \rightarrow (M^{2+}{\cdot}L)_F \quad k_3 \tag{3}$$

$$M^{2+} + L \rightarrow (M^{2+}{\cdot}L)_F \quad k_4 \tag{4}$$

The overall reaction can proceed in one of three ways: (a) a combination of (2) and (3), in which a rapidly formed adduct $(M^{2+}{\cdot}L)_I$ more slowly transforms to the final complex $(M^{2+}{\cdot}L)_F$, (b) a combination of (2) and (4), in which the adduct rapidly forms but is not on the reaction pathway to the final complex, and (c) a simple second-order reaction, (4), only possible where "saturation kinetics" are not observed.

Table I. Values of K_2, k_3, and k_4 for Reactions of M^{2+} with DOTA and TETA at Various pHs at 25 °C and $I = 0.25$ M

M	pH	K_2, M^{-1}	k_3, s^{-1}	k_4, M^{-1} s^{-1}
		DOTA		
Mg	5.0			0.26
	5.8			2.6
	6.8			12
	7.6			42
	8.5			3.3×10^2
				1.3×10^2 [a]
				9.2×10^2 [b]
				4.9×10^2 [c]
				2.3×10^2 [d]
	8.8			6.8×10^2
	9.0			8.0×10^2
	9.4			9.6×10^2
Ca	7.6	$\sim 1.7 \times 10^2$	~66	1.1×10^4
	8.5	1.7×10^3	1.4×10^2	2.4×10^5
	9.4	4.7×10^3	1.4×10^2	6.7×10^5
Sr	7.6			9.5×10^2
	8.5			1.1×10^4
	9.5	7.4×10^2	1.1×10^2	8.2×10^4
Ba	7.6			1.4×10^2
	8.5			1.2×10^3
	9.5	$\lesssim 60$	$\gtrsim 100$	6.8×10^3
Zn	4.6			1.5×10^2
	5.0			5.5×10^2
	5.8			6.1×10^3
Ni	4.0	60	0.033	2.0
	4.3	15	0.17	2.6
	4.8			7.5 [e]
	4.9	29	0.28	8.0
	5.5	94	0.27	25
	6.2	81	0.69	56
	7.0	70	2.0	1.4×10^2
	7.4			2.9×10^2 [e]
Cu	4.0			2.3×10^3
	4.3	1.2×10^2	50	6.0×10^3
	4.6	3.6×10^2	37	1.9×10^4
	4.9	8.8×10^2	29	2.6×10^4
		TETA		
Ca	7.5			35
	8.5			9.5×10^2
	9.4			4.2×10^4
	10.4	3.0×10^3	167	5.1×10^5 [f]
Zn	4.6			2.3×10^3
	5.0			3.5×10^3
Zn	5.9			1.3×10^4
Ni	5.5	14	10	1.4×10^2
	6.1	6	25	1.5×10^2
	7.0	24	13	3.0×10^2
	7.3			3.8×10^2 [e]
	7.5			6.5×10^2 [e]

[a] 15.0 °C. [b] 34.2 °C. [c] $I = 0.1$ M. [d] $I = 0.4$ M. [e] At low $[Ni^{2+}]$ using indicator method; others directly at 570 nm. [f] Using murexide indicator.

The relationship between k_{obsd} and $[M^{2+}]$ can be generally expressed as (5).[2] With condition (a) above, $A = k_3K_2$ and

$$k_{obsd} = \frac{A[M^{2+}]}{1 + B[M^{2+}]} \tag{5}$$

$B = K_2$, while with (b), the "dead-end" complex situation, $A = k_4$ and $B = K_2$. If there is no initial adduct, $B[M^{2+}] < 1$, and a second-order reaction (4) (rate constant A) ensues, although it could still occur via (2) and (3). Values of K_2, k_3,

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[22] pH changes indicate that the resultant metal complex is unprotonated in this pH range.

[23] Only with the Mg^{2+}–DOTA system at pH 5.0 and 5.8 and possibly the Ca^{2+}–TETA reaction at pH 7.6 were there small intercepts for the k_{obsd} vs. $[M^{2+}]$ plot. The values for these were in reasonable agreement with calculated values for the $[H^+]$ dissociation of the ML complex, i.e., k_r in the reaction $M^{2+} + LH^{3-} \rightleftharpoons ML^{2-} + H^+$, k_f/k_r. The value of k_f/k_r was equal to $K_{ML}K_{LH}$, the product of the stability constant[14] and the first ionization constant.[16]

Table II. Formation Rate Constants ($M^{-1}\ s^{-1}$) for Reactions of M^{2+} with Monoprotonated DOTA, TETA, EDTA, Cyclen, and Cyclam at 25 °C

	ligand				
	$H(DOTA)^{3-}$ [a]	$H(TETA)^{3-}$ [a]	$H(EDTA)^{3-}$	cyclenH^+	cyclamH^+
Mg^{2+}	2.2×10^3	...	...	...	...
Ca^{2+}	7.9×10^5	2.3×10^5	1×10^7 [b]	...	...
Sr^{2+}	8.9×10^4	...	5×10^5 [b]	...	...
Ba^{2+}	1.0×10^4	...	...	...	...
Zn^{2+}	1.1×10^7	1.6×10^8	$\sim 10^9$ [c] (3×10^6 [b])[f]	3.3×10^4 [d] 1.3×10^5 [e] (3.9[e])[f]	5.0×10^4 [d] 7.5×10^4 [e] (1.0[e])[f]
Ni^{2+}	3×10^4 (10)[f]	2.5×10^4 (1.3×10^2)[f]	2×10^5 [c] (2×10^3 [b])[f]	66[d]	53[d] (3.3×10^{-3} [d])[f]
Cu^{2+}	1.2×10^9 (5×10^3)[f,g]	...	2×10^9 [c] (3.6×10^5 [b])[f]	2.9×10^6 [d] 5.5×10^6 [e] (0.6[d])[f]	1.8×10^6 [d] 8×10^6 [e] (0.39,[d] 0.08[e])[f]

[a] Values computed from (12) and Figure 3. [b] Reference 1. [c] Reference 2. [d] Reference 10. [e] Reference 11. [f] Estimated rate constant for diprotonated species in parentheses. [g] Best values from limited pH data.

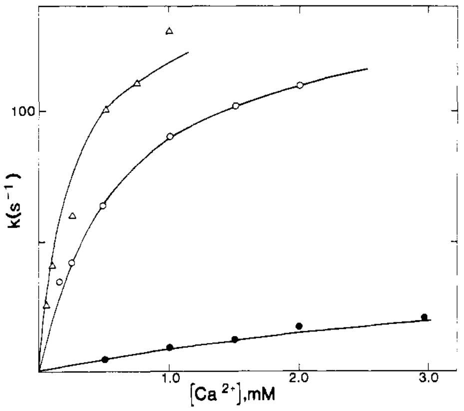

Figure 2. Plots of k_{obsd} vs. excess $[Ca^{2+}]$ for reaction with DOTA at various pHs, at 25 °C and $I = 0.25$ M: (▲ open) pH 9.4; (○) pH 8.5; (●) pH 7.6. Curves drawn correspond to expression 5 with values of A (k_4) and B (K_2) as shown in Table I.

and k_4 are shown for all the systems examined in Table I. An absence of values for K_2 and k_3 indicates that there was no systematic deviation of linearity for the k_{obsd} vs. $[M^{2+}]$ plot. The slope of the linear plot was assigned to k_4. Values of K_2, k_3, and k_4 were obtained from the appropriate plot by inverting (5):

$$\frac{1}{k_{obsd}} = \frac{1}{A[M^{2+}]} + \frac{B}{A} \qquad (6)$$

The variation with pH of the second-order rate constant k_4 obtained from the linear portion of the k_{obsd} vs. $[M^{2+}]$ plot indicates that although LH_2^{2-} is the major ligand species present in most pH conditions in Table I, a less protonated form is the reactive kinetic species. A quantitative treatment of the pH variation shows that this is LH^{3-}. Equations 7–10

$$LH_2^{2-} \rightleftharpoons LH^{3-} + H^+ \quad K_7 \qquad (7)$$

$$LH_2^{2-} + M^{2+} \rightarrow \text{product} \quad k_8 \qquad (8)$$

$$LH^{3-} + M^{2+} \rightarrow \text{product} \quad k_9 \qquad (9)$$

$$d([LH_2^{2-}] + [LH^{3-}])/dt = k_4([LH_2^{2-}] + [LH^{3-}]) \times [M^{2+}] = k_8[LH_2^{2-}][M^{2+}] + k_9[LH^{3-}][M^{2+}] \qquad (10)$$

apply to this situation. The observed second-order rate constant k_4 is related to k_8 and k_9 therefore by the expression

$$k_4 = \frac{k_9 - k_8}{1 + K_7^{-1}[H^+]} + k_8 \qquad (11)$$

In all systems $k_9 >> k_8$ and (except for Cu^{2+} and Ni^{2+} reactions) the second term is negligible compared with the first term on the right-hand side of (11). Therefore usually

$$\log k_4 = \log k_9 - \log (1 + K_7^{-1}[H^+]) \qquad (12)$$

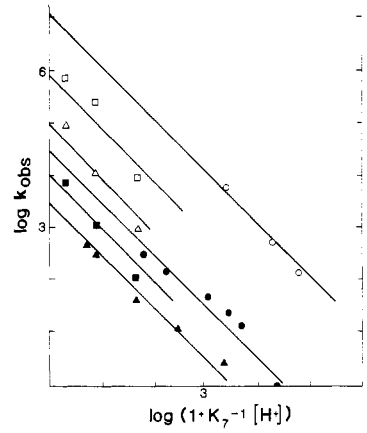

Figure 3. Plots of log k_{obsd} vs. log $(1 + K_7^{-1}[H^+]) \equiv \log X$ for the reaction of metal ions with DOTA, at 25 °C and $I = 0.25$ M: (○) Zn^{2+}; (□) Ca^{2+}; (△) Sr^{2+}; (●) Ni^{2+}; (■) Ba^{2+}; (▲) Mg^{2+}. For Ni^{2+}, $k_{obsd} = k_4 - k_8$, and for the other metal ions, $k_{obsd} = k_4$, the observed second-order rate constant at a specific $[H^+]$.

The plots of log k_4 vs. log $(1 + K_7^{-1}[H^+])$ are shown in Figure 3.[24] All slopes are drawn as −1.0 and the intercept at which log $(1 + K_7^{-1}[H^+]) = 0$ gives the value of k_9, the rate constant for the reaction of LH^{3-}. The values are collected in Table II. Since only a restricted range of pH was possible for Cu^{2+}, a graphical treatment was not used, but the best values of k_8 and k_9 were found by an iterative approach, assuming negligible rate constants for reaction of LH_3^- and LH_4 species. Since the value of k_4 (or K_2k_3) at pH 9.5, where the major species is LH^{3-} for DOTA, is close to that obtained graphically in Figure 3, it was deemed reasonable to use the values of K_2 and k_3 obtained at pH 9.5 for reaction of LH^{3-}; these values are shown in Table I.

In one competition experiment, Cu^{2+} (2.0 mM) and Ni^{2+} (100 mM) were reacted with DOTA (0.1 mM) at pH 4.9 and the formation of the Cu^{2+}–DOTA complex was monitored at 375 nm. The pseudo-first-order rate constant was 6.7 s^{-1} reduced from the value 18.9 s^{-1}, when the Ni^{2+} was omitted. The indicator method indicated that a $[H^+]$ change occurred in (3).

Discussion

The monoprotonated forms of the ligands DOTA and TETA, LH^{3-}, are several orders more reactive than the higher protonated species so that even for reactions of, for example, Mg^{2+} at pH 5.0 where $[LH^{3-}]$ is less than 0.01% of $[LH_2^{2-}]$,

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(24) The successive ionization constants used were as follows: 11.1, 9.2 (K_7), 4.24, 4.18 (DOTA); 11.6, 10.2 (K_7), 4.1, 3.4 (TETA). Values were obtained in 1 M NaCl at 25 °C.[16] The first two pK's differ from values in 0.1 M KCl at 20 °C[14] so that there is an element of uncertainty in the computed rate constants for LH^{3-} reactions collected in Table II.

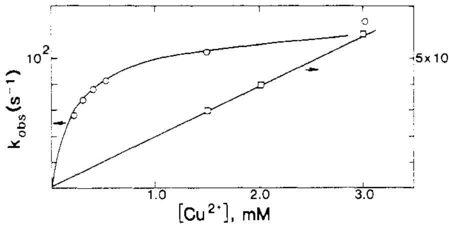
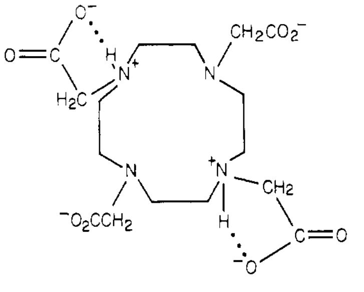


Figure 4. Plots of k_{obsd} vs. [Cu^{2+}] for reaction with TETA (○) and cyclam (□) at pH 4.6, 25 °C, and $I = 0.25$ M. The left-hand ordinate is used for TETA and the right-hand ordinate for cyclam. The curve corresponds to expression 5 with values of $A = 4.8 \times 10^5$ M^{-1} s^{-1} and $B = 3.8 \times 10^3$ M^{-1}.

there is no discernible contribution from the latter to the rate of the reaction. This behavior duplicates those of EDTA and the 12- and 14-membered macrocycles cyclen and cyclam (Table II). The unreactivity of cyclamH_2^{2+} has been ascribed to the two protons being maintained near the coordination site, increasing electrostatic repulsion.[1] A similar explanation for the relative unreactivity of (DOTA)H_2^{2-} (and (TETA)H_2^{2-}) might be offered since a tentative structure **3** has been suggested for (DOTA)H_2^{2-} on the basis of NMR experiments.[16] DOTA and TETA may be considered as two linked ethylenediamine-*N*,*N*′-diacetate (EDDA) residues. Rate constants for reactions of EDDA are sparse, but those for $EDTA^{4-}$ and $H(EDTA)^{3-}$ are plentiful. Comparison of $H(DOTA)^{3-}$, $H(TETA)^{3-}$, and $H(EDTA)^{3-}$ (Table II) shows that rate constants for $H(EDTA)^{3-}$ are only about 5- to 10-fold larger than for the macrocycles. This might suggest that the metal ions are not part of the macrocyclic ring,[16,25] but they surely interact with some, if not all, of the N donor atoms because of the marked stability of many of the metal complexes, especially of DOTA.[14] There are no pronounced effects of changing the ring size from 12 to 14 on the rates for either the tetraacetates or the nonsubstituted cyclen and cyclam, although there is a general trend to higher rates with larger rings.[11] The larger rate constants for $H(DOTA)^{3-}$ and $H(TETA)^{3-}$ compared with those for cyclenH^+ and cyclamH^+ probably arise from more favorable electrostatics. In a compilation of formation rate constants for reaction of Ni^{2+} with ligands of various charge[1] it is noted that there is a decrease of 10^4 in the value for a reaction of product charge 6+ (with NTA^{3-}) compared with that of 2− (with Hen^+). This is a difference at least as great as that between the substituted and unsubstituted macrocycles **1** and **2** reacting with Zn^{2+}, Ni^{2+}, and Cu^{2+}. The acetate residues must however modify the mechanisms in one important respect. For reactions of Ca^{2+}, Sr^{2+}, Ni^{2+}, and Cu^{2+} with DOTA and for Ca^{2+} and Ni^{2+} with TETA the curvature observed for the k_{obsd} vs. [metal ion] plot indicates prior adduct formation, which *may* be on the reaction profile to the final product. Further evidence for the occurrence of the adduct is shown by competition studies. A 50-fold excess of Ni^{2+} over Cu^{2+} competes for adduct formation (but not overall reaction) and reduces the rate constant for overall copper–DOTA complex formation approximately 3-fold. No deviations from linearity for k_{obsd} vs. [Cu^{2+}] are observed with cyclam (Figure 4), where adduct formation would not be anticipated. The magnitude of the formation constant K_2, at least for Ca^{2+}, Sr^{2+}, and Cu^{2+} systems, suggests that the initial adduct involves both a carboxylate and a ring nitrogen coordination. If this is not a "dead-end" complex, then it transforms with H^+ release to the final product (involving more ligand coordination) by a variety of first-order rate constants (see Table II). It has been suggested that the reactions of $H(EDTA)^{3-}$ involve very labile metal ion–acetate bond formation preceding the rate-determining step of coordination to the nitrogen.[26,27] The kinetics of coordination of La^{3+} to H_2CyDTA^{2-} (CyDTA = 1,2-diaminocyclohexane-*N*,*N*,*N*′,*N*′-tetraacetate) suggests a rapid preequilibrium involving La^{3+} coordination to acetate and the metal ion outside the coordination cage formed by N and O donors of CyDTA. This then transforms to the final product.[27] Also of relevance is the recent observation that conversion of a "picket-fence" porphyrin into a tetracarboxylic acid derivative markedly accelerates its rate of metalation. The kinetics conform to rapid complexation of the metal by the carboxylate site followed by rate-determining metal ion transfer to the porphyrin ring.[28]



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Finally, examination of the extensive compilations of rate constants for reactions of metal ions[1] shows that the rate constants for reaction of the Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+} groups with $H(DOTA)^{3-}$ and $H(TETA)^{3-}$ are 3–4 orders of magnitude smaller than those for water exchange or ligation by unidentate or simple multidentate ligands. The differential is very much smaller for Zn^{2+}, Ni^{2+}, and Cu^{2+} ions. It is apparent that a combination of a proton near the active site (hydrogen bonding?) and the steric and strict conformational requirements for coordination of the macrocycle does markedly decelerate the total coordination process.

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Registry No. **1**, 60239-22-7; **2** (R = CH_2COOH), 60239-18-1; Sr, 7440-24-6; Ca, 7440-70-2; Mg, 7439-95-4; Ba, 7440-39-3; Zn, 7440-66-6; Ni, 7440-02-0; Cu, 7440-50-8.

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