Kinetics of the Ligand Exchange and Dissociation Reactions of Calcium–Aminocarboxylate Complexes

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Abstract: The rate constants for the exchange reactions of EDTA and PDTA with their respective calcium complexes have been measured as a function of temperature by the nmr line-broadening technique. The reactions are first order in both calcium complex and incoming ligand concentration. Activation parameters for the tetraanion exchange reactions were determined to be E_a = 12.4 kcal/mol and log A = 11.0 for EDTA and E_a = 15.0 kcal/mol and log A = 11.0 for PDTA. The exchange reactions of BDTA and CyDTA with their calcium complexes are shown to be zero order in incoming ligand concentration and proceed *via* dissociative pathways. The rate constants for the dissociation of the calcium complexes of EDTA, PDTA, BDTA, and CyDTA have been measured by polarimetric and spectrophotometric techniques. The rate constants obtained for the dissociation, k^{CaL}, and hydrogen ion dependent dissociation, $k_H{}^{CaL}$, pathways of these calcium complexes at 25° are as follows: for EDTA, 1.28 sec^{-1} and 1.44 × 10^7 M^{-1} sec^{-1}; for PDTA, 6.6 × 10^{-2} sec^{-1} and 6.83 × 10^6 M^{-1} sec^{-1}; for BDTA, 1.04 × 10^{-4} sec^{-1} and 1.28 × 10^6 M^{-1} sec^{-1}; and for CyDTA, 3.0 × 10^{-5} sec^{-1} and 4.43 × 10^5 M^{-1} sec^{-1}.

Recently, several papers have appeared discussing the symmetric ligand exchange reactions of EDTA[1] and the enantiomeric exchange reactions of PDTA and CyDTA with various metal ion complexes (calcium,[2] cadmium,[3,4] lead,[5,6] strontium,[7] and nickel[8]) of the respective ligands. Only in the case of lead have the reactions of all three of these structurally similar ligands been investigated and the effect on a change in ligand structure evaluated. Whether these effects are quite general or are modified to some extent by the identity of the metal ion is yet to be determined.

In most previous studies of this type, dissociative pathways (usually hydrogen ion or proton catalyzed) have been observed in addition to bimolecular (or ligand dependent) exchange reactions. Such dissociative reactions proved to be the major pathway in this study.

The so-called "Eigen mechanism" of metal ion complex formation reaction proposes the rate determining step to be the loss of water from the primary coordination sphere of the metal ion after the metal ion has formed an outer sphere complex (or solvent-separated ion pair) with the incoming ligand. This general mechanism is well documented for monodentate ligands but is coming under close scrutiny for multidentate ligands. The use of a series of structurally related ligands allows conclusions about the identity of the formation rate-determining step.

In this work we have employed calcium as the metal ion and have extended the investigation to include a fourth ligand BDTA (2,3-diaminobutanetetraacetate), which is structurally intermediate between PDTA and CyDTA. The kinetics of the exchange reactions of EDTA, PDTA, BDTA, and CyDTA (eq 1-4) have been measured *via* nmr

$$Y^{4-} + CaY^{2-} \longrightarrow CaY^{2-} + Y^{4-} \quad (1)$$

$$P^{4-} + CaP^{2-} \longrightarrow CaP^{2-} + P^{4-} \quad (2)$$

$$Cy^{4-} + CaP^{2-} \longrightarrow CaCy^{2-} + P^{4-} \quad (2a)$$

$$B^{4-} + CaB^{2-} \longrightarrow CaB^{2-} + B^{4-} \quad (3)$$

$$Cy^{4-} + CaCy^{2-} \longrightarrow CaCy^{2-} + Cy^{4-} \quad (4)$$

line broadening, polarimetric, and stop flow techniques. Activation parameters for the ligand dependent exchange pathways (first-order in incoming ligand) of reaction 1 and 2 were also measured. The kinetics of ligand independent pathways (*i.e.*, zero order in incoming ligand or dissociative pathways) of reactions 1 and 2 were determined by measuring the rates of reactions 5 and 6, which were found to be

$$CaY^{2-} + Pb^{2+} \longrightarrow Ca^{2+} + PbY^{2-} \quad (5)$$

$$CaP^{2-} + Pb^{2+} \longrightarrow Ca^{2+} + PbP^{2-} \quad (6)$$

independent of the concentration of Pb(II). Under no conditions (high attacking ligand concentration and high ionic strength) could any ligand dependency be observed for reactions 3 and 4. The rate constants of reactions 2, 2a, and 6 were all observed to be the same under comparable pH conditions.

Experimental Section

Materials. Practical grade propylenediamine and *trans*-1,2-diaminocyclohexane were obtained from the Eastman and Aldrich Chemical Co., respectively. The *trans*-1,2-diaminocyclohexane was purified by distillation and subsequent recrystallization as the sulfate salt. 2,3-Diaminobutane was prepared by reductive amination of dimethylglyoxime with Raney nickel as described by Dickey, *et al.*,[9] and was also obtained from the Wyandotte Chemical Corp. as a gift. Separation of the meso and racemic isomers was accomplished by published procedures.[9] The tetraacid form of EDTA was obtained by recrystallization of its disodium salt from acidic solution. Racemic PDTA was prepared by the method of Dwyer and Garvan.[10]

Resolution of Amines. The levo and dextro isomers of propylenediamine were separated by the procedure of Dwyer and Garvan.[10] *l*-1,2-Diaminocyclohexane and *d*-2,3-diaminobutane were prepared according to the procedures of Reinbold and Pearson[11] and Dickey,[9] respectively. The *d*-1,2-diaminocyclohexane and the *l*-2,3-diaminobutane, which were recovered from the initial mother liquors in each of the above procedures, were found to have a minimum optical purity of 90% and were used without further purification.

Preparation of the Active Aminocarboxalate Ligands. In all cases the active ligands were prepared from their respective amines by the procedures of Dwyer and Garvan[10] for the preparation of *d* and *l*-PDTA, with certain modifications introduced by Reinbold and Pearson[11] in the case of *d*- and *l*-CyDTA. The *d*-CyDTA and *l*-BDTA, which were prepared from amines of approximately 90% optical purity, were recrystallized several times to remove the considerably less soluble racemic components. This resulted in material apparently of greater than 98% optical purity. All of the ligands were shown by complexometric titration with primary standard calcium carbonate to be >99% chemically pure.

The specific rotations of 0.5% aqueous solutions of the active acids at the sodium D line were the following: *d*-PDTA, +49.4; *l*-PDTA, −50.0; *d*-BDTA, +49.8; *l*-BDTA, −49.7; *d*-CyDTA; +53.3; *l*-CyDTA, −53.1.

Reagents. All solutions were prepared with deionized and distilled water and stored in polyethylene bottles. The ligand solutions were standardized by titration with a standard calcium solution utilizing Hydroxynaphthol Blue as an indicator. Calcium ion solutions were prepared from the carbonate salt and standardized by titration with standard EDTA. The calcium complexes of each of the ligands were prepared by adding stoichiometric amounts of calcium and the appropriate ligand.

Kinetic Measurements. The kinetics of the ligand-dependent exchange reactions of the EDTA-CaEDTA system and of the PDTA-CaPDTA system were studied by the nuclear magnetic resonance line-broadening technique utilizing both a Varian A-60 spectrometer and a Varian A-60D spectrometer equipped with a variable temperature probe. Probe temperature measurements were made by measuring the chemical shift difference between the OH proton and the methyl protons of methanol or the OH and methylene protons of ethylene glycol according to the appropriate relationships given by Van Geet.[12] No internal reference was employed because TMS[1] (sodium 3-(trimethylsilyl)-1-propanesulfonate), the usual reference in aqueous solutions, contains sodium ion which would interfere with the rate measurements by forming the kinetically inert sodium-EDTA complex.[2a] In the case of the EDTA-CaEDTA system, the full line widths at half-height of the resonance due to either the acetate or ethylenic protons of the complexed ligand were measured from spectra recorded on the 50 Hz scale at a sweep rate of 0.1 Hz sec^{-1}; the line width being taken as the average of at least five separate resonances.

In the case of the PDTA-CaPDTA system, the only useful resonance was the methyl doublet of the complexed ligand. The observed width at half-height and the peak to valley ratio were measured under the same conditions as in the case of EDTA. The line width of the upfield resonance was then calculated utilizing a coupling constant of 6.3 Hz which was measured under conditions of no exchange and assuming a Lorentzian line shape. In order to minimize any errors in this procedure the exchange broadening was kept below 3 Hz.

Test solutions were prepared from concentrated stock solutions of the appropriate ligand and complex. Adjustment of the solution pH was made with concentrated KOH and HCl in the case of the EDTA system. Subsequent to this experimental work, a value of log K = 0.70 was determined for the potassium complex of EDTA.[13] For the PDTA system CsOH (Alfa Inorganics) was employed instead of KOH because of the known complexation of potassium by PDTA.[14,15] Because relatively high concentrations are required for the nmr measurements (0.1–0.3 M) no inert electrolyte could be added to maintain constant ionic strength. The ionic strength of the solutions was normally between 1 and 3 but varied as the pH was changed or as the concentration of the free ligand was varied. All pH measurements were performed at the temperature at which the spectra were recorded. The pK_4 values of both EDTA and PDTA, which were employed in this study, are given in Table I. The values for EDTA were determined from the measured

Table I. pK_4 Values of EDTA and PDTA

EDTA, μ = 2 (KCl)		PDTA, μ = 2 (CsCl)	
pK_4	Temp, °K	pK_4	Temp, °K
9.61	314.7	10.35	363.0
9.76	305.0	10.40	357.8
9.90	298.0	10.46	352.5
9.99	292.5	10.50	345.7

pK_4 values at high ionic strength[3] and the ΔH of ionization of EDTA.[16] The values for PDTA were determined potentiometrically under the same conditions as employed in the kinetic experiments. In order to minimize concentration errors due to solution evaporation during pH measurements at high temperatures, the contents of the sealed nmr tubes were titrated with calcium to determine the concentration of the free ligand after the spectra were recorded.

The kinetics of the ligand independent exchange reactions (*i.e.*, dissociation reactions) of CaEDTA and CaPDTA were also studied by employing Pb(II) as a scavenger ion, following a procedure analogous to that of Margerum, *et al.*[17] Reagent grade sodium acetate was used for ionic strength control at 0.5 M and also served as the buffering agent below pH 7, and 5×10^{-3} M borate-mannitol buffered the reaction above pH 7. The reader is referred to the above reference for a discussion of the requirements of an acceptable scavenging ion and the rationale for the choice of acetate as the ionic strength control medium. A Durrum-Gibson stop flow spectrophotometer was employed to follow the progress of the reaction. The observed rate was taken as the average of two or three successive runs. The molar absorptivities of those species with a significant absorbance are given in Table II.

Table II. Molar Absorptivities

Species	255 nm	260 nm
Acetate ion	0.01	0.01
Pb(II)[a]	840	320
$PbEDTA^{2-}$	2960	1090
$PbPDTA^{2-}$	3770	1570

[a] In 0.5 M acetate ion with correction for acetate absorbance.

The exchange reactions of CaBDTA and CaCyDTA were studied by following the racemization reaction between an optically active ligand and the calcium complex of the ligand of opposite chirality. These reactions were measured at 365 nm on a Perkin-Elmer Model 141 polarimeter with a Sargent Model SR recorder attached as previously described.[5] Tetramethylammonium chloride was employed to control the ionic strength at 0.5 M. The molar rotations of the pertinent species are given in Table III.

Table III. Molar Rotations (365 nm)

Species	$[\alpha]$, (l. deg)/(cm mol)
H-*d*-$BDTA^{3-}$	+4.55
d-$BDTA^{4-}$	−2.3
Ca-*d*-$BDTA^{2-}$	−1.53
H-*d*-$CyDTA^{3-}$	+5.80
d-$CyDTA^{4-}$	+4.4
Ca-*d*-$CyDTA^{2-}$	−1.30

Stability Constants. The stability constants of the calcium complexes of each of the ligands were determined potentiometrically according to the following procedure. Titrations of the calcium–ligand system were performed with the aid of a Corning Model 12 expanded-scale pH meter. The concentration of the ligand was about 0.01 M with calcium ion present in a 1.5–3.5-fold excess. Prior to the titrations, the solutions were bubbled with nitrogen to remove any CO_2 present and were continuously swept with nitrogen to prevent CO_2 absorption during the titration. Utilization of the quite soluble optically active forms of PDTA, BDTA, and CyDTA prevents troublesome precipitation of the tetraacid forms of these ligands in the pH region (2.7–4.4) where the most significant data were taken (Table IV).

Several titrations were performed for each system at different calcium ion concentrations. The temperature was maintained at 25° in a thermostated cell; the ionic strength was controlled with tetramethylammonium chloride. The stability constants were calculated from the titration data with the aid of a computer program

Table IV. Acid Dissociation Constants and Calcium Complex Stability Constants for EDTA, PDTA, BDTA, and CyDTA (T = 25°, μ = 0.5)

Ligand	pK_1	pK_2	pK_3	pK_4	Log K_{CaL}	Log K_{CaHL}	Log $K_{CaL}{}^{CaHL}$
EDTA	1.8	2.89	6.12	10.22	10.28	3.53	3.47
PDTA	2.39	3.09	6.20	11.01	11.41	3.98	3.58
BDTA	2.59	3.63	6.24	12.31	13.08	4.49	3.71
CyDTA	2.63	3.69	6.21	13.09	13.68	4.45	3.85

by an iterative least-squares procedure based on eq 7, where $[L]_T$

$$a^*[L]_T + [H^+] = \sum_{n=0}^{n=4} n[H_nL] + \sum_{n=0}^{n=1} n[MH_nL] \quad (7)$$

is the analytical concentration of the ligand and a^* is the number of moles of base added per mole of ligand present. The first, second, and third acid dissociation constants of each of the ligands were determined by an analogous procedure in the absence of calcium ion.

The concentration of hydrogen ion which appears on the left side of eq 7 was calculated from the relationship $p[H^+] = pH + \log F$. The factor F may be considered to allow for the activity of hydrogen ion, the residual liquid junction potential, and any other systematic errors in the pH measurements. The value of the factor F was determined to be 0.85 by the procedure outlined by McBryde.[18]

Results

Ligand Dependent Exchange Reactions. The kinetics of the ligand exchange reactions were related to the broadening of the recorded spectra by the slow exchange approximation, valid under conditions when $\delta_w\tau \gg 1$, where δ_w (rad sec^{-1}) is the chemical-shift difference between the exchanging species and τ (sec) is the average lifetime in a particular environment. In this case, the average lifetime of a particular ligand on a particular metal ion, τ_{CaL}, is related to the line widths by eq 8 where $W'_{1/2}$ and $W_{1/2}$ are the full

$$1/\tau_{CaL} = \pi(W'_{1/2} - W_{1/2}) \quad (8)$$

line widths at half-height in the presence and absence of exchange, respectively.[19] In these experiments the lifetime was determined as a function of the free ligand concentration at a constant pH. The value of $W_{1/2}$ was taken to be the width of the appropriate resonance in the absence of any excess ligand at the same pH. Such a choice prohibits the measurement of exchange due to dissociation of CaL, since any dissociation process would also occur in solution without excess ligand. Under these conditions the lifetime is related to the observed rate constant by eq 9. A plot of $1/\tau_{CaY}$

$$1/\tau_{CaL} = k_{obsd}[L]_T \quad (9)$$

vs. $[Y]_T$ is shown in Figure 1. In every case the intercepts were zero within experimental error in accordance with eq 9.

For the EDTA system, in the pH region being investigated (8.5-11.0), only two exchange processes need be considered, eq 10 and 11; thus the observed rate constant is re-

$$Y^{4-} + CaY^{2-} \xrightarrow{k_Y^{CaY}} CaY^{2-} + Y^{4-} \quad (10)$$

$$HY^{3-} + CaY^{2-} \xrightarrow{k_{HY}^{CaY}} CaY^{2-} + HY^{3-} \quad (11)$$

lated to the specific rate constants for the two exchange pathways by eq 12. Plots of $k_{obsd}(K_4 + [H^+])/[H^+]$ *vs.*

$$k_{obsd} = k_Y^{CaY}\left\{\frac{K_4}{K_4 + [H^+]}\right\} + k_{HY}^{CaY}\left\{\frac{[H^+]}{K_4 + [H^+]}\right\} \quad (12)$$

$K_4/[H^+]$ whose slopes and intercepts are the values of k_Y^{CaY} and k_{HY}^{CaY}, respectively, are shown in Figure 2. The values of the specific rate constants for the EDTA system are given in Table V. Activation parameters for the tetraanion exchange were determined, from a plot of $T[\ln k_Y^{CaY}]$ *vs.* T (Figure 3), to be E_a = 12.4 kcal/mol and log A = 11.0 (ionic strength 1-3).

For the PDTA system the situation is somewhat more complex. When racemic PDTA is employed, two pairs of exchange processes must be considered (eq 13-16), of

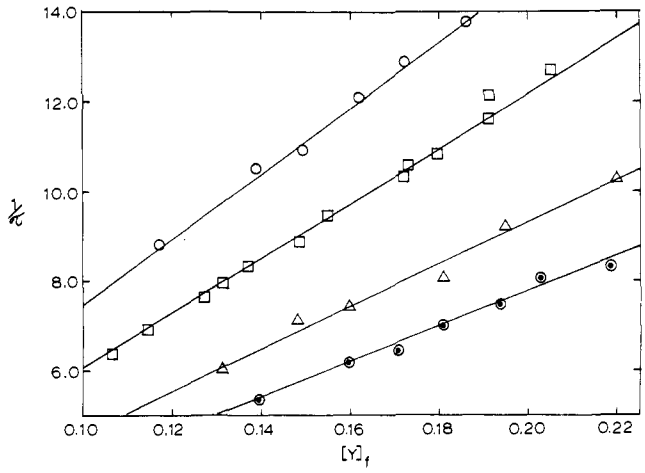

Figure 1. Lifetime of CaEDTA as a function of free ligand concentration: T = 314.7°K; pH ○ 9.20, △ 9.10, □ 8.90, ⊙ 8.80.

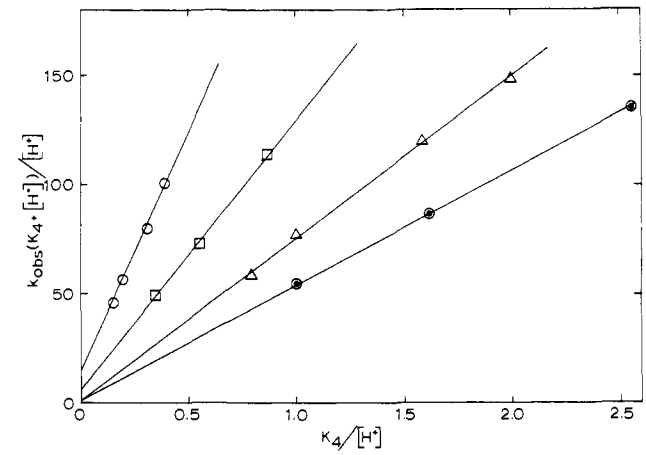

Figure 2. Resolution of k_Y^{CaY} and k_{Hy}^{CaY}: Temp (°K) ○ 314.7, □ 305.0, △ 298, ⊙ 292.5.

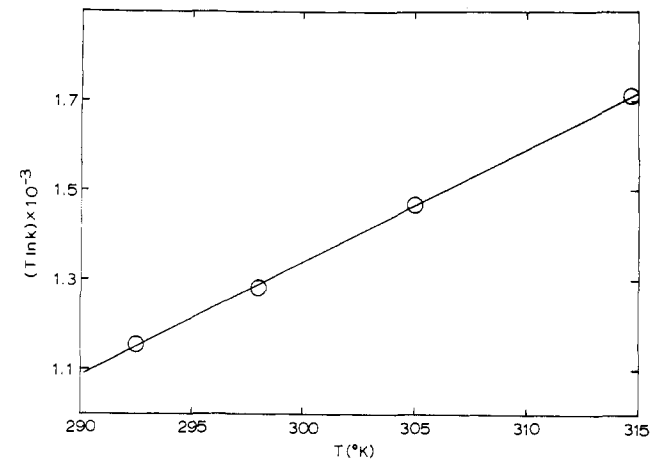

Figure 3. Activation plot for the tetraanion exchange reaction of EDTA with CaEDTA.

Table V. Rate Constants for the Ligand-Dependent Exchange Reactions of EDTA (ionic strength = 1-3) (error quoted is one standard deviation)

Temp, °K	k_Y^{CaY}, M^{-1} sec^{-1}	k_{HY}^{CaY}, M^{-1} sec^{-1}
314.7	230 ± 15	10 ± 3
305.0	123 ± 7 (120)[a]	6 ± 4 (5)[a]
298.0	74 ± 4	
292.5	52 ± 3	

[a] Reference 1.

$$d\text{-}P^{4-} + Ca\text{-}d\text{-}P^{2-} \xrightarrow{k_{d\text{-}P}^{Ca\text{-}d\text{-}P}} Ca\text{-}d\text{-}P^{2-} + d\text{-}P^{4-} \quad (13)$$

$$H\text{-}d\text{-}P^{3-} + Ca\text{-}d\text{-}P^{2-} \xrightarrow{k_{H\text{-}d\text{-}P}^{Ca\text{-}d\text{-}P}} Ca\text{-}d\text{-}P^{2-} + H\text{-}d\text{-}P^{3-} \quad (14)$$

$$d\text{-}P^{4-} + Ca\text{-}l\text{-}P^{2-} \xrightarrow{k_{d\text{-}P}^{Ca\text{-}l\text{-}P}} Ca\text{-}d\text{-}P^{2-} + l\text{-}P^{4-} \quad (15)$$

$$H\text{-}d\text{-}P^{3-} + Ca\text{-}l\text{-}P^{2-} \xrightarrow{k_{H\text{-}d\text{-}P}^{Ca\text{-}l\text{-}P}} Ca\text{-}d\text{-}P^{2-} + H\text{-}l\text{-}P^{3-} \quad (16)$$

which the first two are true symmetric exchanges while the latter involve the exchange of enantiomers. Since these two processes cannot be distinguished under these conditions, the values of k_P^{CaP} and k_{HP}^{CaP} (Table VI) represent the average of the specific rate constants of the symmetric and enantiomeric exchange pathways. The values of the specific rate constants of the symmetric exchange reactions ($k_{d\text{-}P}^{Ca\text{-}d\text{-}P}$ and $k_{H\text{-}d\text{-}P}^{Ca\text{-}d\text{-}P}$) were then determined by employing a single enantiomer (*d*-PDTA) as both the complexed and free ligand. As can be seen from the data in Table VI, the rate constants for the symmetric and enantiomeric exchange reactions are equal within experimental error. Resolution and activation plots are shown in Figures 4 and 5, respectively. E_a and log A for the tetraanion exchange were found to be 15.0 kcal/mol and 11.1, respectively.

Table VI. Rate Constants for the Ligand-Dependent Exchange Reactions of PDTA (error quoted is one standard deviation)

Temp, °K	k_P^{CaP},[a] M^{-1} sec^{-1}	$k_{d\text{-}P}^{Ca\text{-}d\text{-}P}$, M^{-1} sec^{-1}	k_{HP}^{CaP}, M^{-1} sec^{-1}	$k_{H\text{-}d\text{-}P}^{Ca\text{-}d\text{-}P}$, M^{-1} sec^{-1}
363.0	121 ± 8	112 ± 7	7 ± 4	4 ± 2
357.8	84 ± 4	87 ± 5	4 ± 2	2 ± 1
352.5	57 ± 3			
345.7	41 ± 3			

[a] $k_P^{CaP} = (k_{d\text{-}P}^{Ca\text{-}d\text{-}P} + k_{l\text{-}P}^{Ca\text{-}d\text{-}P})/2$.

Dissociation Rate Constants. The exchange reactions of CaEDTA and CaPDTA with lead acetate were found by stopped-flow spectrophotometry to be first order in the calcium complexes and zero order in lead. An eight- to tenfold excess of lead to calcium complex was maintained in each reaction. Figures 6 and 7 show the dependence of the observed first-order rate constant on the hydrogen ion concentration, which is consistent with the general dissociative mechanism observed by Margerum and Pausch[17] for the alkaline earth complexes of CyDTA, where the rate determining step is either reaction 17 or 18. The observed rate

$$ML^{2-} \xrightarrow{k^{ML}} L_T + M^{2+} \quad (17)$$

$$ML^{2-} + H^+ \xrightarrow{k_H^{ML}} L_T + M^{2+} \quad (18)$$

$$L_T + Pb^{2+} \longrightarrow PbL^{2-} \quad (19)$$

constant is therefore related to the specific rate constants k^{ML} and k_H^{ML} by eq 20. The resolved rate constants and

$$k_{obsd} = k^{ML} + k_H^{ML}[H^+] \quad (20)$$

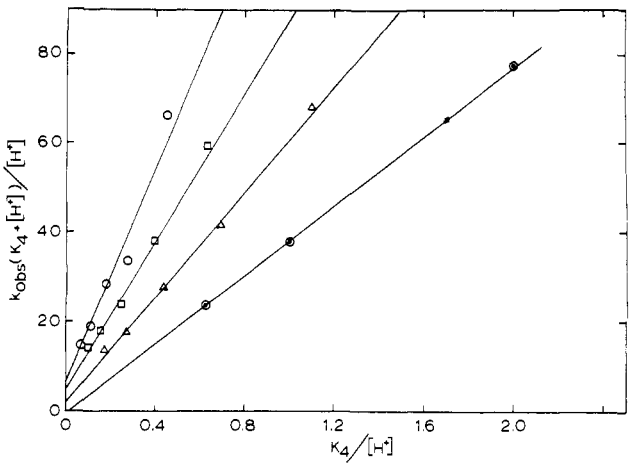

Figure 4. Resolution of k_L^{CaL} and k_{HL}^{CaL}: Temp (°K) ○ 363.0, □ 357.8, △ 352.5, ⊙ 345.7.

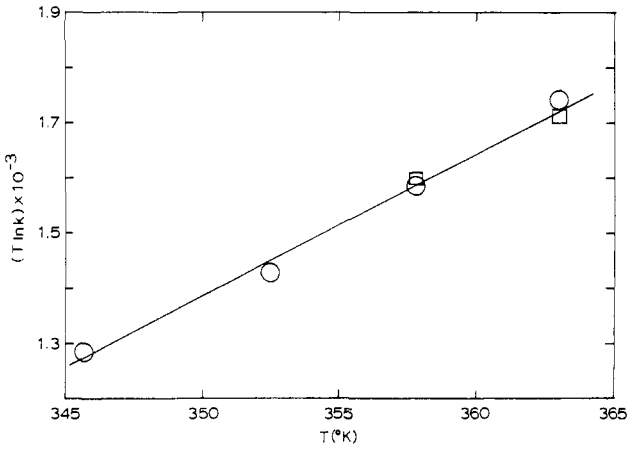

Figure 5. Activation plot for the tetraanion exchange reaction of PDTA with CaPDTA: ○ from the exchange of *dl*-PDTA with Ca-*dl*-PDTA, □ from the exchange of *d*-PDTA with Ca-*d*-PDTA.

their standard deviations in the presence of 0.5 M sodium acetate are listed in Table VII. The value for the proton assisted dissociation rate constant can also be interpreted as dissociation of the protonated complex and the corresponding rate constant is calculated from the acidity constant of each complex and included in Table VII.

The racemization reactions between equal concentrations of Ca-*d*-BDTA and *l*-BDTA and of Ca-*d*-CyDTA with *l*-CyDTA were found to be first order in the respective calcium complex and zero order in free ligand concentration. Even at relatively high concentrations (0.1 M), no ligand dependency was observed. Substitution of CaPDTA was shown to proceed at the same rate (at a given pH) whether the incoming species is CyDTA, PDTA, or Pb(II). The dependence of the observed rate constant on the hydrogen ion concentration is shown in Figure 8 for BDTA and CyDTA. The dissociative mechanism can be described again by reactions 17 and 18. The resolved rate constants and their standard deviations are listed in Table VII.

Table VII. Rate Constants for the Dissociation of the CaL Complexes (T = 25°, μ = 0.5) (error quoted is one standard deviation)

Ligand	k_H^{CaL}, M^{-1} sec^{-1}	k^{CaL}, sec^{-1}	pH range	k^{CaHL}
EDTA	(1.44 ± 0.03) × 10^7 2.0 × 10^7 [a]	1.28 ± 0.07	6.4-7.9	4.88 × 10^3
PDTA	(6.83 ± 0.41) × 10^6	(6.6 ± 0.5) × 10^{-2}	7.2-7.9	1.80 × 10^3
BDTA	(1.28 ± 0.06) × 10^6	(1.04 ± 0.08) × 10^{-4}	8.9-12.5	2.49 × 10^2
CyDTA	(4.43 ± 0.10) × 10^5 4.14 × 10^5 [b]	(3.0 ± 0.1) × 10^{-5}	9.1-13.0	6.25 × 10

[a] Reference 7, T = 32°, $\mu \simeq 2$. [b] Reference 17, T = 25°, μ = 0.5.

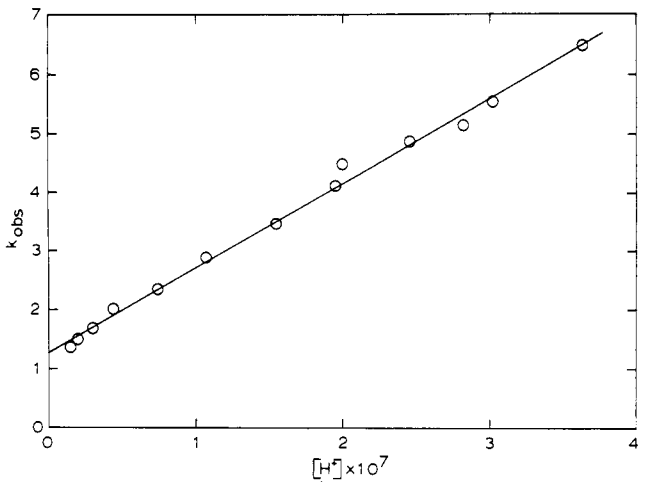

Figure 6. Hydrogen ion dependence of the observed first-order dissociation rate constant of CaEDTA.

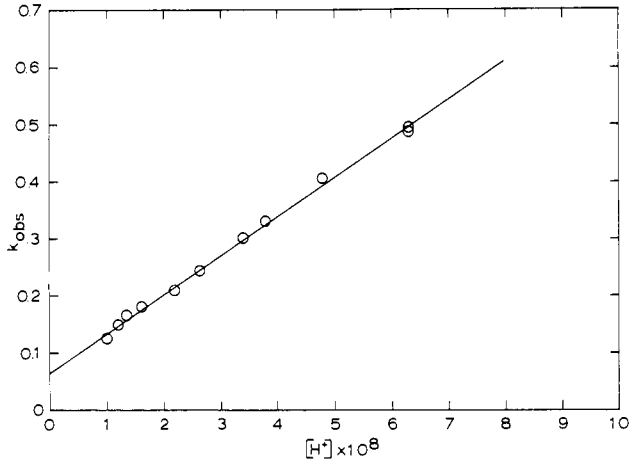

Figure 7. Hydrogen ion dependence of the observed first-order dissociation rate constant of CaPDTA.

Discussion

Dissociation Rate Constants. The values of the intrinsic dissociation rate constants (k^{CaL}) in Table VII illustrate the large differences in kinetic behavior of these ligands. The decreasing values of k^{CaL} with increased substitution on the ethylenic carbons of the ligands is interpreted in terms of the increased energy barrier to the rotation about the ethylenic backbone, which accompanies the breaking of the first calcium-nitrogen bond. This decrease in the dissociation rate constants has also been observed for the strontium complexes of EDTA, $k^{SrY} = 30$,[7] and CyDTA $k^{SrCy} = 0.03$.[17] This intrinsic dissociation rate has been observed only rarely. Other pathways to product are usually more rapid.

It is of interest to compare the values of the formation rate constants of these complexes, which are calculated from their dissociation rate constants and stability constants and are tabulated in Table VIII, with the values predicted from the characteristic water substitution rate constant of calcium ion according to eq 21 (*e.g.*, the general

$$k_{Ca}{}^{L} = K_{CaL}k^{CaL} = K_{os}k^{Ca\text{-}H_2O} \qquad (21)$$

mechanism proposed by Eigen.[20] The predicted value of $k_{Ca}{}^{L}$ is 2.5×10^{10} based on $K_{os} = 50$[17] for the outer sphere association constant between the 2+ calcium ion and the 4− ligand and $k^{Ca\text{-}H_2O} = 5 \times 10^8$.[20] Although the agreement is remarkably good for EDTA and PDTA (see Table VIII), it is far from satisfactory for the calcium complexes of BDTA and CyDTA. It must be noted that the water-loss rate constant for aqueous Ca(II) is still subject to some uncertainty[20] but seems to be in the range $1\text{-}5 \times 10^8$ sec^{-1}. This formation rate constant is so large as to approach the diffusion-controlled limit. As has been pointed out[20c] in such a case, the use of K_{os}, which implies an equilibrated outer-sphere complex, is not completely valid. The outer and inner sphere substitutions may be somewhat coupled and, with these limitations in mind, the resulting small errors will not be considered further.

Table VIII. Calculated Formation Rate Constants of CaL Complexes (μ = 0.5, 25°)

Ligand	$k_{Ca}{}^{L}$, M^{-1} sec^{-1}	$k_{Ca}{}^{HL}$, M^{-1} sec^{-1}
EDTA	2.4×10^{10}	1.7×10^7 2.3×10^7 [a]
PDTA	1.7×10^{10}	1.7×10^7
BDTA	1.2×10^9	7.5×10^6
CyDTA	1.4×10^9	1.7×10^6

[a] Reference 23, T = 25°, μ = 0.01.

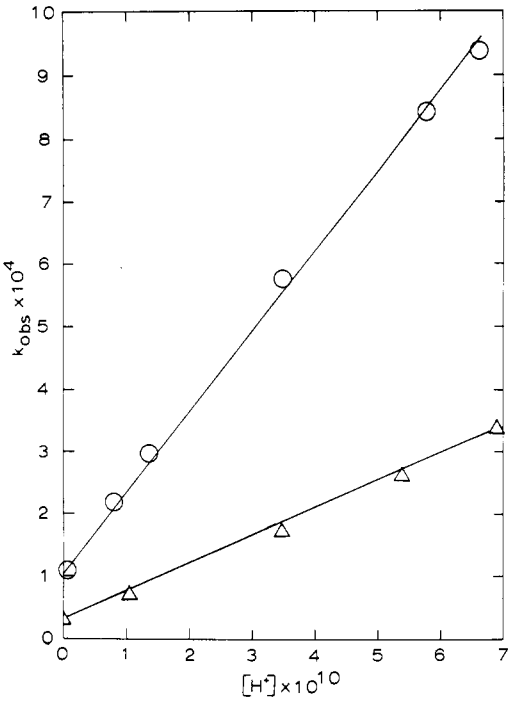

Figure 8. Hydrogen ion dependence of the observed first-order dissociation rate constant: O of CaBDTA, Δ of CaCyDTA.

The observed decrease in the formation rate constants of the calcium complexes of BDTA and CyDTA can best be explained as a shift in the rate determining step away from first bond formation for EDTA and PDTA to some degree of multiple bond formation for BDTA and CyDTA. The latter process necessarily involves rotation about the carbon-carbon bonds between the successive binding sites of the ligand and a decrease in the formation rate constants would not be surprising in light of the larger rotational barriers presented by the added alkyl substituents of BDTA and CyDTA. The same behavior is characteristic of strontium for which formation rate constants of 1.5×10^{10} [7] and 1.0×10^8 [17] can be calculated from dissociation rate constants for SrEDTA and SrCyDTA, respectively. These compare with the Eigen mechanism predicated value of 2.5×10^{10}. Arguments that K_{os} differs for CaEDTA and CaCyDTA due to different approach distance do not seem capable of causing such a large decrease in formation rate constant.

Proton-Dependent Dissociation Rate Constants. The observed decrease in the values of the proton-dependent dissociation rate constants (k_H^{CaL}) of these calcium complexes as the identity of the ligand changes from EDTA through CyDTA is consistent with the values reported for the analogous reactions of the lead complexes of EDTA, 390 M^{-1} sec^{-1} in 1 M KNO_3[21] (it should be noted that this value has been incorrectly quoted elsewhere[5,22]), PDTA, 200 M^{-1} sec^{-1} in 0.5 M KNO_3,[5] and CyDTA, 23 M^{-1} sec^{-1} in 0.1 M $NaClO_4$.[22] Analogous proton-dependent dissociation rate constants for other metals for which more than one of the ligands is known are included in Table IX.

Table IX. Proton-Catalyzed Dissociation Rate Constants of Metal Aminocarboxylate Complexes

Metal	k_H^{MEDTA}, M^{-1} sec^{-1}	k_H^{MCyDTA}, M^{-1} sec^{-1}
Ca	144×10^5 [m]	4.43×10^5
Sr	1×10^8 [f]	6.06×10^6 [g]
Pb	390[a,b]	23[c]
Ni	8.0×10^{-4} [d]	3.6×10^{-4} [c]
Cu	3.5[e]	3.9[c]
Zn	1.2×10^2 [h,l]	1.7×10^2 [c]
Co	17.8[i]	3.2[c]
Cd	750[j]	42[k]

[a] Reference 21. [b] Reference 5. [c] Reference 22. [d] Reference 25. [e] Calculated from formation rate constant from ref 26. [f] Reference 7. [g] Reference 17. [h] Reference 27 (corrected to 25°) (or 2×10^8, ref 29). [i] Reference 28 (corrected to 25°). [j] Reference 2. [k] Reference 30. [l] Reference 29. [m] Or 347×10^5, ref 2b.

From these hydrogen ion catalyzed dissociation rate constants can be calculated formation rate constants of the metal with the protonated ligand (eq 22).

$$k_{HL}^{M} = k_H^{ML} K_{stab} K_{HY} \qquad (22)$$

Values of log K_{stab} used in these calculations are as follows: CdEDTA, 16.46; CdCyDTA, 19.88; ZnEDTA, 16.26; ZnCyDTA, 19.30; CoEDTA, 16.31; CoCyDTA, 19.53. Values of these formation rate constants are shown in Table X along with rate of water loss and the formation rate constant calculated *via* a water loss mechanism (K_{os} = 13 for $M^{2+} + HL^{3-}$ [22]). Two sets of metal ions are apparent: group I in which there is little or no difference between the observed values for different ligands (actually $HCyDTA^{3-}$ reacting somewhat faster than $HEDTA^{3-}$) and which also agree with a water loss rate constant and group II which shows decreasing values of formation rate constants as the ligand grows more bulky. Group I comprises Ni^{2+}, Co^{2+}, Cu^{2+}, Zn^{2+}, and Cd^{2+} and group II comprises Ca^{2+}, Sr^{2+}, and Pb^{2+}. A similar grouping of these metals has been noticed by Margerum, Menardi, and Janes.[22] They find that group I metal ions (Co, Ni, Cu, and Zn) show excellent agreement with an Eigen water loss mechanism while group II metals (Mg, Ca, and Mn) dissociate at 1/10 to 1/600 of the rate expected from an Eigen formation mechanism. Strontium and barium were later shown to behave as group II ions and cadmium would be classed as group I using their criteria. These observations and dramatically different activation parameters for the two groups led to a proposed "simultaneous bond dissociation" mechanism for group II metals. Whatever the exact nature of this process, we find that additional substituents on the ethylenic backbone carbon atoms of the ligand make more pronounced the divergence from an Eigen outer-sphere complex water loss mechanism. This ligand specificity might be due to the second metal-ligand bond formation (chelation) being rate determining in the formation of the complex from a metal ion and a protonated ligand. Larger substituents on the ligand backbone impede this step and slow the formation reaction. Lead is interesting in that its formation rate constant with EDTA agrees with the best estimate of k^{-H_2O} but the CyDTA value is much slower. It is somewhat of a borderline case.

Eigen originally anticipated three categories of metal ions:[20] (i) water loss rate constants $>10^7$ sec^{-1} for which ion pair formation or chelation may contribute to the rate and hence cause the formation rate to be ligand dependent, (ii) rates $<10^7$ sec^{-1} for which the formation rate is strictly limited by water loss rate, and (iii) very slow water loss rates which may be limited by rate of metal ion hydrolysis. None of the metals referred to in Table X falls into Eigen's third category but there is substantial agreement between Eigen's categories i and ii and our group II and I, respectively. Also, group II metals seem to be those which do not form strong complexes with ammonia or amines. Perhaps the nitrogen of EDTA does not form a very strong bond to these metals and two acetate groups must bond (as well as a nitrogen) before the rate-determining step.

An alternate view recognizes that the formation reaction with protonated ligand involves the reaction of a ligand *chelated* to a proton.[31] The stability constant of the proton ligand chelate increases from EDTA through CyDTA, leaving a smaller fraction of unchelated protonated species of CyDTA available than is the case for BDTA < PDTA < EDTA. The acetate groups are partially bonded to the proton and hence are not totally free for first-bond formation. If only the nonchelated species were reactive due to the additional step of proton-ligand chelate ring breaking, the diminished formation reaction rate of CyDTA < BDTA < PDTA < EDTA is rationalized. Quantitatively, however, the predicted rate constant (eq 23) for the model that che-

$$k_{HL}^{Ca} = k_{Ca}^{-H_2O} K_{os} \alpha_{nc} = k_{Ca}^{-H_2O} K_{os} \frac{1}{K_c + 1} \qquad (23)$$

α_{nc} = fraction of HL present in nonchelated or open form

K_c = proton–ligand chelate stability constant

Table X. Formation Rate Constants of Protonated Ligands Calculated from Dissociation Rate Constants

	k_{HEDTA}^{M}	k_{HCyDTA}^{M}	$k_{HEDTA}^{M}/k_{HCyDTA}^{M}$	Water-loss mechanism (M^{-1} sec^{-1})	k^{-H_2O}, sec^{-1}
Ca	1.7×10^7 [d]	1.7×10^6	10	6×10^9	5×10^8
Sr	4×10^9	2×10^4	2×10^5	2×10^{10}	5×10^8
Pb	2.5×10^{10}	5.7×10^7	4.4×10^3	3×10^{10}	2.5×10^9
Ni	1.8×10^5	3.6×10^5	0.50	3.6×10^5 [a]	2.7×10^4
Cu	1.3×10^9 [b]	1.6×10^{10}	0.08	2.6×10^9	2×10^8
Zn	1.4×10^8 [c]	1.8×10^9	0.08	3.9×10^8	1.1×10^6
Co	2.0×10^6	5.8×10^7	0.035	1.4×10^7	1.1×10^6
Cd	1.3×10^9	1.7×10^9	0.76	4×10^9	3×10^8

[a] This value is defined as agreeing with k_{HCyDTA}^{Ni} by its use in selecting K_{os}.[22] [b] Measured directly.[26] [c] Or 2×10^9, measured directly.[29] [d] Or 3.7×10^7, ref 2b.

Table XI. Extent of Proton Chelation Effect on Rate of Calcium Complexation with Protonated Ligands

Ligand	K_c	$1/(K_c + 1)$	$10^{-7} \times (k_{Ca^{-H_2O}} K_{os}\alpha_{nc})$, M^{-1} sec^{-1}	$10^{-7}k_{HL}^{Ca}$, M^{-1} sec^{-1} (measured)
EDTA	1	0.50	330[a]	1.7
PDTA	5.7	0.15	98[a]	1.7
BDTA	49	0.22	13[a]	0.75
CyDTA	100	0.01	3.3[a]	0.17

[a] These values should be compared to 650 M^{-1} sec^{-1}, the value predicted by the Eigen mechanism if proton chelation is not considered.

lated protonated ligands are unreactive does not give agreement with measured rate constants (Table XI), leaving the hindered rotation for second-bond formation as responsible for the major disagreement with an Eigen formation fraction rate.

The hydrogen ion dependent dissociation pathway of these calcium complexes can be envisioned as a two-step mechanism represented by eq 24 and 25.

$$CaL^{2-} + H^+ \underset{k_{-H}}{\overset{k_H^{CaL}}{\rightleftharpoons}} CaHL^- \quad (24)$$

$$CaHL^- \underset{k_{Ca}^{HL}}{\overset{k^{CaHL}}{\rightleftharpoons}} Ca^{2+} + HL^{3-} \quad (25)$$

If the rate determining step is assigned as the dissociation of the protonated complex (reaction 25) the value of k^{CaHL} can be calculated from the values of k_H^{CaL} found in Table VII and the respective values of K_{CaL}^{CaHL} found in Table IV. The values of k^{CaHL} determined by this procedure are given in Table VII. These two possibilities are kinetically indistinguishable. However, if the addition of the proton to the complex were to be rate determining, then the values of k^{CaHL} in Table VII must be reassigned as k_{-H}. This assignment seems unrealistic in light of the rather small values of k_{-H} which would be obtained; therefore we have assigned the rate determining step to the dissociation of the protonated complex (reaction 23). The values of the formation rate constants which were calculated from the appropriate equilibrium constants, K_{CaHL}, are given in Table VIII. The agreement between our calculated value and that determined by Rechnitz and Lin[23] for calcium-EDTA is quite good considering the difference in ionic strength.[32]

Ligand-Dependent Exchange Reactions. Unfortunately, due to the lack of any observable ligand dependency for the exchange reactions of either BDTA or CyDTA with their respective calcium complexes, little information was obtained concerning the effect of a change in the structure of the ligands on this type of reaction. However, an upper limit of 3×10^{-5} can be placed on the value of the rate constant for the enantiomeric exchange reaction of CyDTA, which leads to a minimum ratio of k_Y^{CaY}/k_{Cy}^{CaCy} of about 2×10^6. In the case of the calcium system, the ratio of the exchange rate constants is at least 1000 times greater than the inverse ratio of the stability constants (log K_{CaCy} − log K_{CaY} = 13.68 − 10.28 = 3.4). The values of the analogous exchange rate constants of the lead complexes of EDTA and CyDTA are 65[2] (temp, 32°; μ = 2), and 3.77×10^{-2} (temp, 25°; μ = 0.5), respectively, which yields a ratio of k_Y^{PbY}/k_{Cy}^{PbCy} of about 10^3. It is hardly surprising that this ratio is nearly identical with the inverse ratio of the stability constants of these lead complexes, log K_{PbCy} = 20.9[24] and log K_{PbY} = 18.0,[16] since the identity of the attacking ligand was found to have only a small effect on the exchange rate constants.[6] These considerations certainly indicate that the structural effects on these ligands on this type of reaction are quite dependent on the identity of the metal ion.[33]

It is of interest that the values of the frequency factor are the same for reactions 1 and 2 (log A = 11.1) but that the activation energy for reaction 1 was 2.6 kcal less than for reaction 2 (E_a = 12.4 and 15.0 kcal/mol). This implies that there is little difference in the probability of a collision leading to formation of the activated complex but that the 2.6 kcal difference is a measure of the increased difficulty of reaching the activated complex after the collision.[34]

Supplementary Material Available. Tables XII-XVIII, rate constants of individual kinetic runs, will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JACS-75-315.

References and Notes

(1) Abbreviations used throughout this paper are the following: EDTA or Y^{4-}, ethylenediaminetetraacetate; PDTA or P^{4-}, 1,2-diaminopropanetetraacetate; BDTA or B^{4-}, 2,3-diaminobutanetetraacetate; and CyDTA or Cy^{4-}, *trans*-2-diaminocyclohexanetetraacetate.
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(33) The rate of reaction 1 measured in this work may be low by as much as a factor of 4 based on a log K_{stab} = 0.7 for potassium-EDTA complex,[13] total potassium concentration of ~0.8 *M*, and assuming that the potassium complex reacts much more slowly with CaEDTA than does the free tetraanion.
(34) Tables XII-XVIII, rate constants of individual kinetic runs upon which this work is based, will appear following these pages in the microfilm edition of this volume of the journal. See paragraph at end of paper regarding supplementary material.