Nuclear Magnetic Resonance Study of Rate and Mechanism of Exchange Reactions Involving (Ethylenedinitrilo)tetraacetatocadmate(II)[1]

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Application of nuclear magnetic resonance (nmr) to the study of metal chelate exchange reactions by measurement of line widths is illustrated. Experimental results for exchange reactions of (ethylenedinitrilo)tetraacetatocadmate(II) are presented and interpreted. The mechanism of nucleophilic attack by excess (ethylenedinitrilo)tetraacetate (EDTA) is elucidated by studying the effect of various ligands upon the rate of partial unwrapping of EDTA from the metal ion. The rate of this intramolecular process is determined by matching the shapes of computed AB patterns with those exhibited by nonequivalent acetate protons in the metal chelate.

Introduction

Exchange studies of multidentate ligands fall into two categories: (1) nucleophilic substitution (SN) reactions, in which excess ligand is added to a metal chelate, presumably forming intermediates in which both ligand molecules are coordinated to the metal ion

$$MY_B + Y_A \rightleftarrows [Y_A MY_B] \rightleftarrows MY_A + Y_B$$

and (2) electrophilic substitution (SE) reactions

$$M_B Y + M_A \rightleftarrows [M_A Y M_B] \rightleftarrows M_A Y + M_B$$

in which excess metal is added to the metal chelate, presumably forming intermediates in which both metal ions are coordinated to the ligand. A subclass of SE reactions is the dissociation of protonated metal chelates or "acid-catalyzed" dissociation.

Margerum and co-workers[2] have utilized spectrophotometric methods for kinetic studies of unsymmetrical SN ($Y_A \neq Y_B$) and SE ($M_A \neq M_B$) reactions involving (ethylenedinitrilo)tetraacetic acid (EDTA) and radiochemical methods for symmetrical SE ($M_A = M_B$) reactions. Rogers, Aikens, and Reilley[3] studied the kinetics of unsymmetrical SN reactions involving metal–dye and metal–EDTA chelates by means of spectrophotometry. A number of workers have studied unsymmetrical SE reactions of EDTA by polarographic techniques, including Ackermann and Schwarzenbach,[4] Tanaka and co-workers,[5,6] Koryta and Zabransky,[7] and Aylward and Hayes.[8]

In any study of symmetrical SN reactions ($Y_A =$ Y_B), an experimental problem is the "tagging" of ligand molecules to provide a means of following the course of the reaction. C^{14} labeling has been employed,[9] but not in any study involving EDTA. An alternative method is the use of the optically active EDTA analog, *d*-(1,2-propylenedinitrilo)tetraacetic acid (PDTA), as in the work of Bosnich,[10] Bosnich, Dwyer, and Sargeson,[11] and Cruz and Reilley,[12] thereby labeling ligand molecules by means of optical activity. However, because rates of PDTA reactions are characteristically several times slower than the rates of corresponding EDTA reactions, caution must be observed in relating these results to those of EDTA.

The nmr method is based upon labeling ligand molecules, and even parts of ligand molecules, by means of their nuclear spins. This permits measurement of exchange rates of SN and SE reactions under steady-state conditions, thereby dispensing with mixing problems. In addition, nmr, by indicating certain intramolecular exchange rates, is capable of providing detailed mechanistic information which would be extremely difficult to obtain by other means.

In this paper, evidence is given for the existence of mixed-ligand precursors, which are present in extremely low concentrations. A disadvantage of nmr is the need for using fairly high concentrations of solute (*e.g.*, 0.2 *M* EDTA). Cd–EDTA was chosen for this study because it is diamagnetic, and its reaction rates fall optimally within the kinetic "window" of the 60-Mc nmr spectrometer.

Experimental Section

Nmr Measurements.—All spectra were recorded using a Varian A-60 nmr spectrometer with the V-6057 variable temperature system. Sodium 3-(trimethylsilyl)propanesulfonate, available from Eastman, was used as an internal standard. The temperature of all samples was 28°, the ambient temperature of the cell compartment. A sweep width of 50 cps and a sweep rate of 0.1 cps² was employed. A radiofrequency field intensity of 0.05

(1) This work was supported in part by National Institutes of Health Grant RG GM-08349; abstracted in part from the Ph.D. thesis of James L. Sudmeier; presented at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.

(2) T. J. Bydalek and D. W. Margerum, *J. Am. Chem. Soc.*, **83**, 4326 (1961); *Inorg. Chem.*, **1**, 852 (1962); **2**, 678 (1963); **2**, 683 (1963); D. W. Margerum, D. B. Rorabacher, and J. F. G. Clarke, Jr., *ibid.*, **2**, 667 (1963); D. B. Rorabacher and D. W. Margerum, *ibid.*, **3**, 382 (1964); D. W. Margerum, *Record Chem. Progr.*, **24**, 237 (1963).

(3) D. W. Rogers, D. A. Aikens, and C. N. Reilley, *J. Phys. Chem.*, **66**, 1582 (1962).

(4) H. Ackermann and G. Schwarzenbach, *Helv. Chim. Acta*, **35**, 485 (1952).

(5) N. Tanaka and M. Kamada, *Bull. Chem. Soc. Japan*, **35**, 1596 (1962).

(6) N. Tanaka, R. Tamamushi, and M. Kodama, *Z. Physik. Chem.* (Frankfurt), **14**, 141 (1958).

(7) J. Koryta and Z. Zabransky, *Collection Czech. Chem. Commun.*, **25**, 3153 (1960).

(8) G. H. Aylward and J. W. Hayes, *Anal. Chem.*, **37**, 195 (1965).

(9) R. G. Wilkens, *J. Chem. Soc.*, 4521 (1957).

(10) B. Bosnich, Ph.D. Thesis, Australian National University, Canberra A.C.T., 1962.

(11) B. Bosnich, F. P. Dwyer, and A. M. Sargeson, *Nature*, **186**, 966 (1960).

(12) C. J. Cruz and C. N. Reilley, Division of Analytical Chemistry, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.

mgauss gave maximum signal-to-noise without appreciable saturation and was used for recording all EDTA resonances. The optimal radiofrequency field intensity for recording the sodium 3-(trimethylsilyl)propanesulfonate peak was found to be 0.03 mgauss. By averaging the results of three or more scans, an estimated precision of ±0.01 in the measurement of valley-peak ratios and ±0.02 cps in the measurement of line widths was obtained. These limits are believed to be imposed primarily by fluctuations in the magnet water temperature, caused by rather crude heat-exchange control.

In a typical experiment, the initial sample volume was 0.5 ml. Then small increments of a second reagent were added directly to the sample tube by means of a 2-ml capacity Gilmont microburet. Preliminary experiments showed that removal of dissolved oxygen by bubbling with nitrogen did not result in appreciable changes in line widths, and no attempt was made to remove dissolved oxygen thereafter.

The pH values were measured at room temperature (25–26°) using a Leeds and Northrup Model 7401 line-operated pH meter equipped with a Model 124138 microelectrode assembly. pK_a values were determined using semiautomatic recording of pH titration curves. Relative viscosity values were determined at room temperature using a conventional Ostwald viscometer.

Chemicals.—Chemicals of the highest available purity were used, generally without further purification. EDTA was obtained from the Fisher Scientific Co. Disodium iminodiacetate, obtained from Eastman, was dissolved in water, the solution was neutralized with 2 equiv of hydrochloric acid, and iminodiacetic acid was precipitated by addition of ethanol. After filtering and drying, the material was redissolved in water; 1 equiv of potassium hydroxide was added, followed by 1 equiv of hydrochloric acid, and the material was precipitated by addition of ethanol once again. After an additional repetition of this procedure, flame tests showed negligible sodium ion to be present. N-methyliminodiacetic acid and N,N,N',N'-tetramethylethylenediamine were obtained from the Columbia Organic Chemical Co. Nitrilotriacetic acid was obtained from the Hampshire Chemical Co. Deionized water was used in preparation of all solutions.

In order to avoid excessive inert salt concentrations which would increase solution viscosities and influence reaction kinetics, the Cd–EDTA stock solution was prepared by combination of EDTA, KOH, and Cd(OH)₂ in exact proportions. The Cd-(OH)₂ was prepared by dropwise addition of potassium hydroxide solution into hot, stirred cadmium nitrate solution. After precipitation was complete, the solution was stirred for 3 hr at a temperature of approximately 90° and allowed to age overnight. The resulting Cd(OH)₂ was filtered, rinsed with water, and rinsed finally with ethanol. After drying 24 hr at 120°, the white solid was analyzed by EDTA titration. Solid EDTA was dissolved by addition of 2 equiv of KOH, and equimolar Cd-(OH)₂ was then added. In order to ensure achievement of precise stoichiometry, the potential of a portion of solution in acetate buffer was tested using a mercury-pool electrode.[13]

Additional EDTA or Cd(OH)₂ was added until the precise stoichiometric point was achieved. The sensitivity of this method is such that 0.3 mole % of either cadmium or EDTA in excess can be detected. The resulting solution was 0.76 M in K₂Cd–EDTA and had a pH of 6.7.

Results and Discussion

Nmr Spectrum of Cd–EDTA.—Cd–EDTA (CdY^{-2}) is not present above pH 11 or below pH 2.8 at the high concentration typically required for nmr work. Above pH 11, cadmium precipitates as the hydroxide, Cd-(OH)₂; below pH 2.8, the complex exists predominantly as the soluble protonated complex CdHY⁻; and below pH 1.8, the complex CdH₂Y precipitates. The nmr spectrum of 1:1 Cd–EDTA in aqueous solution between pH 5 and 11 in the absence of any excess ligand
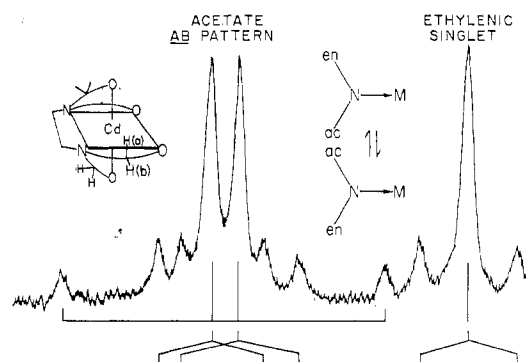
(13) R. W. Schmid and C. N. Reilley, *J. Am. Chem. Soc.*, **78**, 5513 (1956).

Figure 1.—Nmr spectrum of Cd–EDTA.

is shown in Figure 1. The six satellite peaks are caused by the presence of 25% spin $^1/_2$ isotopes in naturally occurring cadmium as reported earlier.[14]

The nmr spectrum of free EDTA consists of a singlet attributable to the four ethylenic protons and, at somewhat lower field strength, a more intense singlet attributable to the eight acetate protons.[15] For simplicity, the structure of Cd–EDTA given in Figure 1 does not show all the individual ethylenic and acetate protons. One or more carboxylate groups in this structure may in reality be substituted by a water molecule. The relative abundance of such species is not known. In any case, the rate of displacement of carboxylate groups in comparison to the speed of nmr measurements is sufficiently rapid so that all four carboxylate groups are equivalent. The observation that all ethylenic protons are equivalent requires that rapid partial rotation about the ethylenic carbon–carbon bond (d to l conversion) take place.

The acetate AB pattern is caused by nonequivalence of protons on any acetate arm when the adjacent metal–nitrogen bond is intact.[14] As shown in the insert in Figure 1, when this bond is intact, three different groups (cadmium ion, acetate group, and ethylenic "backbone") are attached to the nitrogen atom, and this is sufficient cause for nonequivalence of the adjacent acetate protons.[16] The two protons on a particular group may interchange their magnetic environments by breaking the metal–nitrogen bond, allowing the nitrogen atom to invert, and re-forming the metal–nitrogen bond with the acetate groups interchanged. If the rate of this process is rapid enough, all acetate protons are equivalent, and a single resonance is observed for all acetate protons. As will be shown, determination of the interchange rate can provide valuable information in regard to reaction mechanisms.

Lifetime Broadening.—When sufficient strong acid or free EDTA (at appropriate pH values) is added to a solution containing Cd–EDTA, broadening of the EDTA resonances is observed. This broadening is caused by a decrease in the lifetime of EDTA in the complexed state as the rate of intermolecular exchange

(14) R. J. Day and C. N. Reilley, *Anal. Chem.*, **36**, 1073 (1964).
(15) R. J. Kula, D. T. Sawyer, S. I. Chan, and C. M. Finley, *J. Am. Chem. Soc.*, **85**, 2930 (1963).
(16) H. S. Gutowsky, *J. Chem. Phys.*, **37**, 2196 (1962).

increases[17] and is sometimes known as "lifetime broadening."

An illustration of lifetime broadening is given in Figure 2. Frame A shows a portion of the AB pattern of Cd–EDTA with no excess EDTA present. Frame B shows the effect of adding 20% excess EDTA at pH 9.6. Only the acetate proton singlet of free EDTA is shown, the ethylenic singlet occurring immediately upfield of the chelate AB pattern. At higher pH values, the resonances of free EDTA would superimpose upon those of the chelate, allowing no interpretation to be made. Thus, it is only the downfield protonation shift,[15,18] corresponding in this case to $^2/_3$ mole of acid per mole of free EDTA, which allows separate observation of all resonances. As the amount of excess EDTA is increased (60 and 100% in frames C and D), greater broadening of the chelate AB pattern is observed. The ethylenic singlet of the chelate (not shown) is also observed to broaden. The effect of lifetime broadening upon the shape of the acetate AB pattern will be discussed later.

Viscosity Corrections.—In attempting to determine quantitatively the intermolecular exchange rate in the type of experiment depicted in Figure 2, it must be noted that addition of free EDTA is accompanied by an increase in the solution viscosity, which may in itself cause broadening. Any change in homogeneity of the magnetic field or tuning of the nmr spectrometer also affects line width measurements. Therefore, at least three contributions to line width must be considered: (1) natural line width, $1/\pi T_2$ (dependent upon temperature, viscosity), (2) instrumental broadening, $1/\pi T_2'$ (dependent upon tuning of instrument), and (3) lifetime broadening, $1/\pi\tau$ (dependent upon chemical kinetics, in the slow-exchange limit). The total apparent line width, $1/\pi T_2^*$, in cps measured at one-half maximum peak height, is equal to the sum of these terms, of $1/\pi T_2^* = 1/\pi T_2 + 1/\pi T_2' + 1/\pi\tau$, where T_2^* is the apparent transverse relaxation time (in seconds), T_2 is the transverse relaxation time, and τ is the lifetime of the observed species. The slow-exchange approximation is valid only under the condition $\delta\omega\tau \gg 1$, where $\delta\omega$ is the chemical-shift difference in radians/sec between the two exchanging species.[17] The width of the singlet of sodium 3-(trimethylsilyl)propanesulfonate was adopted as the measure of instrumental broadening. This assumes that T_2 of this compound is very large compared to T_2'.

Solutions of EDTA (K_4Y) and of Cd–EDTA at various concentration levels were prepared, and a small amount of sodium 3-(trimethylsilyl)propanesulfonate was added to each. The apparent line widths of the ethylenic singlets of free EDTA, $1/\pi T_2^*_{c(EDTA)}$, Cd–EDTA, $1/\pi T_2^*_{c(chelate)}$, and of the acetate singlet of free EDTA, $1/\pi T_2^*_{a(EDTA)}$, were determined. Subtracting the instrumental broadening associated with each determination, it was possible to

(17) H. S. Gutowsky and A. Saika, *J. Chem. Phys.*, **21**, 1688 (1953).
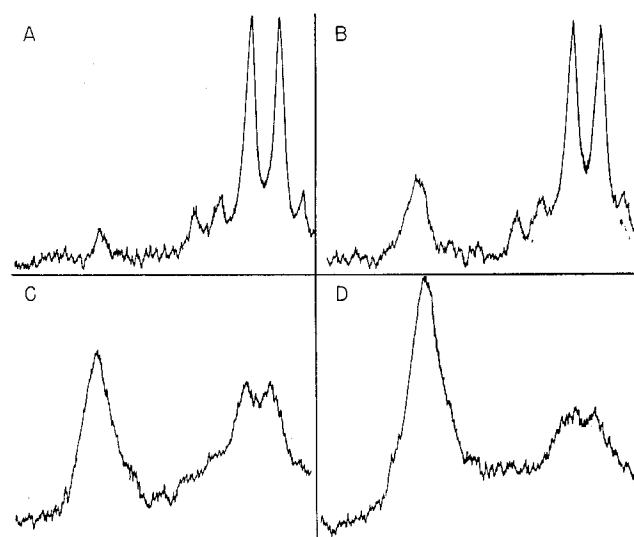(18) J. L. Sudmeier and C. N. Reilley, *Anal. Chem.*, **36**, 1698 (1964).
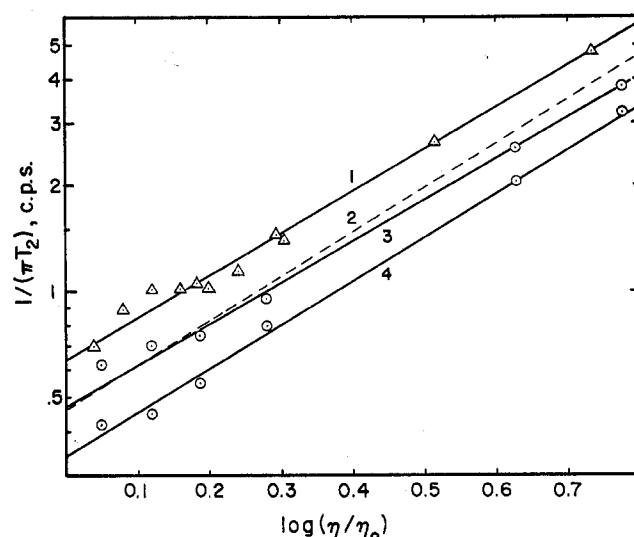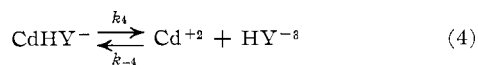

Figure 2.—Lifetime broadening of Cd–EDTA resonances.

Figure 3.—Natural line width of various EDTA resonances for various relative viscosities at 28°: line 1, ethylenic, Cd–EDTA; line 2, acetate, Cd–EDTA; line 3, ethylenic, EDTA (Y^{-4}); line 4, acetate, EDTA (Y^{-4}).

construct linear plots of log $(1/\pi T_2)$ *vs.* log (η/η_0), or viscosity relative to water, as shown in Figure 3. Line 1 is a plot of the natural line width of ethylenic protons of the chelate $1/\pi T_{2c(chelate)}$, line 3 represents the ethylenic protons of free EDTA, $1/\pi T_{2c(EDTA)}$, and line 4 represents the acetate protons of free EDTA, $1/\pi T_{2a(EDTA)}$. Line 2 is assumed to represent the acetate protons of the chelate, $1/\pi T_{2ab(chelate)}$, and will be discussed later.

Increasing the concentrations of EDTA and of Cd–EDTA sufficiently to attain viscosities of approximately log $(\eta/\eta_0) = 0.3$ caused distinct line broadening. The fact that this is a viscosity effect is further shown by sharpening of spectral lines at 75°.

In order to achieve viscosities higher than log $(\eta/\eta_0) = 0.3$, it was necessary to add materials such as potassium acetate (KOAc), potassium nitrate, and glycerine to the EDTA and Cd–EDTA solutions. Additions of KOAc and KNO$_3$ were found to produce nearly
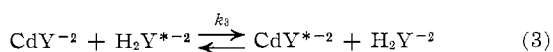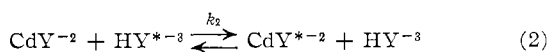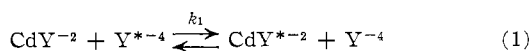
the same amount of line broadening per unit increase in viscosity as did EDTA or Cd–EDTA, thereby ensuring continuity of slopes in Figure 3. Because of its extremely high solubility, KOAc proved most satisfactory for this purpose. The observation that glycerine is almost four times less effective than EDTA, Cd–EDTA, or KOAc in causing line broadening per unit viscosity is attributed to decreased microscopic viscosity caused by the nonionic character of glycerine.

From lines 1, 3, and 4 in Figure 3, the natural line widths of the three corresponding singlet resonances may be determined in a solution of known viscosity. (See Appendix for the empirical formula used in calculating relative viscosities of mixtures.)

Exchange Reactions.—The following reactions were considered

$$CdY^{-2} + Y^{*-4} \underset{}{\overset{k_1}{\rightleftarrows}} CdY^{*-2} + Y^{-4} \qquad (1)$$

$$CdY^{-2} + HY^{*-3} \underset{}{\overset{k_2}{\rightleftarrows}} CdY^{*-2} + HY^{-3} \qquad (2)$$

$$CdY^{-2} + H_2Y^{*-2} \underset{}{\overset{k_3}{\rightleftarrows}} CdY^{*-2} + H_2Y^{-2} \qquad (3)$$

$$CdHY^{-} \underset{k_{-4}}{\overset{k_4}{\rightleftarrows}} Cd^{+2} + HY^{-3} \qquad (4)$$

The over-all rate of disappearance of (spin-labeled) Cd–EDTA is given by

$$\text{rate} = k_1[CdY^{-2}][Y^{-4}] + k_2[CdY^{-2}][HY^{-3}] + \\ k_3[CdY^{-2}][H_2Y^{-2}] + k_4[CdHY^{-}] \quad (5)$$

The proton is assumed to exchange very rapidly between CdY^{-2}, $CdHY$, and CdH_2Y, and the sum of their concentrations, C_{MY}, is given by the expression

$$C_{MY} = [CdY^{-2}] + [CdHY^{-}] + \\ [CdH_2Y] = [CdHY^{-}]\left\{1 + \frac{K_{MHY}}{[H^+]} + \frac{[H^+]}{K_{MH_2Y}}\right\} \quad (6)$$

where

$$K_{MHY} = \frac{[H^+][CdY^{-2}]}{[CdHY^{-}]} = 10^{-2.80}$$

and

$$K_{MH_2Y} = \frac{[H^+][CdHY^{-}]}{[CdH_2Y]} = 10^{-1.80}$$

(determined at 25° and $\mu = 1$). B_1 is defined as the fraction of total complex in the monoprotonated form or $B_1 = [CdHY^{-}]/C_{MY}$. Values of α have their usual significance, i.e., $\alpha_2 = [H_2Y^{-2}]/C_Y$, $\alpha_3 = [HY^{-3}]/C_Y$, and $\alpha_4 = [Y^{-4}]/C_Y$, where C_Y is the total concentration of uncomplexed EDTA. The acidic dissociation constants of EDTA at 25° and $\mu = 2$ were found to be $K_2 = 10^{-2.60}$, $K_3 = 10^{-6.25}$, and $K_4 = 10^{-9.90}$.

Equation 5 can be expressed in terms of C_{MY}. The lifetime of a particular ligand on a particular metal ion, $1/\tau_{MY}$ (whether the chelate is protonated or not), is obtained by dividing this expression by C_{MY}, yielding

$$1/\tau_{MY} = \frac{\text{rate}}{C_{MY}} = k_1[Y^{-4}] + k_2[HY^{-3}] + k_3[H_2Y^{-2}] + \\ B_1\{-k_1[Y^{-4}] - k_2[HY^{-3}] - k_3[H_2Y^{-2}] + k_4\} \quad (7)$$

It is assumed that $[CdH_2Y]$ is negligible. Equation 7 may be expressed in terms of α factors as shown in eq 8.
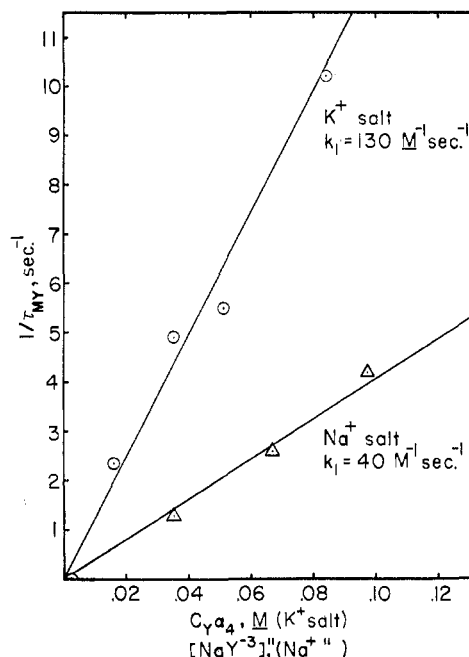

Figure 4.—Reciprocal lifetime of Cd–EDTA at various values of $C_Y\alpha_4$ and $[NaY^{-3}]$ (pH 8–10).

$$1/\tau_{MY} = k_1 C_Y\alpha_4 + k_2 C_Y\alpha_3 + k_3 C_Y\alpha_2 + B_1\{-k_1 C_Y\alpha_4 - \\ k_2 C_Y\alpha_3 - k_3 C_Y\alpha_2 + k_4\} \quad (8)$$

In a solution containing equimolar Cd–EDTA and monoprotonated free EDTA (HY^{-3}) (pH 8), resonances for the two species are individually observable and extremely sharp, indicating no appreciable exchange. Under these conditions, reactions involving $CdHY^{-}$ are suppressed, and only the first three terms in eq 8 are operative. As the pH is raised, increasing the value of α_4, the free EDTA peaks undergo upfield shifts, and all EDTA resonances (free and complexed) undergo lifetime broadening. At pH 9.6, the spectrum appears as shown in Figure 2, frame D. Line width measurements of all three singlets yield approximately equal rates of broadening, but it was most convenient to monitor the acetate singlet of free EDTA, a valid procedure when the concentrations of free and complexed EDTA are equal (i.e., $1/\tau_{MY} = C_Y/\tau_Y C_{MY}$[17]).

Figure 4 shows a plot of reciprocal lifetime of Cd–EDTA vs. $C_Y\alpha_4$ for the potassium salts (K_2CdY, K_3HY, K_4Y) and $[NaY^{-3}]$ for sodium salts (Na_2CdY, Na_3HY, Na_4Y). A striking decrease in reactivity (greater than threefold) in changing from potassium to sodium salts is observed. Sodium ion is known to form weakly stable complexes with EDTA (Y^{-4}), but potassium ion has no appreciable tendency to do so.[19] It should be noted that the X axis in Figure 4 actually corresponds to $[NaY^{-3}]$ in the sodium salt case, rather than $C_Y\alpha_4$ as originally defined. There is also some evidence[20] for the formation of a protonated sodium complex ($NaHY^{-2}$), which may have caused low rates in previous studies of reactions involving HY^{-3} where

(19) G. Schwarzenbach and H. Ackermann, *Helv. Chim. Acta*, **30**, 1798 (1947).

(20) V. Palaty, *Can. J. Chem.*, **41**, 18 (1962).

TABLE I

SUMMARY OF RATE CONSTANTS

	This work (28°)	μ	Lit. (25°)	μ	Method[a]	Ref
k_1	$1.3 \times 10^2 \ M^{-1} \sec^{-1}$	2.5	...			
k_2	$<3 \ M^{-1} \sec^{-1}$	2.5	...			
k_3	$1.4 \ M^{-1} \sec^{-1}$	1.6	$2.0 \times 10^{-1} \ M^{-1} \sec^{-1}$ [b]	0.12	OR	10
k_4	$12 \sec^{-1}$	1.6	$2.0 \sec^{-1}$	0.12	OR	10
			$10.8 \sec^{-1}$ [c]	0.5	DC	6
k_{-4}	$1 \times 10^9 \ M^{-1} \sec^{-1}$	1.6	$3.7 \times 10^9 \ M^{-1} \sec^{-1}$ [c]	0.5	DC	6
			$8.5 \times 10^8 \ M^{-1} \sec^{-1}$ [c]	0.1	DC	7
			$5.3 \times 10^8 \ M^{-1} \sec^{-1}$	0.5	DC	8
			$6.1 \times 10^8 \ M^{-1} \sec^{-1}$	0.5	AC	8

[a] OR = optical rotation; DC = dc polarography; AC = ac polarography. [b] Entering ligand is d-PDTA. [c] Not corrected for chloro and acetato complexes of Cd^{+2}.

sodium ion was present. The slope of the line corresponding to potassium salts in Figure 4 yields the rate constant $k_1 = 130 \ M^{-1} \sec^{-1}$ at $\mu = 2.5$ and 28°.

The results in Figure 4 are obtained over a pH range of approximately 8.0 to 10.0. As $1/\tau_{MY}$ increases, $\delta\omega$, the separation between corresponding resonances of free and complexed EDTA, decreases because of the upfield protonation shift of free EDTA. An accelerated tendency to decrease the value of $\delta\omega\tau$ and thus to invalidate the slow-exchange approximation results. The minimum value of $\delta\omega\tau$ attained in this work is 10, corresponding to the greatest value of $1/\tau_{MY}$ shown in Figure 4.

The negligible Y intercept indicates a value of k_2 which is too small to measure by the method described here. Allowing for experimental error, an upper limit of $k_2 < 3 \ M^{-1} \sec^{-1}$ is estimated.

When the pH of a solution containing equimolar monoprotonated EDTA (HY^{-3}) and Cd–EDTA is lowered from 8.0 to 2.0, the amount of lifetime broadening of all resonances is observed to increase steadily until precipitation of CdH_2Y and/or H_4Y occurs. Under these conditions, $[Y^{-4}]$ is negligibly small, but $[CdHY^-]$ is appreciable, and several B_1 terms in eq 8 must therefore be considered. A group of data obtained in the pH range 4–6 is plotted in Figure 5 as $1/\tau_{MY}B_1$ vs. $C_Y\alpha_2(1/B_1 - 1)$. The slope of 1.4 $M^{-1} \sec^{-1}$ is equal to k_3, and the intercept of 12 $\sec^{-1}$ is equal to k_4 (both at 28° and $\mu = 1.6$).

The only literature value comparable to our k_3 is the rate constant $2.0 \times 10^{-1} \ M^{-1} \sec^{-1}$ obtained by Bosnich[10] for the reaction of Cd–EDTA and diprotonated d-PDTA (H_2P^{-2}) under the following conditions: 25°, $\mu = 0.12$ (0.06 M in $NaClO_4$), and pH 4.75–7.00. The difference between this value and our value of $k_3 = 1.4 \ M^{-1} \sec^{-1}$ is attributed to (1) different ionic strengths, (2) possible entering ligand effects causing slower attack by HP^{-3} than by HY^{-3}, and (3) formation[20] of $NaHP^{-2}$ in Bosnich's work. It is significant to note the sixfold decrease in the rate of the reverse reaction ($CdP^{-2} + H_2Y^{-2}$), for which a rate constant of $3.3 \times 10^{-2} \ M^{-1} \sec^{-1}$ was determined.

Rate constants of $k_4 = 2.0 \sec^{-1}$ and $0.2 \sec^{-1}$ for the first-order dissociation of $CdHY^-$ and $CdHP^-$, respectively, were found by Bosnich at 25° and $\mu = 0.12$. Tanaka, *et al.*,[6] found k_4 of $CdHY^-$ to be 10.8 $\sec^{-1}$ at 25° and $\mu = 0.5$. Therefore our value of k_4
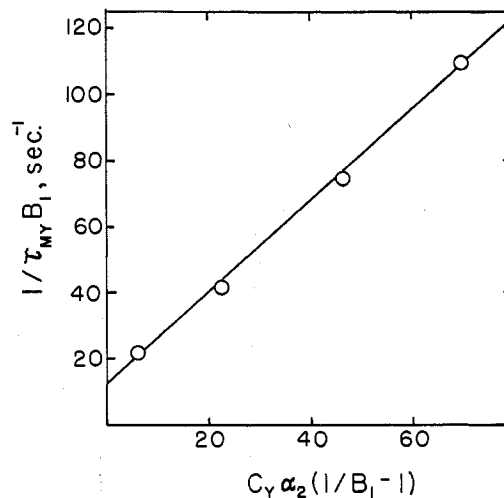

Figure 5.—Reciprocal lifetime of Cd–EDTA at various pH values (4–6).

$= 12 \sec^{-1}$ at 28° and $\mu = 1.6$ is in very good agreement with previous work.

It should be noted that reactions other than (2) and (3) could have been considered, such as $CdHY^- + Y^{-4}$ and $CdHY^- + HY^{-3}$, but since they would lead to transition states identical in composition with those formed in reactions 2 and 3 ($CdHY_2^{-5}$ and $CdH_2Y_2^{-4}$, respectively), they cannot be distinguished from these reactions at any pH value. We have arbitrarily chosen to consider only the reactions of the most abundant species in the particular experimental pH range.

From the value of k_4 and various stability constants the rate of the reverse reaction k_{-4} is determined. At equilibrium

$$k_4[CdHY^-] = k_{-4}[Cd^{+2}][HY^{-3}] \qquad (9)$$

and

$$k_{-4} = \frac{k_4[CdY^{-2}][H^+]}{K_{MHY}[Cd^{+2}][HY^{-3}]} = \frac{k_4 K_{CdY} K_4}{K_{MHY}} =$$

$$\frac{(12)(10^{15.0})(10^{-9.9})}{10^{-2.8}} = 1 \times 10^9 \ M^{-1} \sec^{-1} \qquad (10)$$

where K_{CdY} is the stability constant of Cd–EDTA (determined at 30° and $\mu = 0.1$[21]) and K_4 is the acid dissociation constant of HY^{-3}. This result is in good agreement with previously reported values.[6-8]

Mechanism of S_N Reaction.—When a molecule of

(21) V. L. Hughes and E. L. Martell, *J. Phys. Chem.*, **57**, 604 (1953).

free EDTA attacks a molecule of Cd–EDTA and displaces the complexed ligand, the process is imagined to proceed by a series of steps in which the entering ligand wraps onto the metal ion as the exiting ligand unwraps from the metal ion. The resulting mixed-ligand intermediates are expected to be unstable and to exist in very low concentrations.

A great number of geometrical isomers can be imagined to exist in which two molecules of EDTA are coordinated to a single octahedral metal ion, particularly when all the aquated species are considered. Figure 6 identifies the various mixed-ligand intermediates and gives their multiplicities. Diagonal elements, for example, represent nonhydrated species (*i.e.*, having no water molecules in the primary coordination sphere of the metal ion), and off-diagonal elements represent hydrated species. Each number in the matrix represents the maximum number of geometrical isomers obtained under the following assumptions: (1) initial attack by carboxylate group (suggested by molecular models to be much more facile than initial attack by nitrogen atoms); (2) subsequent attack by adjacent nitrogen atoms, forming a glycinate "foothold"; (3) continuity of wrapping, *i.e.*, carboxylate groups on opposite ends of the EDTA molecule may not coordinate to metal ion prior to formation of the second metal–nitrogen bond. All S$_N$ reaction paths begin at a point on the Y axis in Figure 6 and proceed to a point on the X axis *via* various intermediates. Because of the large number of intermediates, the number of reaction paths is very large. For example, proceeding along the diagonal alone results in 26 possible reaction paths.

In order to evaluate the relative importance of these mechanisms, various compounds simulating fragments of EDTA were added to solutions of Cd–EDTA, and their relative effectiveness in causing AB interchange was determined.

At some point in the over-all displacement reaction, the first nitrogen atom of the original EDTA ligand is displaced. The formation of this extent of unwrapping may be studied by observation of the shape of acetate AB patterns. Figure 7 shows the center portions of some AB patterns as a function of AB interchange rate. The outer members of the AB quartet are of such low intensity as to be of little use in this study. Using a chemical-shift difference of $\Delta\nu_{ab} = 11.0$ cps, a spin coupling constant of $J_{ab} = 16.7$ cps, and an apparent transverse relaxation time of $T_2{}^*{}_{ab} = 0.30$ sec, these spectra were computed using the computer program of Saunders and Yamada[22] for various interchange rates. By matching the shapes of observed and computed AB patterns, interchange rates may be determined. In practice, the comparison is facilitated by using the valley–peak ratio. The computer program was supplemented with a sorting routine for yielding this ratio directly, in addition to the computed spectrum.

Figure 8 gives the working curves obtained from

(22) M. Saunders and F. Yamada, *J. Am. Chem. Soc.*, **85**, 1882 (1963).
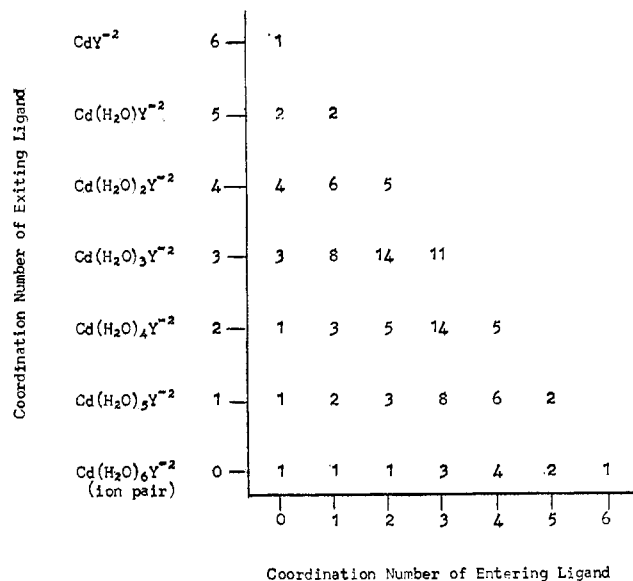

Figure 6.—Multiplicity of possible mixed-ligand intermediates for the reaction $CdY^{-2} + Y^{*-4} \rightleftarrows CdY^{*-2} + Y^{-4}$.
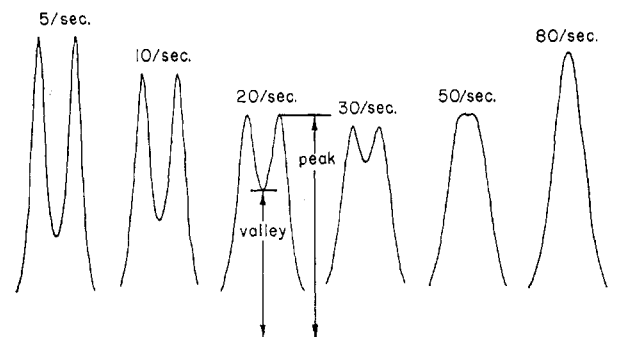

Figure 7.—Effect of AB interchange rate upon shape of central portion of AB quartet.
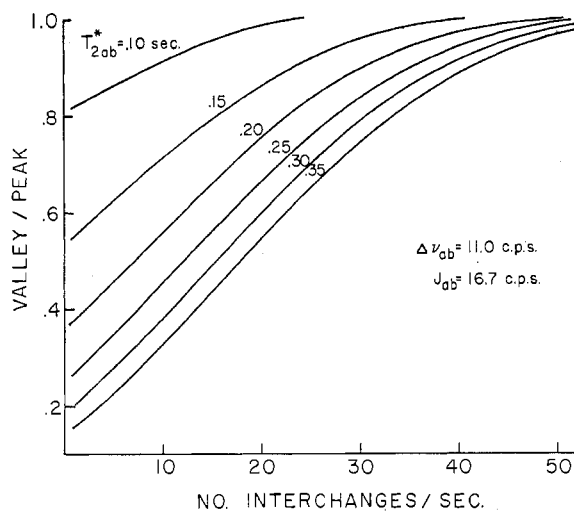

Figure 8.—Valley/peak ratio of central portion of AB patterns at various values of interchange rate.

computed AB patterns for various values of $T_2{}^*{}_{ab}$. With these curves, the interchange rate of any AB pattern of known valley–peak ratio and $T_2{}^*{}_{ab}$ value can be determined. Obviously, the interchange rate depends rather strongly upon $T_2{}^*{}_{ab}$.

In the absence of independent evidence regarding either the normal AB interchange rate occurring in solution with no excess ligand present, or T_{2ab}, it is necessary to make certain assumptions. It is observed that lines 1 and 3 in Figure 3 are parallel, and the following relationship is found to exist at any value of viscosity

$$T_{2c(chelate)} = 0.73 T_{2c(EDTA)} \tag{11}$$

This indicates either that the rate of tumbling of Cd–EDTA molecules is slower than that of free EDTA (Y^{-4}) molecules or that intramolecular broadening mechanisms (*e.g.*, quadrupole broadening by N^{14}) are more important in the metal chelate. In any case, viscosity affects the ethylenic protons in both compounds in a proportionate manner. Therefore, this proportionality is assumed to apply to the acetate protons as follows

$$T_{2ab(chelate)} = 0.73 T_{2a(EDTA)} \tag{12}$$

Line 2 in Figure 3 is derived from this assumption. It was convenient to construct working curves from line 2 in Figure 3 and the expression for total line width mentioned earlier so as to yield $T_2*_{ab(chelate)}$ directly at any value of viscosity. With the aid of these curves and Figure 8, interchange rates for Cd–EDTA, as a function of the nature and concentration of excess ligand, were determined.

The following ligands were employed: (1) N,N-dimethylglycine (DMG), (2) N,N,N',N'-tetramethyl-ethylenediamine (TetraMeen), (3) iminodiacetic acid (IDA), (4) N-methyliminodiacetic acid (MIDA), and (5) nitrilotriacetic acid (NTA). The high degree of steric hindrance in ligands such as DMG and Tetra-Meen prevents the formation of appreciably stable mixed-ligand compounds which are known to form between Cd–EDTA and unsubstituted glycine or ethylenediamine. Any ligand which forms a stable mixed complex is not an adequate model of EDTA (which forms no stable $Cd(Y)_2^{-6}$ complex), and the above compounds were found by potentiometric titra-tion not to form complexes of this type. This was accomplished by determining the change in pK_a value of the ligand resulting from the addition of equimolar Cd–EDTA, maintaining constant ionic strength (μ = 1) by addition of KNO_3 as needed. Diethylene-triamine (dien), for example, is highly effective in causing AB interchange but, because of the high sta-bility of its mixed complexes with Cd–EDTA, is not particularly useful in elucidating the mechanism of attack by EDTA.

Concentrations of nonprotonated ligands were in-creased by adding increments of potassium hydroxide to solutions containing Cd–EDTA and equimolar monoprotonated ligand. Complete displacement of EDTA by incoming ligand is very infrequent, as shown by the observation that even at very high AB inter-change rates, the isotope satellites of the ethylenic singlet remain very sharp. Because the "kinetic windows" for AB interchange and isotope splitting are approximately equal ($\Delta\nu_{ab}$ = 11.0 cps and J_{cx} = 12.0
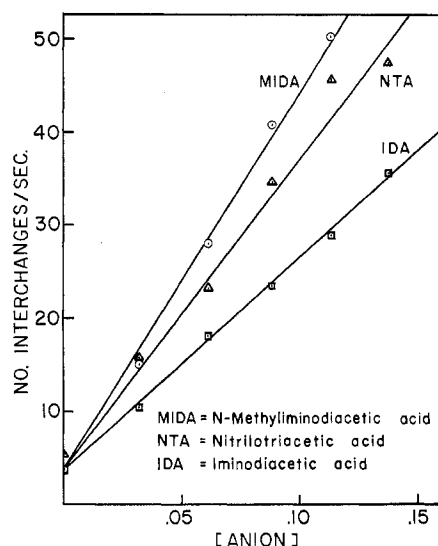

Figure 9.—AB interchange rates at various concentrations of lig-ands in fully anionic form.

cps), the average lifetime of EDTA in the complexed state is at least an order of magnitude greater than the average lifetime of a particular AB configuration. Figure 9 shows the rate of AB interchange *vs.* concen-tration of various ligand anions. The most effective ligand in causing AB interchange is MIDA; next most effective, NTA; and third most effective, IDA. On the other hand, DMG and TetraMeen were found to cause no detectable increase in interchange rate.

No protonated ligand showed any appreciable tend-ency to increase the interchange rate, confirming that the presence of a proton on the nitrogen atom of a ligand considerably impedes the formation of the metal–nitrogen bond. The common intercept of 4 inter-changes/sec tends to indicate that water molecules alone have some ability to cause AB interchange. The rate of water-induced interchange has an important bearing upon the over-all form of metal–EDTA nmr spectra.[14] It should be noted, however, that because it is a direct consequence of the assumed values of T_{2ab} on line 2 in Figure 3, no real significance can be attached to this intercept value.

Information concerning the rate of breaking metal–nitrogen bonds would be very useful. The AB inter-change rate, however, is expected to be directly pro-portional to this rate. Although the ratio of inversion to metal–nitrogen bond breaking rates is unknown, statistically its value must be equal to or less than 1:2. When a metal–nitrogen bond breaks and the nitrogen atom undergoes one or more inversions, there is at least a 50% chance that if it returns to the metal ion, it will possess the prior configuration.

Figure 9 shows that the ligands which are most effective in causing AB interchange contain three co-ordinating groups—a nitrogen atom and at least two carboxylate groups. Therefore, it appears to be the formation of the third bond which is most effective in breaking the metal–nitrogen bond of the exiting EDTA molecule. This suggests a three-and-three transition state—*i.e.*, one in which three groups of
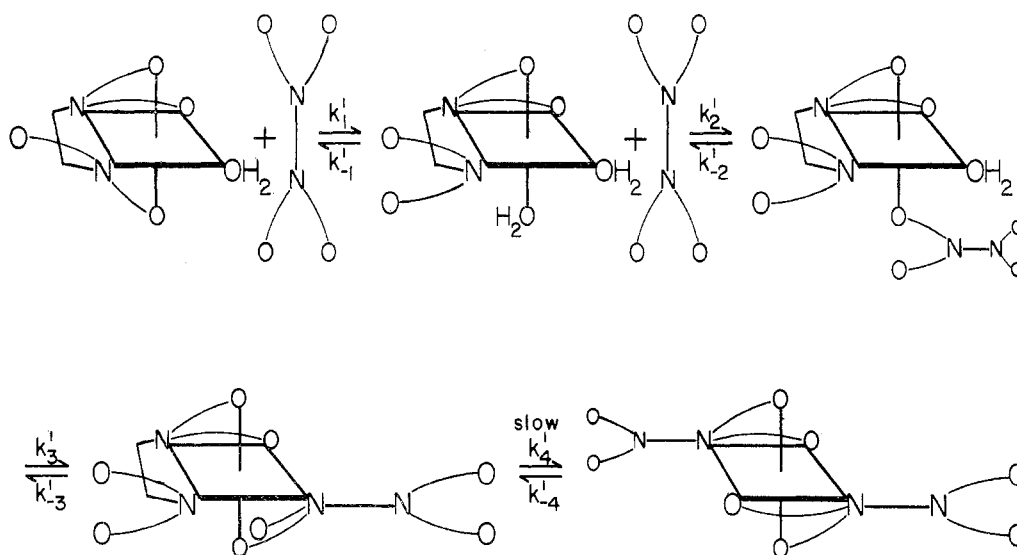
Figure 10.—Proposed mechanism of S_N reactions of Cd–EDTA and EDTA.

each EDTA molecule are coordinated to the metal ion. Furthermore, it suggests that direct displacement of the nitrogen atom by an entering carboxylate group is more rapid than a water-assisted displacement, which could have occurred with addition of DMG or TetraMeen.

The mechanism proposed in Figure 10 is felt to satisfy best the experimental results and the steric requirement of intermediates. The first step in the reaction, designated k_1', is a rapid displacement of the polar carboxylate group by an entering water molecule. The second step, designated k_2' is a rapid displacement of the polar water molecule by a carboxylate group of the attacking EDTA molecule. Molecular models reveal that the diaquated chelate is far more favorable to initial attack than monoaquated chelate. Initial attack by the nitrogen atom of an entering ligand on either monoaquated or diaquated species is greatly hindered. In step k_3', the nitrogen atom adjacent to the initially bonded carboxylate group rapidly displaces a water molecule of hydration.

In the rate-determining step designated k_4', concerted rotation about the ethylenic carbon–carbon bond, thus breaking the metal–nitrogen bond, and direct displacement by the carboxylate group are postulated. The transition state shown in Figure 10 is the least sterically hindered three-and-three intermediate.

Results obtained by Bosnich[10] and Cruz and Reilley[11] indicate that the rate of displacement of PDTA from a metal chelate is characteristically an order of magnitude slower than that of the corresponding displacement. Including the ethylenic carbon–carbon bond, rotation in the rate-determining step would account for this observation because of the greater energy barrier to rotation in PDTA. Ahmed and Wilkens[23] have shown that the rate of dissociation of C-substituted ethylenediamine molecules from their Ni(II) and

Cu(II) chelates similarly depends upon the rotational energy barrier accompanying rupture of the first metal–nitrogen bond.

In comparing AB interchange rates with the intermolecular exchange rate in reaction 1, it is found that MIDA forms the half-unwrapped transition state at least four times more rapidly than EDTA. This is attributed to a greater value of k_2' for MIDA because of its smaller bulk and ionic charge.

By the same argument, the fact that NTA (with its ionic charge of -3) is less effective in causing AB interchange than MIDA (with its ionic charge of -2) is explained. The somewhat surprising fact that the bulkier MIDA is more effective than IDA in causing AB interchange may be explained by a smaller value of the rate designated k_{-3}' in the former compound caused by the presence of the methyl group.

When AB interchange rates are determined as a function of increasing intermolecular exchange, e.g. as shown in Figure 2, the AB pattern shapes are fully accounted for in terms of lifetime broadening without predicting any increase in the interchange rate. This indicates that the interchange rate is not appreciably greater than the intermolecular exchange rate and further supports the mechanism shown in Figure 10, because a nitrogen atom of the exiting ligand is not removed from the metal ion at any stage prior to formation of the critical species.

Mechanism of S_E Reactions.—There has been some speculation regarding the location of labile protons in protonated chelates such as $CdHY^-$. Our chemical-shift measurements indicate that the downfield shifts accompanying conversion of CdY^{-2} to $CdHY^-$ are 6.6 cps for acetate protons and 3.6 cps for ethylenic protons. Considering that full protonation of a carboxylate group is expected to shift the adjacent acetate protons approximately 12 cps downfield and that full protonation of a nitrogen atom is expected to shift adjacent acetate and ethylenic protons approximately 45 cps downfield,[18] the conclusion must be that the

(23) A. K. S. Ahmed and R. G. Wilkens, *J. Chem. Soc.*, 3700 (1959); 2895, 2901 (1960); R. G. Wilkens, *ibid.*, 4475 (1962).
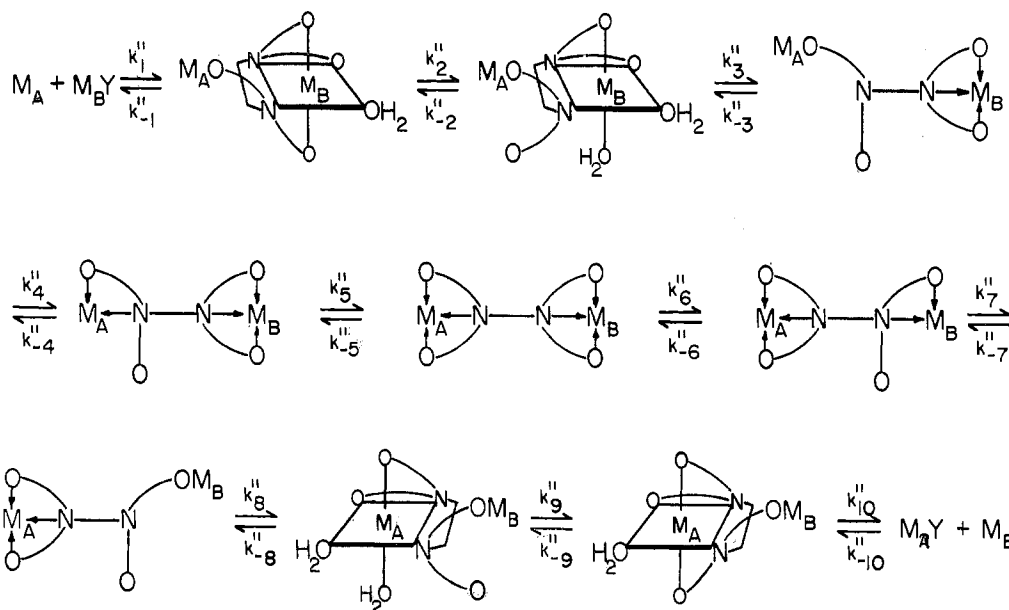
Figure 11.—Proposed mechanism of S_E reactions of Cd–EDTA.

labile proton spends virtually all its time coordinated to carboxylate groups.

Some authors have visualized the mechanism of the acid-catalyzed dissociation of $CdHY^-$ (reaction 5) as the simultaneous rupture of five metal–EDTA bonds in a position of maximum extension. Bosnich,[10] for example, attributed the tenfold decrease in the rate of reaction 5 in going from $CdHY^-$ to $CdHP^-$ to the inductive effect of the methyl group in the latter compound upon the bond-rupturing process. Stepwise rupture of the bonds as shown by Margerum, *et al.*,[2] for S_E reactions would appear to be more probable. The rate of certain steps may then depend upon the height of rotational barriers in a manner which would offer a more satisfactory explanation of Bosnich's results.

Figure 11 proposes a mechanism for S_E reactions involving two metal ions, M_A and M_B, and one molecule of EDTA (or its analogs). This is a general mechanism in that it may also apply to cases of symmetrical exchange ($M_A = M_B$) and to cases in which one of the "metals" is a proton, *e.g.*, acid-catalyzed dissociation of $CdHY^-$. In the latter case, certain modifications are necessary only because of the monodentate character of the proton. That is, when M_A is a proton, the step designated k_4'' leads simply to a protonated nitrogen atom with both carboxylate groups free, and the step designated k_5'' is eliminated.

Margerum, *et al.*,[2] have shown that the rate of dissociation of Ni–EDTA is determined by the stability of iminodiacetate complexes with various attacking metals, including protons. This implies that the acid-catalyzed dissociations of metal–EDTA chelates proceed *via* the same intermediates as all other S_E reactions.

Appendix

In order to avoid tedious viscosity measurements, the following empirical formula[24] was sometimes employed in this study for calculation of relative viscosities

$$\log (\eta/\eta_0) = \sum_{i=1}^{n} V_i C_i$$

where V_i is the viscosity coefficient of the ith component and C_i is the concentration of the ith component. It was found to be reasonably linear for individual components and reasonably additive (5–10%) for multicomponent mixtures for the rather highly concentrated solutions (0.2–8.0 M) employed in this study. Some viscosity coefficients of various compounds at 25° are listed in Table II.

TABLE II

	V (M^{-1} at 25°)		V (M^{-1} at 25°)
K_4Y	0.40	TetraMeen	0.10
K_3HY	0.46	K_2IDA	0.16
K_2H_2Y	0.32	KHIDA	0.10
K_2CdY	0.40	K_2MIDA	0.16
KOAc	0.11	KHMIDA	0.10
Glycerine	0.09	K_3NTA	0.18
K_2DMG	0.10	K_2HNTA	0.15
KHDMG	0.09		

(24) Similar to the equation of Suryanarayana and Venkatesen in R. H. Stokes and R. Mills, "Viscosity of Electrolytes and Related Properties," Pergamon Press Inc., New York, N. Y., 1965.