under Grants GM-12596 and GM-20424 (to Wayne State University) and the National Science Foundation under Grants GP14781X and GP43418X (to Purdue University). The contributions of R. B. Cruz (W.S.U.) and R. A. Bauer (P. U.) to preliminary investigations on this topic are also gratefully acknowledged.

Registry No. $\mathrm{Cu(OH)_3^-}$, 12443-58-2; $\mathrm{Cu(OH)_4^{2-}}$, 17949-75-6; 2,3,2-tet, 4741-99-5; $\mathrm{Et_2}$-2,3,2-tet, 54020-32-5; cyclam, 295-37-4; *meso*-$\mathrm{Me_2}$ cyclam, 41076-15-7; $\mathrm{Et_4}$ dien, 123-12-6.

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Metal Ion Catalyzed Racemization and α-Proton Exchange of *N,N*-Dicarboxymethyl-D-phenylglycine

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Received December 4, 1974 AIC40815V

The base-catalyzed racemization of *N,N*-dicarboxymethyl-D-phenylglycine $\mathrm{Cm_2}$-D-Phgly^{3-}, $(^-\mathrm{O_2CCH_2})_2\mathrm{NCH(Ph)CO_2}^-$, has been studied in the absence and presence of metal ions in aqueous solution at 60.0°. Within experimental error, the rates of racemization and α-proton exchange with $\mathrm{D_2O}$ are the same both for the free $\mathrm{Cm_2}$-D-Phgly^{3-} and for its complexes. The rates of racemization were observed to follow a rate law dominated by a term which was first order in $\mathrm{OH^-}$ concentration. This behavior together with the exchange results suggests a mechanism in which rate-determining α-proton removal by $\mathrm{OH^-}$ is followed by rapid reprotonation of the resulting symmetric carbanion intermediate. The predominant species present in solution and their decreasing rates of inversion are as follows: Pb($\mathrm{Cm_2}$-D-Phgly)$^-$, 3.08×10^{-2} > Cu($\mathrm{Cm_2}$-D-Phgly)(OH)$^{2-}$, 2.31×10^{-2} > Ni($\mathrm{Cm_2}$-D-Phgly)$^-$, 2.01×10^{-2} >> Zn($\mathrm{Cm_2}$-D-Phgly)(OH)$^{2-}$, 0.381×10^{-2} >>> $\mathrm{Cm_2}$-D-Phgly^{3-}, $5.8 \times 10^{-6}\ M^{-1}\ \mathrm{sec}^{-1}$. When bound to these metal ions, the ligand undergoes racemization at rates up to 5000 times faster than observed for the free $\mathrm{Cm_2}$-D-Phgly^{3-}. The abilities of these metal ions to accelerate this racemization are compared with their activities in promoting the hydrolysis of amino acid esters.

Optically active amino acids have been observed to racemize in aqueous solution only at high temperatures (>100°).[1,2] When coordinated to the inert metal ions Co(III)[3-5] and Pt(II),[6] however, they undergo racemization under much milder conditions (35–40°). In contrast to the detailed racemization studies of cobalt(III)–amino acid complexes, little has been reported on the effect of labile metal ions on amino acid racemization. Gillard and Phipps[7] reported that alanine in the complex Cu(L-Ala)$_2$ racemizes in less than 12 hr at an unspecified temperature at pH values equal to or greater than 12. Also they noted that racemization occurred more slowly than α-proton exchange with $\mathrm{D_2O}$, suggesting that protonation of the carbanion intermediate was stereoselective. Our attempts to repeat these studies were thwarted by precipitation of a Cu(II) complex as $\mathrm{OH^-}$ was added to bring the pH to 12. An earlier report[8] indicated that only a trace of L-Ala racemized in a solution containing Cu(II) or Al(III) at 100° and pH 9.7. This result together with our precipitation difficulties suggests that Gillard and Phipps' results may be incorrect.

Studies[9,10] of amino acids in the absence of metal ions at 60° in nonaqueous solvents showed that D-phenylglycine racemized more rapidly than other common amino acids. Rates of racemization and α-proton exchange were the same. Although the rates of racemization were substantially slower in water solvent (studied at 115°),[11] it appeared to us that D-phenylglycine may be sufficiently reactive for study of its racemization under mild conditions in the presence of labile metal ions. To simplify equilibria involving the metal ions and the amino acid, D-phenylglycine was converted to *N,N*-dicarboxymethyl-D-phenylglycine, $(HO_2CCH_2)_2NCH(Ph)CO_2H$, Cm$_2$-D-PhglyH$_3$, for these studies. Rates of racemization and α-proton exchange have been carried out in the absence and presence of several metal ions in water solvent with a view toward understanding the mechanism and metal ion activities in the catalysis of amino acid racemization.

Experimental Section

Reagents and Instrumentation. Metal ion solutions of reagent grade metal ion nitrate salts were standardized *via* ion-exchange techniques. Aliquots of the metal ion solutions were passed through Dowex 50W-X8 strongly acidic cation-exchange resin, and the effluent solutions were titrated with standardized sodium hydroxide solution to the phenolphthalein end point.

Proton nuclear magnetic resonance spectra (pmr) were measured on a Varian A-60 or Hitachi Perkin-Elmer R-20B spectrometer. Solutions for pmr measurements were prepared from D_2O which was 99.75 atom % deuterium, and pD was adjusted using NaOD (pD = pH + 0.4).[12] All chemical shifts were measured in ppm downfield relative to internal DSS, 2,2-dimethyl-2-silapentane-5-sulfonic acid, sodium salt, $(CH_3)_3SiCH_2CH_2CH_2SO_3Na$, in D_2O–NaOD solutions.

Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter with associated Bausch and Lomb double-grating monochromator and xenon light source.[13] The polarimeter was zeroed before each measurement with the solvent using a jacketed 1-dm polarimeter cell at 25°. Absorption spectra were recorded on a Beckman DB-G grating spectrophotometer.

All pH measurements were made with a Beckman SS-3 pH meter using a Beckman 39301 glass electrode, which was standardized at 25.0° by use of at least two of the buffer solutions: pH 4.01, 7.00, or 10.00. Doubly distilled water was used throughout this work.

Preparation of *N,N*-Dicarboxymethyl-D-phenylglycine, Cm$_2$-D-PhglyH$_3$. *N,N*-Dicarboxymethyl-D-phenylglycine was prepared by modifying a procedure given by Leach[14] for the synthesis of *N*-carboxymethyl-D-phenylglycine, Cm-D-Phgly. One hundred millimoles of bromoacetic acid and 50 mmol of D-phenylglycine were separately neutralized with NaOH to a pH of about 12 (the bromoacetic acid at 0°). The sodium bromoacetate solution was slowly added over a 15-min period to the D-Phgly$^-$ solution at 50° and more NaOH (~5 *M*) was added as needed to maintain the pH above 11. The reaction mixture was maintained at 50° for 1 hr after addition of the bromoacetate solution was completed. Then enough HCl was added to lower the pH to 2–3. On cooling to room temperature, a white precipitate formed. Pmr spectra of the precipitate (from several of the above preparations) indicated up to 10% contamination of the Cm$_2$-D-PhglyH$_3$ with Cm-D-PhglyH$_2$.

The precipitate was redissolved in water (~250 ml) and along with the reaction solution put onto a 2.5 × 80 cm column of Dowex 50W-X4 (100-200 mesh) cation-exchange resin in the H$^+$ ion form. The pH of the sample solution must be less than 3; otherwise, the phenylglycine derivatives will precipitate in the column. The product was eluted with H_2O followed by 0.1 *M* NH_3 solution.[15] Acidic fractions collected from the column were evaporated under vacuum at approximately 50° until a precipitate formed and then cooled to room temperature. Pmr spectra were used to monitor the fractions. Pure Cm$_2$-D-PhglyH$_3$ was obtained from all column fractions up until the last two fractions before NH_3 started to pass through the column. These last two fractions contained a mixture of Cm$_2$-D-PhglyH$_3$ and Cm-D-PhglyH$_2$ and pure Cm-D-PhglyH$_2$, respectively. The pmr spectrum of Cm$_2$-D-Phgly^{3-} in 1.50 *M* NaOD gives the following: C_6H_5, 7.43 (s); CH, 4.38 (s); CH_2, AB pattern with A 3.18, B 2.88, and *J* = 16.0 Hz. This spectrum may be compared with the pmr spectra of D-Phgly$^-$ in 0.2 *M* NaOD [C_6H_5, 7.42 (s); CH, 4.35 (s)] and Cm-D-Phgly^{2-} in 2.0 *M* NaOD [C_6H_5, 7.38 (s); CH, 4.15 (s); CH_2, 3.07 (s)].

The yield of Cm$_2$-D-PhglyH$_3$ was approximately 70%. Potentiometric titration with CO_2-free NaOH solution gave an equivalent weight of 139; the calculated value is 133.6. $[M]^{25}{}_D$ −352° (*c* 1, 5 *M* HCl). This may be compared with the molar rotations of Cm-D-PhglyH$_2$ {$[M]^{25}{}_D$ −313° (*c* 1, 5 *M* HCl)} and D-PhglyH {$[M]^{25}{}_D$ −246° (*c* 1, 5 *M* HCl)}. The literature value for L-Phgly is $[M]^{25}{}_D$ +254° (*c* 1, 5 *M* HCl).[16] *Anal.* Calcd for $(HO_2CCH_2)_2NCH(C_6H_5)CO_2H$: C, 53.93; H, 4.90. Found: C, 53.54; H, 5.06.

Titrations. Solutions were maintained under a nitrogen atmosphere during titrations using prepurified nitrogen which had been passed through concentrated aqueous NaOH. The temperature of the solutions was held at 25.0 or 60.0° by circulating constant-temperature water through the jacketed titration cell. Ionic strengths were adjusted to 0.10 *M* by addition of KNO_3 solution.

To determine the hydroxide ion concentration of solutions at 60° from the pH read on the pH meter of these solutions, the pH values of a series of solutions (0.10 *M* ionic strength) of known hydroxide ion (KOH) concentration were measured at 60° on the pH meter after calibrating the meter with pH 7.00 and 10.00 buffer solutions at 25.0°. A plot was made of the pH read at 60°, pH$_{60}$, *vs.* [OH$^-$], the known hydroxide ion concentration. It fit the following equation: $pH_{60} = 0.93 \log [OH^-] + 12.69$.

Titration curves of Cm$_2$-D-PhglyH$_3$ with equimolar Cu(II) and Zn(II) showed the formation of the hydroxo complexes M(Cm$_2$-D-Phgly)(OH)$^{2-}$ at high pH. Stability constants, K_{OH}, for their formation were calculated for both metal ions.

$$M(Cm_2\text{-D-Phgly})^- + OH^- \rightleftharpoons M(Cm_2\text{-D-Phgly})(OH)^{2-} \quad (1)$$

$$K_{OH} = [M(Cm_2\text{-D-Phgly})(OH)^{2-}]/[M(Cm_2\text{-D-Phgly})^-][OH^-] \quad (2)$$

All calculations were performed on an IBM 360-65 digital computer using data from 20 to 80% of the buffer region. Free hydroxide ion concentrations of the titration solutions were obtained from the equation relating pH$_{60}$ and [OH$^-$] noted above.

Kinetics Measurements. Racemization. Solutions for the racemization kinetics were made up under a stream of N_2 adjusting the ionic strength to 0.10 *M* with KNO_3 and the pH to the desired value with KOH solution. Concentrations of the complex were varied so as to obtain large (~0.500°) initial observed rotations. In all cases, 100 ml of solution was made up, the solution filtered, the initial rotation measured at 25°, and the solution then put into the 60° bath. Ten to twelve aliquots were removed over a period of at least 2 half-lives. Each aliquot was immediately put in an ice bath to stop racemization, and when cooled, its rotation was measured at 25°. The pH at 25° of each aliquot was also checked to be certain that it remained constant throughout the run. For Cu(II) and Ni(II), the visible absorption spectrum of one of the high-pH kinetics run solutions was scanned before and after the run and found to be unchanged for both metal ions. These results indicated that no decomposition of the complexes occurred under the conditions of the kinetics studies.

Because of the time (>30 min) required to equilibrate the pH electrodes at 60° and hysteresis effects[17] of electrodes on cooling, it was not possible to make reliable pH measurements at 60° on solutions used in the kinetic studies. Thus the pH values of these solutions were determined at 25°. The pH$_{25}$ values were converted to pH$_{60}$ by measuring the pH at both 25 and 60° of a series of solutions covering a pH range (~9.2–12) at least as large as that used in the kinetics studies and identical in composition with those solutions. Plots of pH$_{60}$ *vs.* pH$_{25}$ gave straight lines which fit the following equations for solutions of the different M(Cm$_2$-D-Phgly) complexes: Cu(II), $pH_{60} = 0.85pH_{25} + 0.60$; Zn(II), $pH_{60} = 0.67pH_{25} + 2.57$; Pb(II), $pH_{60} = 0.66pH_{25} + 2.69$; Ni(II), $pH_{60} = 0.94pH_{25} - 0.43$. The pH$_{60}$ values were then converted to actual OH$^-$ concentrations using the relationship described in the previous section.

For each kinetics run, plots of log $[M]_\lambda{}^{25}$ *vs.* time were made for six different wavelengths, the slope calculated for each wavelength using a least-squares calculation and the average value of the slope from the six wavelengths used for the calculation of the observed rate constant, k_{obsd}, where $k_{obsd} = -2.303(\text{slope})$. The rate constants, k', for inversion, that is, for conversion of the D to the L enantiomer of Cm$_2$-D-Phgly, are equal to half of k_{obsd},[18] the rate constant for racemization. Racemization kinetics studies of the ligand alone were carried out similarly, except for a higher ionic strength (0.85), and the data were treated the same.

Deuterium-Exchange Studies. For deuterium-exchange studies on the free ligand, D_2O solutions of 0.05 *M* Cm$_2$-D-Phgly^{3-} were adjusted to the desired pD with NaOD. The ionic strength was not adjusted by adding KNO_3 and the pD was determined only at 25°. A 0.4–0.6-ml aliquot of the solution was placed in a pmr tube and thermostated in a constant-temperature bath at 60.0°. The exchange was followed by pmr until the signal of the exchanging methine proton was no longer seen in the spectrum (~5% H, 95% D).

A larger volume of the solution was used to determine the racemization rate in order that a direct comparison of the exchange and racemization rates could be made. Aliquots (0.6 ml) were re-

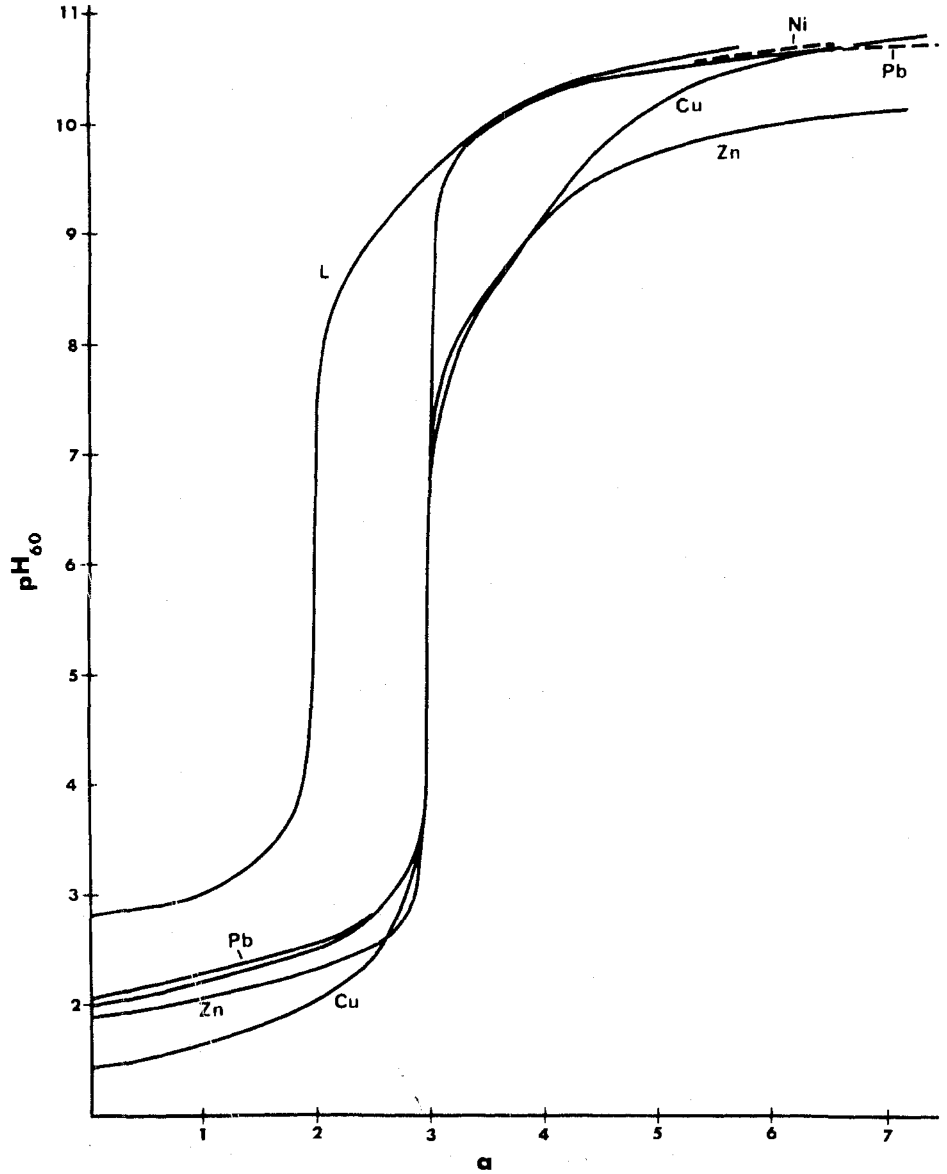


Figure 1. Potentiometric titration curves at 60.0° of Cm_2-D-PhglyH_3, L (4.00 m*M*), and 1:1 solutions of Cm_2-D-PhglyH_3 with Cu(II) (2.00 m*M*), Zn(II) (5.00 m*M*), Pb(II) (5.00 m*M*), or Ni(II) (5.00 m*M*). Dashed lines indicate precipitate formation and *a* is moles of base per mole of ligand.

moved and diluted to 6.0 ml with H_2O for ORD measurement such that the racemization was followed through at least 1 half-life.

Exchange rates were determined from log (methine proton intensity) *vs.* time plots. All intensities of the methine proton signal were relative to the phenyl protons and determined by integration of the spectrum (the average of at least six integrations per spectrum). Slopes were determined as for the racemization studies and k_{ex} calculated using $k_{ex} = -2.303$(slope). Rate constants for racemization, k_{rac}, were calculated from log α_{obsd} *vs.* time plots, where $k_{rac} = -2.303$(slope).

The smaller rate constant (k_{CH_2}) for methylene proton (of the $-CH_2CO_2^-$ groups) exchange was obtained from the slope of log (methylene proton intensity) *vs.* time plots using the same procedure as for k_{ex}.

Deuterium-exchange studies were also carried out on the metal ion complexes of Cm_2-D-$Phgly^{3-}$ and compared with the racemization rates. Metal ion solutions used for exchange studies were deuterated before making up the solutions of the complexes by evaporating an appropriate amount of standardized metal ion solution to dryness, adding 1 ml of D_2O and evaporating again. This cycle was repeated four times; then the solid was stored over P_4O_{10} overnight.

In a typical exchange run, a 10-ml solution of 0.1 *M* M(Cm_2-D-Phgly)$^-$ (with 5% excess ligand to prevent precipitation of the metal at this high concentration and pD) was adjusted to the desired pD and filtered. Samples were removed for the initial optical rotation and pmr measurements before putting it into the 60° bath. Aliquots were periodically removed (usually every 60 min) for rotation (0.6 ml diluted to 6.0 ml) and pmr (0.4 ml) measurements.

Although pmr spectra of these solutions could be obtained for the Zn(II) and Pb(II) complexes, in the pD range of interest, 10.5–11.5, it was found that the methine proton signal was very near or even under the HOD signal. The pmr spectrum of a 1:1 Cm_2-D-$Phgly^{3-}$–Zn^{II} solution at pD 10.4 gave a broadened phenyl signal at 7.45 ppm (2.5 Hz at half-height), a CH resonance at 4.49 ppm (1 Hz), and a broad methylene signal at 3.26 ppm (5.0 Hz). The 1:1 Cm_2-D-$Phgly^{3-}$–Pb^{II} solution at pD 11.1 showed a splitting of the phenyl signal into two principal peaks at 7.45 and 7.48 ppm with a total width at half-height of the peaks of 2.5 Hz; the methine proton occurred at 4.78 ppm and the CH_2 at 3.59 ppm.

Integrations of the methine proton were greatly improved in the Pb(II) runs by adding 0.04 ml of ~6 *M* NaOD directly to the pmr tube to precipitate all of the Pb(II) ion as $Pb(OD)_2$. For Zn(II) runs, the Cm_2-D-$Phgly^{3-}$ was liberated from the Zn(II) ion by adding even more base (total of 0.06 ml of 6 *M* NaOD added to the 0.4 ml of 0.1 *M* complex in the pmr tube) to give the soluble zincate ion, $[Zn(OD)_4]^{2-}$.

For the runs involving paramagnetic Ni(II), the ligand was freed from the Ni(II) by direct addition of excess solid KCN to the pmr

Table I. Rate Constants for the Inversion of Cm_2-D-$Phgly^{3-}$, Pb(Cm_2-D-Phgly)$^-$, Cu(Cm_2-D-Phgly)(OH)$^{2-}$, Ni(Cm_2-D-Phgly)$^-$, and Zn(Cm_2-D-Phgly)(OH)$^{2-}$ at 60.0° and 0.1 *M* Ionic Strength (KNO_3)

$[OH^-]$, m*M*	$10^5k'$, sec^{-1}	$[OH^-]$, m*M*	$10^5k'$, sec^{-1}	$[OH^-]$, m*M*	$10^5k'$, sec^{-1}	$[OH^-]$, m*M*	$10^5k'$, sec^{-1}
No Metal Ion[a] (5.00 m*M*)		2.00 m*M* Cu(II)		5.00 m*M* Pb(II)		5.00 m*M* Zn(II)	
50.0	0.301	0.26	2.00	0.32	1.06	0.96	0.64
100	0.327	0.37	2.16	0.48	1.51	1.05	0.66
300	0.275	0.60	2.67	0.54	1.58	1.10	0.67
500	0.445	0.91	3.72	0.60	1.72	1.78	1.01
832	0.766	1.00	3.30	0.76	2.09	1.82	0.96
10.0 m*M* Ni(II)		1.38	3.87	0.93	2.59	2.46	1.03
0.20	0.97	1.86	5.23	1.10	2.92	3.16	1.24
0.55	1.80	2.14	6.61	1.48	4.03	3.63	1.39
0.58	2.20	2.82	7.41	1.86	5.58	3.80	1.50
0.89	2.38	3.47	8.39	2.34	7.29	5.01	1.92
1.00	2.87	3.98	11.7	2.88	8.55	5.13	1.98
1.41	3.46	5.62	14.6	3.80	11.7	5.62	2.28
1.95	4.75	6.92	17.2			7.41	3.13
2.45	5.61	7.59	19.0			9.12	3.84
		10.00	24.0				

[a] Ionic strength was 0.85 *M* (KNO_3).

tube containing the Ni(Cm_2-D-Phgly)$^-$ complex.[19] The soluble, diamagnetic $[Ni(CN)_4]^{2-}$ complex formed immediately as evidenced by the change in color from green to yellow.

Results

The titration curve (Figure 1) of Cm_2-D-$PhglyH_3$ shows an inflection after the addition of 2 equiv of base corresponding to the removal of the carboxymethyl protons to give Cm_2-D-$PhglyH^{2-}$. The ammonium proton is removed at higher pH to give Cm_2-D-$Phgly^{3-}$. Titration curves (Figure 1) of solutions containing equimolar Cm_2-D-$PhglyH_3$ and Cu(II), Zn(II), Ni(II), or Pb(II) show one buffer region up to the addition of 3 equiv of base. In this pH region the green color of the Cu(II) and Ni(II) complexes appears and the ORD of the four complexes develops, indicating the formation of the M(Cm_2-D-Phgly)$^-$ complexes.

At higher pH the Cu(II) and Zn(II) solutions take up another 1 equiv of base indicating formation of hydroxo complexes M(Cm_2-D-Phgly)(OH)$^{2-}$. The near-uv absorption and ORD spectra of these two solutions show minor changes in this pH region as well. The Cu^{II}–Cm_2-D-$Phgly^{3-}$ solution ORD maximum shifts from 355 nm for Cu(Cm_2-D-Phgly)$^-$ to 340 nm for Cu(Cm_2-D-Phgly)(OH)$^{2-}$. The uv shoulder in the absorption spectrum also shifts to shorter wavelength. The ORD spectrum of the Zn(II) solution only indicates an increase in intensity at high pH; no maxima are observed down to 300 nm. The ORD spectra of the Ni(II) and Pb(II) solutions remain unchanged from pH 8 to pH 11.5, which is consistent with the lack of hydroxo complex formation with these metal ions. Values of log K_{OH} at 60.0° and 0.10 *M* ionic strength obtained for two different Cu(II) titrations were 4.63 ± 0.03 and 4.57 ± 0.01; for two different Zn(II) titrations they were 4.56 ± 0.04 and 4.63 ± 0.02. The difference between the values for the two titrations in each case is probably due to the difficulties encountered in reproducing pH readings at 60°. The log K_{OH} value of 4.6 for Cu(Cm_2-D-Phgly)(OH)$^{2-}$ formation compares with 4.4 for the similar $[Cu(NTA)(OH)]^{2-}$ at 25° where NTA is $N(CH_2CO_2^-)_3$;[20] the log K_{OH} value of 4.6 for Zn(Cm_2-D-Phgly)(OH)$^{2-}$ formation compares with 3.55[20] at 25° for $[Zn(NTA)(OH)]^{2-}$.

The Ni(II) and Pb(II) solutions give nearly identical titration curves. They do not indicate any further complex formation up to the pH where precipitates, probably their hydroxides, begin to form. The formation of monohydroxo complexes of Cu(II) and Zn(II) but not of Ni(II) and Pb(II) was observed previously for the related divalent metal nitrilotriacetates (NTA).[21]

Kinetics. Racemization. Inversion of Cm_2-D-$Phgly^{3-}$ is slow even in very basic solutions at 60°. As shown in Table I, k' does increase on increasing the hydroxide ion concentration, but even at 0.8 *M* OH^-, k' is only 7.7×10^{-6} sec^{-1}. A least-squares calculation on a plot of k' *vs.* $[OH^-]$ for Cm_2-D-$Phgly^{3-}$ at 60° gives $k' = 2.2 \times 10^{-6} + (5.8 \times 10^{-6})[OH^-]$.

Rate constants, k', for inversion of the ligand when coordinated to equimolar Pb(II), Cu(II), Ni(II), or Zn(II) are also presented in Table I. These data follow the rate law

$$\text{rate} = k_1[\text{complex}] + k_2[\text{complex}][OH^-] \tag{3}$$

where

$$k' = k_1 + k_2[OH^-] \tag{4}$$

Least-squares analyses of plots of k' *vs.* $[OH^-]$ (as shown in Figure 2) yield the following values for k_1(intercept) and k_2(slope), respectively: Cu(II), 1.25×10^{-5} sec^{-1} and 2.31×10^{-2} M^{-1} sec^{-1}; Ni(II), 0.74×10^{-5} sec^{-1} and 2.01×10^{-2} M^{-1} sec^{-1}; Zn(II), 0.175×10^{-5} sec^{-1} and 0.381×10^{-2} M^{-1} sec^{-1}; Pb(II), -0.150×10^{-5} sec^{-1} and 3.08×10^{-2} M^{-1} sec^{-1}. Correlation coefficients for these plots were 0.990 or higher. As can be seen from Figure 2, the contribution of k_1 to the overall rates is very small, and there is some question as to the significance of the k_1 values.

Attempts were made to include other metal ions in this study, but 1:1 solutions of these ions with Cm_2-D-$Phgly^{3-}$ either gave precipitates in basic solutions (Cd(II), Mg(II), Al(III), Fe(III), Er(III), UO_2^{2+}), showed very little or no change in rotation over a 24-hr period at pH 11.1 at 60° (La(III) and Nd(III)), or were air sensitive (Mn(II)).

Attempts were also made to study the racemization of D-phenylglycine and *N*-carboxymethyl-D-phenylglycine in the presence of Cu(II). Most of our attempts to make a 2:1 D-$Phgly^-$–Cu^{II} solution gave precipitates at high pH. In the pH range 6–8, a blue complex does form in 2:1 solutions (5.0 m*M* Cu(II)) but then very quickly precipitates from solution confirming a literature report[22] that it is not very soluble. Even at 2.5 m*M* Cu(II), a 2:1 D-Phgly–Cu^{II} solution at pH 9 gives a precipitate after standing a few minutes at room temperature. On the other hand, at lower concentration (0.625 m*M*) and higher temperature (51°) under an N_2 atmosphere, 2:1 D-$Phgly^-$–Cu^{II} racemized at pH 9.3 with a half-time of approximately 60 hr. At 69° and pH 9.0, this system gave a half-time of about 10 hr, but an attempt at 60° and pH 9.0 gave a precipitate. It is not clear what equilibria are involved in determining the observed precipitation behavior. Many attempts were made to study the 2:1 D-$Phgly^-$–Cu^{II} complex at pH 9–9.5 in mixed aqueous solvents (including 50% EtOH, 50% acetone, 50% acetonitrile, and 20% DMSO), but all ended with the formation of a precipitate after being at 60° overnight and often much sooner.

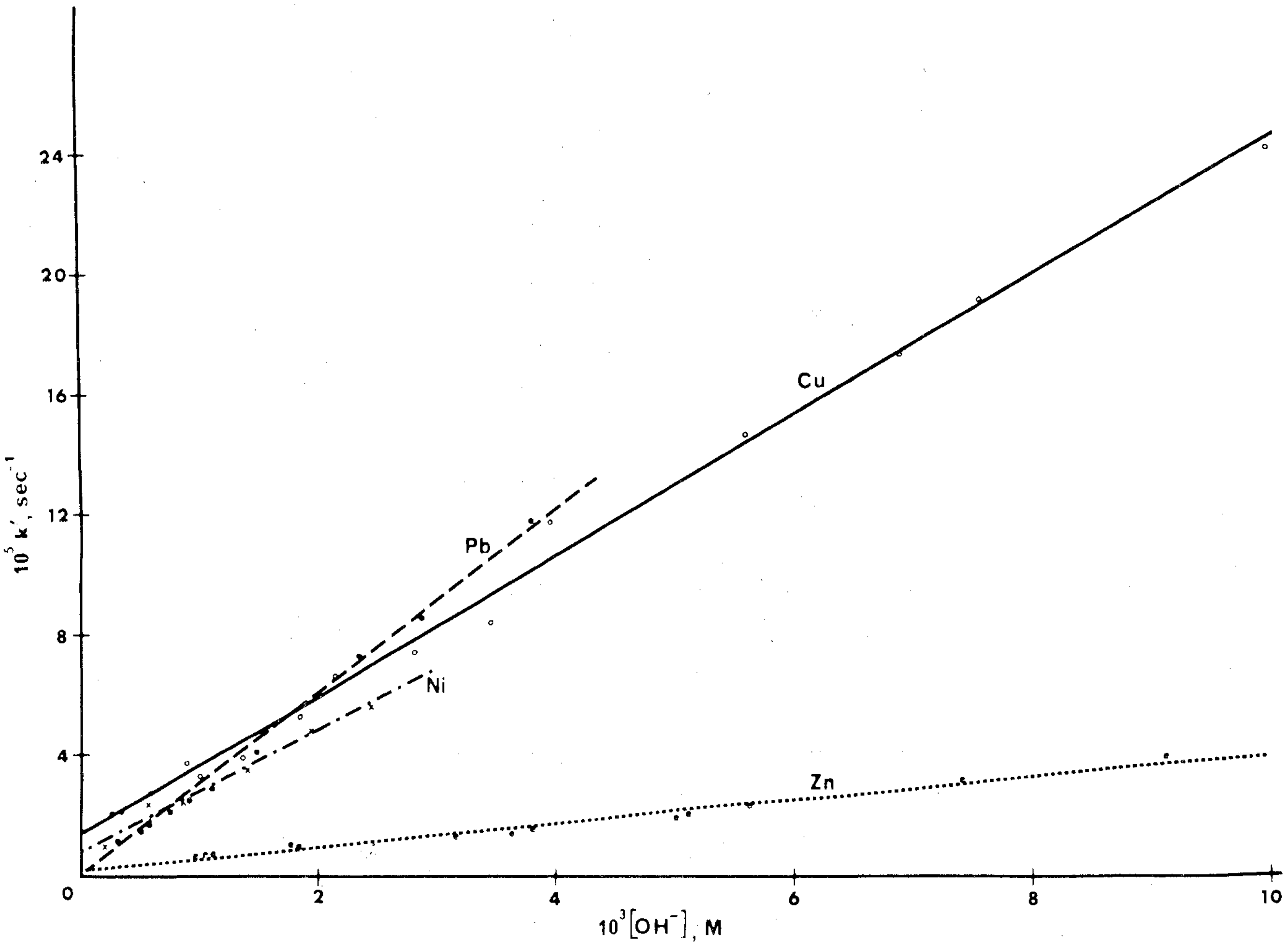


Figure 2. Plot of the inversion rate constant, k', *vs.* $[OH^-]$ for 1:1 Cm_2-D-$Phgly^{3-}$ complexes of Cu(II), Ni(II), Pb(II), and Zn(II).

A 1:1 Cu^{II}–*N*-carboxymethyl-D-phenylglycine, Cm-D-PhglyH, solution gives a precipitate at pH ~8.5. However, a 2.5 m*M* Cu(II) solution containing 2:1 Cm-D-$Phgly^{2-}$–Cu(II) at 60° and pH 10.13 gave a racemization half-time of about 2 hr. At 49° and pH 10.20, this system gave a half-time of about 6 hr and, at 60° and pH 10.03, gave a value of approximately 9.3 hr.

Kinetics. Exchange. In order to determine the relative rates of racemization and α-proton exchange in Cm_2-D-$Phgly^{3-}$ and its metal complexes, rate constants for racemization (k_{rac}) and α-proton exchange (k_{ex}) were determined on the same solutions. Because of the high concentrations required for the nmr exchange studies, these solutions are of much higher ionic strength than those used in the detailed racemization studies (Table I). Thus the rate constants, k_{ex} or k_{rac} (Table II), may not be compared directly with k' values in Table I. Values of k_{ex} were generally reproducible to within ±6%. The larger errors associated with the exchange rates are at least in part due to inaccuracies in integrating pmr peak areas.

Also given in Table II are rate constants, k_{CH_2}, for the much slower exchange of the four methylene protons of the *N*-carboxymethyl groups, both in the free ligand and in its metal complexes. The reproducibility of these values is significantly poorer ranging from ±10 to ±25%. This is probably due to a small amount of ligand decomposition which causes a measurable decrease in the pH of some solutions during the long times required to observe exchange of the CH_2 protons.

Table II. Rate Constants for Proton Exchange and Racemization of Cm_2-D-$Phgly^{3-}$, $M(Cm_2\text{-D-}Phgly)^-$, and $M(Cm_2\text{-D-}Phgly)(OH)^{2-}$ at 60°

	[Ligand], mM	pD_{25}	10^6 k_{ex}, sec^{-1}	10^6 k_{rac}, sec^{-1}	10^6 k_{CH_2}, sec^{-1}
No metal ion	50.0	*a*	2.85	2.38	1.04
Ni(II)	100	11.1	38.3	38.8	10.8
	100	11.4	46.3	47.6	
Pb(II)	100	11.0	34.7	35.0	8.5
	100	11.1	38.2	44.0	2.81
	80	11.8	101.5	118.9	13.2
Zn(II)	41.0	10.4	3.99	3.10	0.53
	100	11.2	7.27	9.05	1.91
	100	11.7	15.0	16.0	2.6

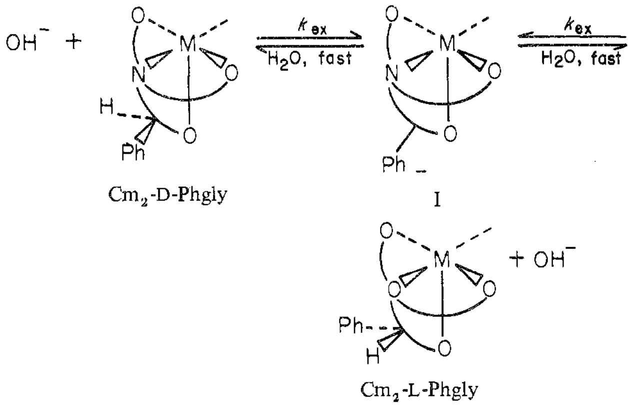
[a] $[OH^-] = 1.5$ *M*.

Discussion

Kinetic studies of the base-catalyzed racemization of free amino acids[1,2,11] as well as of their Co(III) complexes[4] support a mechanism which involves rate-determining abstraction of the α-proton by OH^-. The resulting carbanion intermediate is presumed to lose its asymmetry by adopting a planar geometry at the α carbon. Reprotonation of this carbanion gives equal amounts of the two enantiomers.

The first-order term in OH^- concentration for racemization of Cm_2-D-$Phgly^{3-}$ and its metal ion complexes supports this mechanism (Scheme I) in these systems as well. For such a mechanism where protonation of the carbanion intermediate gives equal amounts of the D and L enantiomers, the rate constant for proton exchange (k_{ex}) will be twice that (k') for conversion of the D to the L enantiomer. This is true because only half of the D ligands that are deprotonated (*i.e.*, undergo H^+ exchange) are converted to the L isomer by protonation of the symmetric carbanion intermediate I. Since the rate of

Scheme I



Cm_2-D-Phgly

I

Cm_2-L-Phgly

racemization is twice that of inversion ($k_{rac} = 2k'$), k_{rac} will be equal to k_{ex} for this mechanism.

In studies designed specifically to examine the relative values of k_{ex} and k_{rac} (Table II), it is found that k_{ex} is equal to k_{rac} within experimental error. These results support a planar intermediate which gives equal amounts of the D- and L-amino acid on protonation.

The rates of inversion, k' (Table I), follow a rate law (eq 3) which shows a term (k_2) which is first-order in OH^- concentration and a much smaller term (k_1) which is independent of OH^-. This latter term is not sufficiently reliable to warrant discussion, but it could correspond either to a path in which H_2O acts as the deprotonation base or to one in which OH^- abstraction of the α proton occurs in a protonated form of the compound. For the uncoordinated Cm_2-D-$Phgly^{3-}$, it could correspond to intramolecular deprotonation by a $-CO_2^-$ group.

Equilibrium studies showed that under the basic conditions of the racemization studies at 60.0°, the free ligand is present as the unprotonated Cm_2-D-$Phgly^{3-}$; the complexes of Pb(II) and Ni(II) are present as $M(Cm_2$-D-$Phgly)^-$, and the complexes of Cu(II) and Zn(II), as $M(Cm_2$-D-$Phgly)(OH)^{2-}$. The k_2 rate constants for inversion of the ligand in these species decreased in the following order: $Pb(Cm_2$-D-$Phgly)^-$, 3.08×10^{-2} > $Cu(Cm_2$-D-$Phgly)(OH)^{2-}$, 2.31×10^{-2} > $Ni(Cm_2$-D-$Phgly)^-$, 2.01×10^{-2} >> $Zn(Cm_2$-D-$Phgly)(OH)^{2-}$, 0.381×10^{-2} >>> Cm_2-D-$Phgly^{3-}$, 5.8×10^{-6} M^{-1} sec^{-1}. When there is coordination to the metal ion, the rate constant for base-catalyzed inversion of the ligand is from 600 to 5000 times larger than that for the free ligand.

The positive metal ion presumably promotes proton removal either by making the α proton more positive and susceptible to removal by a base or by stabilizing the transition state in which the proton is being abstracted. One might hope to find some correlation of the catalytic abilities of metal ions in this study with those of other studies in which the electron-withdrawing properties of the metal ions are important. For example, the rates of ester hydrolysis[23] in the complexes $M(NH_2CH_2CO_2Et)^{2+}$ decrease with M as follows: Cu(II) > Zn(II) > Ni(II). A similar trend for the ester hydrolysis of the *N,N*-dicarboxymethyl–amino acid ester complex, $M(O_2CCH_2)_2NCH_2CO_2Et$, was also observed:[24] Pb(II) > Cu(II) > Zn(II) > Ni(II). Except for a reversal in the order of Pb(II) and Cu(II), the same trend was observed[25] for the hydrolysis of ethyl oxalate in $M(O_2CCO_2Et)^+$. Except for the unusually slow rate of racemization in $Zn(Cm_2$-D-$Phgly)(OH)^{2-}$, the racemization trend is similar to those observed for the ester hydrolyses. Because of the high pH values required for the inversion studies, hydroxo complexes of Zn(II) and Cu(II) were involved. The additional negative charge on these complexes would be expected to reduce the inversion rates of these metal ion complexes as compared to the ester hydrolyses where hydroxo complexes were not present. This may account for the unexpectedly slow rate of racemization of $Zn(Cm_2$-D-$Phgly)(OH)^{2-}$.

Acknowledgment. This investigation was supported by PHS Research Grant No. GM-12626 from the National Institute of General Medical Sciences.

Registry No. Cm_2-D-$Phgly^{3-}$, 54062-85-0; $Pb(Cm_2$-D-$Phgly)^-$, 54063-02-4; $Cu(Cm_2$-D-$Phgly)(OH)^{2-}$, 54063-03-5; $Ni(Cm_2$-D-$Phgly)^-$, 54063-04-6; $Zn(Cm_2$-D-$Phgly)(OH)^{2-}$, 54063-05-7; Cm_2-D-$PhglyH_3$, 54062-86-1; bromoacetic acid, 79-08-3; D-phenylglycine, 875-74-1.

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