Proton Exchange and Mutarotation of Chelated Amino Acids *via* Carbanion Intermediates[1]

D. A. Buckingham, L. G. Marzilli, and A. M. Sargeson

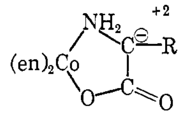
Contribution from the Research School of Chemistry, Australian National Laboratory, Canberra, Australia. Received May 8, 1967

Abstract: The rate of α-proton exchange and mutarotation of coordinated L-(+)-valine and L-(+)-alanine in the ions D- and L-$[Co(en)_2AA]^{2+}$ have been measured. The rates and rate laws $R = k[Co][OH^-]$ were the same for both processes and were similar for both amino acids. For one configuration about the cobalt ion the equilibrium concentrations of D and L amino acids were established as D-$[Co(en)_2$-D-$(val)]^{2+}$/D-$[Co(en)_2$-L-$(val)]^{2+} = 1.70 \pm 0.14$ and D-$[Co(en)_2$-D-$(ala)]^{2+}$/D$[Co(en)_2$-L-$(ala)]^{2+} = 1.0 \pm 0.2$ at 34.3°. The degree of stereospecificity is discussed in relation to the predictions of a conformational analysis.

The stereospecificity incorporated in dissymmetric complex ions containing optically active ligands has received some attention,[2-4] but few studies have been devoted to measuring the equilibrium constants between the possible diastereoisomers. The absence of data on this aspect of coordination compounds arises partly because in the inert complexes it is often difficult to establish equilibrium, and in the more labile systems it is difficult to freeze the equilibrium and measure the concentration of the components. For the inert complexes the preparative procedures used often lead to the presence of several species, but frequently there is no guarantee that equilibrium has been established.

The degree of specificity is important if we are to understand the significant factors which lead to isomer discrimination; some hope of evaluating these factors arises from the conformational analysis of chelated complexes which has been pioneered by Corey and Bailar.[2] Their calculations suggest that the structure of the D-$Co(en)_3^{3+}$ ion,[5] where the chelated rings adopt the k conformation,[6] is ~1.8 kcal/mole more stable than the D-k′k′k′ form. Such calculations are largely empirical and the energy difference obtained is frequently a small difference between large values. Conformational calculations have been found widely successful for organic compounds, however, where there is good agreement with experiment. Their value has yet to be widely established for coordination compounds, and the present paper is concerned with the measurement of the equilibrium constants between the isomers D-$[Co(en)_2$L-$(val)]^{2+}$/D-$[Co(en)_2$-D-$(val)]^{2+}$ and D-$[Co(en)_2$-L-$(ala)]^{2+}$/D-$[Co(en)_2$-D-$(ala)]^{2+}$ and the conformational predictions for the stability of these species.

The means of establishing the equilibrium between the $[Co(en)_2(val)]^{2+}$ ions was suggested by pmr studies of α-amino acid complexes[7,8] which showed that the α-CHR– proton undergoes base-catalyzed exchange in aqueous solution. This raised the possibility of mutarotation of coordinated amino acids. Moreover, it was conceivable that the exchange involved the formation of a coordinated carbanion



which could either react with solvent water to retain or invert the asymmetric grouping about the carbon atom. This leads to the establishment of the equilibrium

$$\begin{tikzcd}
OH^- + \text{D-}[Co(en)_2\text{-D-}(AA)]^{2+} \arrow[r, shift left] & \text{D-}[Co(en)_2\text{-D-}(AA-H)]^+ + H_2O \arrow[l, shift left] \arrow[d, shift right] \\
OH^- + \text{D-}[Co(en)_2\text{-L-}(AA)]^{2+} \arrow[r, shift left] & \text{D-}[Co(en)_2\text{-L-}(AA-H)]^+ + H_2O \arrow[l, shift left] \arrow[u, shift right]
\end{tikzcd} \qquad (1)$$

and effectively leads to equilibration between the doubly charged ions since the concentration of the deprotonated species is minute.

In addition to the attainment of the diastereoisomeric equilibrium mixture, the mechanism of the base-catalyzed reaction and the relationship between the proton exchange rate and the rate of mutarotation are also of interest.

Experimental Section

All materials used were reagent grade, except KCl which was Analar. All rotations were measured in 1-dm cells with a Perkin-Elmer 141 polarimeter fitted with a Zeiss monochromator (12-mm quartz prism) and a quartz–halogen lamp. Proton magnetic resonance spectra were measured using a Perkin-Elmer R10 or a Varian A-60 spectrometer using sodium trimethylsilylpropanesulfonate as an internal standard reference. A Northern Scientific NS544 time-averaging computer was coupled with the Perkin-Elmer instrument. Visible spectra were obtained on a Cary 14 spectrophotometer.

DL-$[Co(en)_2$-DL-$(val)]I_2$ has been prepared previously.[9]

DL-$[Co(en)_2$-L-$(val)]I_2$ was prepared by the method used for the preparation of DL-$[Co(en)_2(sar)]I_2$[10] except that after heating the reaction mixture at 75° for 30 min, the solution was neutralized with concentrated HCl. The product was recrystallized from hot water with NaI, yield 13.5 g. The absence of $[Co(en)_3]I_3$ was

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[1] Abbreviations used in this paper are: en = ethylenediamine, trien = triethylenetetramine, gly = glycinate, val = valinate, ala = alaninate, sar = N-methylglycinate, AA = amino acid anion, SbO-*d*-tart = antimonyl-*d*-tartrate, thr = threonate, pn = 1,2-diaminopropane.

[2] E. J. Corey and J. C. Bailar, Jr., *J. Am. Chem. Soc.*, **81**, 2620 (1959).

[3] A. M. Sargeson in "Transition Metal Chemistry," R. L. Carlin, Ed., Marcel Dekker Inc., New York, N. Y., 1966, p 303.

[4] J. H. Dunlop and R. D. Gillard, *Advan. Inorg. Chem. Radiochem.*, **9**, 185 (1966).

[5] K. Nakatsu, M. Shiro, Y. Saito, and H. Kuroya, *Bull. Chem. Soc. Japan*, **30**, 795 (1957).

[6] It has been pointed out to us by C. E. Schäffer that Figures 2 and 3 in ref 2 give mirror-image forms for the conformation denoted as k. The nomenclature used in this article and previous articles has been standardized on Figure 3, ref 2.

[7] D. H. Williams and D. H. Busch, *J. Am. Chem. Soc.*, **87**, 4644 (1965); J. B. Terrill and C. N. Reilley, *Inorg. Chem.*, **5**, 1988 (1966).

[8] K. R. Turnbull, Ph.D. Thesis, Australian National University, 1965.

[9] D. A. Buckingham and J. P. Collman, *Inorg. Chem.*, in press.

[10] (a) D. A. Buckingham, S. F. Mason, A. M. Sargeson, and K. R. Turnbull, *ibid.*, **5**, 1649 (1966); (b) C. T. Liu and B. E. Douglas, *ibid.*, **3**, 1356 (1964).

verified by eluting a sample of the product from an ion-exchange column (Bio-Rad Dowex 50W X2 200–400 mesh) with 1 *M* KCl.

D-[Co(en)$_2$-L-(val)]I$_2$·H$_2$O. A mixture of DL-[Co(en)$_2$-L-(val)]I$_2$ (13.5 g) and silver acetate (8.1 g) in water containing several drops of acetic acid was shaken for several minutes, and the resulting AgI was removed and washed with hot water. The filtrate and washings were combined (175 ml) and sodium antimonyl-(+)-tartrate (NaSbO-(+)-tart) (8.0 g) was added. The solution was filtered and evaporated slowly under vacuum and several fractions of diastereoisomer were removed, each of similar optical purity (total yield 6.3 g). This material was recrystallized without change in optical purity, $[\alpha]_D$ +200° for a 0.1% solution. *Anal.* Calcd for D-[Co(en)$_2$-L-(val)](SbOC$_4$H$_4$O$_6$)$_2$: C, 23.55; H, 3.95; N, 8.08. Found: C, 23.75; H, 3.99; N, 7.89. The diastereoisomer was ground with excess NaI in a small volume of water, and the iodide salt was collected and fractionally recrystallized from warm water. The most soluble fractions gave $[\alpha]_{546}$ +470° for a 0.1% solution, and the rotation was unchanged by further recrystallization. *Anal.* Calcd for D-[Co(en)$_2$-L-(val)]I$_2$·H$_2$O: C, 19.06; H, 4.98; N, 12.35. Found: C, 18.98; H, 5.01; N, 12.48.

L-[Co(en)$_2$-L-(val)]I$_2$·H$_2$O. The filtrate from the diastereoisomer was treated with NaI and the complex iodide recovered. It was then treated with Na(SbO-(−)-tart) (8.0 g) which resulted in several small fractions of inactive diastereoisomer and not the desired L-[Co(en)$_2$-L-(val)](SbO-(−)-tart)$_2$ salt. The solution was then treated with NaI and the complex iodide collected in fractions. The least soluble fractions were discarded as largely unresolved material but the more soluble fractions were optically impure L-[Co(en)$_2$-L-(val)]I$_2$·H$_2$O (3.0 g). Fractional recrystallization of this salt resulted in L-[Co(en)$_2$-L-(val)]I$_2$·H$_2$O (0.4 g) which had $[\alpha]_{546}$ −663° for a 0.1% solution, and this rotation remained unaltered throughout further fractionation. *Anal.* Calcd for L-[Co(en)$_2$-L-(val)]I$_2$·H$_2$O: C, 19.06; H, 4.98; N, 12.35. Found: C, 18.98; H, 4.75; N, 12.53. The infrared spectra of the two diastereoisomers of [Co(en)$_2$-L-(val)]I$_2$·H$_2$O confirmed the presence of water of crystallization (3500 cm^{-1}).

D-[Co(en)$_2$-L-(val)]Cl$_2$·1.5H$_2$O was obtained by shaking an aqueous suspension of the iodide salt with AgCl, removing the excess silver salts, and evaporating the solution to dryness. *Anal.* Calcd for D-[Co(en)$_2$-L-(val)]Cl$_2$·1.5H$_2$O: C, 27.48; H, 7.43; N, 17.81. Found: C, 27.36; H, 7.72; N, 17.81.

DL-[Co(en)$_2$-DL-(val)]Cl$_2$·H$_2$O was obtained in a manner simila to that for the active form except that crystallization occurred when the volume was reduced. *Anal.* Calcd for DL-[Co(en)$_2$-DL-(val)]Cl$_2$·H$_2$O: C, 28.13; H, 7.34; N, 18.23. Found: C, 27.70; H, 7.24; N, 18.25.

L-[Co(en)$_2$-L-(ala)]I$_2$. The preparation and resolution of this compound followed the procedure of Liu and Douglas,[10b] $[M]_{546}$ −3700°. *Anal.* Calcd for L-[Co(en)$_2$-L-(ala)](SbOC$_4$H$_4$O$_6$)$_2$·2H$_2$O: C, 20.59; H, 3.92; N, 8.01. Found: C, 20.73; H, 4.03; N, 7.89. *Anal.* Calcd for L-[Co(en)$_2$-L-(ala)]I$_2$: C, 16.14; H, 4.26; N, 13.44. Found: C, 16.16; H, 4.23; N, 13.32.

L-[Co(en)$_2$-L-(ala)]Cl$_2$·1.5H$_2$O was prepared in an analogous manner to that for the valine complex. *Anal.* Calcd for L-[Co(en)$_2$-L-(ala)]Cl$_2$·1.5H$_2$O: C, 23.02; H, 6.90; N, 19.18. Found: C, 22.89; H, 6.46; N, 19.45.

Nmr Equilibration Studies. A solution of D-[Co(en)$_2$-L-(val)]Cl$_2$·1.5H$_2$O (0.2 g in 15 ml of 0.02 *M* NaOH) was warmed at 34.3° for 80 min ($\sim 10t_{1/2}$) and then neutralized with 10.6 *N* HCl. The water was removed under reduced pressure. The residue was then completely dissolved in D$_2$O and the N-H protons were allowed to exchange to simplify the pmr spectrum. Then a drop of 10 *N* DCl was added to move the HOD signal and the pmr spectrum recorded. The areas under the absorption peaks arising from the α protons in the two diastereoisomers were measured four times with a Gelman planimeter (±1% variation for each doublet).

Also a basic solution of L-[Co(en)$_2$-L-(ala)]Cl$_2$·1.5H$_2$O (0.18 g in 3 ml of 0.05 *M* NaOH) was kept at 34.3° for 56 min ($10t_{1/2}$) and then neutralized with 1.5 ml of 0.1 *N* HCl. A D$_2$O solution was prepared as for the valine complex. The pmr spectrum was recorded using a time-averaging computer (500 runs).

NaOH solutions were prepared by dilution of standard BDH solutions with CO$_2$ and ion-free distilled water and standardized. The NaOD solutions were prepared by dilution of a standardized solution of NaOD made by adding sodium slowly to D$_2$O.

Polarimetric Equilibration Studies. Weighed samples of optically pure D-[Co(en)$_2$-L-(val)] iodide or chloride salts, L-[Co(en)$_2$-L-(val)]I$_2$·H$_2$O, and L-[Co(en)$_2$-L-(ala)]I$_2$ were dissolved in NaOH or NaOD solutions (10 ml) which had been equilibrated at the desired temperature. Rotation changes observed at 546 mμ for a 0.1% solution were of the order of 0.100 to 0.200° for the valine complexes and, at 450 mμ, 0.100° for the alanine compound. Each reading was accurate to ±0.002°. Rates were reproducible to better than ±5%. The ionic strength was adjusted with KCl.

Hydrogen-exchange rates were followed with the nmr spectrometer. The ionic strength was adjusted with the complexes to μ = 0.5 or 1. The NaOD solutions were the same as those used in the equilibration studies.

Results

In basic solution, the coordinated amino acid was found to mutarotate without change in the configuration about the Co(III) center, and the following equilibria were established

$$\text{D-[Co(en)}_2\text{-L-(val)]}^{2+} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{D-[Co(en)}_2\text{-D-(val)]}^{2+} \quad K_1 \tag{2}$$

$$\text{L-[Co(en)}_2\text{-L-(val)]}^{2+} \rightleftharpoons \text{L-(Co(en)}_2\text{-D-(val)]}^{2+} \quad 1/K_1 \tag{3}$$

$$\text{L-[Co(en)}_2\text{-D-(ala)]}^{2+} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{L-[Co(en)}_2\text{-L-(ala)]}^{2+} \quad K_2 \tag{4}$$

In the above reactions, equilibria 2 and 3 are "mirror images" and are treated together. When either D-[Co(en)$_2$-L-(val)]I$_2$·H$_2$O or L-[Co(en)$_2$-L-(val)]I$_2$·H$_2$O was dissolved in NaOH at 34.3° and allowed to equilibrate, the final rotations were equal but of opposite sign within experimental error (Table I). Furthermore, within experimental error, the visible absorption spectra and the half-life for equilibration were the same for both ions, respectively. The equilibrium mixture obtained from D-[Co(en)$_2$-L-(val)]$^{2+}$ contained 63 ± 2% D-[Co(en)$_2$-D-(val)] and 37 ± 2% D-[Co(en)$_2$-L-(val)]$^{2+}$ using the polarimetric data. The mixture obtained from a single

Table I. Rate Data of Equilibration[a] of the [Co(en)$_2$(AA)]I$_2$ Isomers

[OH$^-$], $M \times 10^2$	μ, M	k_{obsd}, sec^{-1} × 10^5	k_{calcd}, M^{-1} sec^{-1} × 10^2	$[\alpha]_{546}$, deg[h]
		(+)$_{589}$-[Co(en)$_2$-L-(val)]I$_2$·H$_2$O, $[\alpha]_{546}$ 470°		
2.0	0.025	199	9.95	
2.0	0.026[f]	203	10.2	
10.0	0.106[f]	679	6.79	
2.0	0.105	134	6.70	599
1.0	0.105	66.0	6.60	598
0.2	0.107	13.8	6.90	591
0.155	0.107	10.5	6.77	597
2.0	0.525	77.0	3.83	592
0.155	0.507	5.63	3.63	
2.0	1.025	57.8	2.89	597
1.45[e]	1.020	57.8	3.99	
0.155	0.006	24.1	15.6	599
0.155	0.006[g]	25.1	16.2	−591
2.0[b]	0.105	56.3	2.81	605
1.0[b]	0.105	28.1	2.81	599
2.0[c]	0.105	19.6	0.98	607
		(−)$_{589}$-[Co(en)$_2$-L-(ala)]I$_2$		
10.0	0.505	413	4.13	
5.0	0.555	206	4.12	
1.0	0.515	41.3	4.13	
5.0	1.055	178	3.56	
0.348[e]	0.508	18.1	5.02	
5.0[d]	0.555	144	2.88	
5.0[b]	0.555	88.8	1.78	

[a] At 34.3° unless stated otherwise. [b] 25°. [c] 15°. [d] 30°. [e] D$_2$O. [f] Cl$^-$ salt. [g] (−)$_{589}$-[Co(en)$_2$-L-(val)]I$_2$·H$_2$O, $[\alpha]_{546}$ − 670°. [h] Equilibrium rotation.

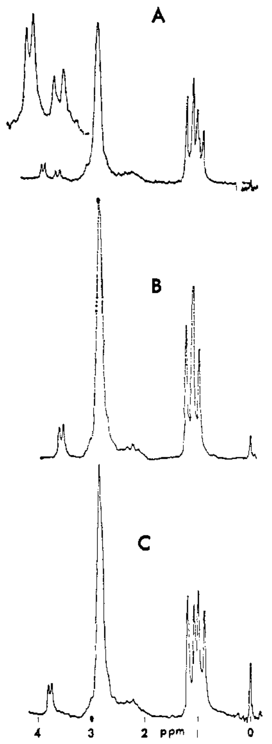

Figure 1. Pmr spectra (60 Mc) of D-$[Co(en)_2$-L-(val)$]Cl_2$ (B), D-$[Co(en)_2$-D-(val)$]Cl_2$ (C), and the equilibrium mixture (A).

experiment with L-$[Co(en)_2$-L-(val)$]^{2+}$ gave 61% LL and 39% LD. Using the former results the equilibrium constant and free-energy change were calculated as $K_1 = 1.70 \pm 0.14$ at 34.3° and $\Delta G_{34.3°} = -0.30$ kcal/mole. The value of K_1 was independent of ionic strength, temperature, and $[OH^-]$ within the accuracy of the measurements.

Reactions 2 and 4 were carried out on a larger scale and the equilibrium mixture was quantitatively recovered. The pmr spectra for the two mixtures are given in Figures 1 and 2 and, although the pmr spectra of the isomers of both $[Co(en)_2$-L-(val)$]^{2+}$ and $[Co(en)_2$-L-(ala)$]^{2+}$ have been reported and discussed previously,[11] the salient points are reiterated here. For $[Co(en)_2$-L-(val)$]^{2+}$ deuterated on nitrogen, the signal due to the hydrogen on the α carbon is split into a doublet by the proton on the tertiary carbon of the isopropyl group. The doublet is centered about 3.78 ppm for the L-$[Co(en)_2$-L-(val)$]^{2+}$ ion and about 3.57 ppm for the D-$[Co(en)_2$-L-(val)$]^{2+}$ ion[11] (Figure 1). The pmr spectrum of the equilibrium mixture D-$[Co(en)_2$-L-(val)$]^{2+}$–D-$[Co(en)_2$-D-(val)$]^{2+}$ is also given in Figure 1a, and the ratio of the areas under the respective doublet signals in the equilibrium mixture gives the isomeric ratio at 60 ± 3% D-$[Co(en)_2$-D-(val)$]^{2+}$ and 40 ± 3% D-$[Co(en)_2$-L-(val)$]^{2+}$ in agreement with the polarimetric results. The larger splitting in the signal of the minor isomer (5 cps) makes it appear to be even less intense when compared with that of the major isomer (4 cps).

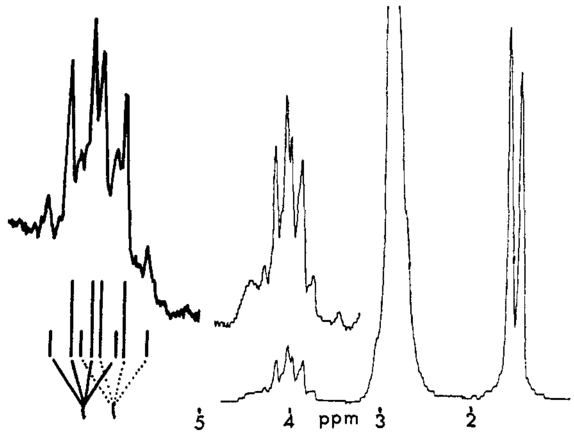

Figure 2. Pmr spectra (60 Mc) of the equilibrium mixture D-$[Co(en)_2$-L-(ala)$]Cl_2$ and D-$[Co(en)_2$-D-(ala)$]Cl_2$.

The α-H absorption for the D-$[Co(en)_2$-L-(ala)$]^{2+}$ ion is a quartet centered about 3.98 ppm, and that for L-$[Co(en)_2$-D-(ala)$]^{2+}$ is a quartet about 4.15 ppm,[11] arising from a coupling with the CH_3 protons (J = 7 cps). Previously, this region of the spectrum was not so well resolved in the isomer mixture and had the appearance of a quintet.[11] However, the spectrum was correctly assigned as two superimposed quartets. In the spectrum in Figure 2 the two overlapping quartets appear as an octet ($\Delta\delta \sim 10$ cps). Although the separation of signals is not large, it is clear that the two isomers are present in approximately equal concentrations, and from several spectra the error was estimated as ±5%.

Kinetics of Equilibration. The rate constants, $k_{eq} = k_1 + k_2$, measured for the attainment of equilibria 2–4, are given in Table I. Rates were followed for at least three half-lives, the infinity values were taken between 6 and 10 × $t_{1/2}$, and linear plots of log $(\alpha_t - \alpha_\infty)$ *vs.* t were obtained. At the highest temperature, 34.3°, some base hydrolysis (1%) occurred and allowance was made for this decomposition. However, the decomposition was negligible at the lower temperatures.

Both the valine and alanine compounds gave similar kinetic behavior. The systems followed the same rate law for equilibration

$$R = k_{eq}[Co][OH^-]$$

The values of k_{eq} were similar at the same ionic strength and varied in the same manner with ionic strength, decreasing as μ increased and levelling off at $\mu = \sim 0.5$ M. In D_2O, the rate was faster than in H_2O by a similar factor (~1.3) for both systems. Linear plots of log k_{eq} *vs.* $1/T$ were obtained, and the values of the activation energy for the systems were $E_a = 17.1 \pm 1$ kcal/mole for alanine and $E_a = 17.5 \pm 1$ kcal/mole for valine.

Kinetics of Proton Exchange. In Table II, the rate constants for proton exchange on the α-hydrogen of DL-$[Co(en)_2$-DL-(ala)$]Cl_2$, DL-$[Co(en)_2$-DL-(val)$]Cl_2$, and

Table II. Rate Constants for Hydrogen Exchange in the $[Co(en)_2(AA)]^{2+}$ Isomers at 34.3°

Compound	$[OD^-]$, M	k_{obsd}, sec^{-1}	k_{calcd}, M^{-1} sec^{-1} × 10^2
DL-$[Co(en)_2$-DL-(val)$]^{2+}$ [a]	0.0145	4×10^{-4}	2.7 ± 1
D-$[Co(en)_2$-L-(val)$]^{2+}$	0.0145	6×10^{-4}	4.0 ± 1
DL-$[Co(en)_2$-DL-(ala)$]^{2+}$ [b]	0.0290	1.5×10^{-3}	5.3
DL-$[Co(en)_2$-DL-(ala)$]^{2+}$ [b]	0.0145	7.7×10^{-3}	5.3
DL-$[Co(en)_2$-DL-(ala)$]^{2+}$ [b]	0.00348	1.9×10^{-4}	5.4
DL-$[Co(en)_2$-DL-(ala)$]^{2+}$ [c]	0.0290	7.0×10^{-4}	2.4

[a] $\mu = 1.0$ M. [b] $\mu = 0.5$ M. [c] 27°.

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(11) D. A. Buckingham, L. Durham, and A. M. Sargeson, *Australian J. Chem.*, 20, 257 (1967).

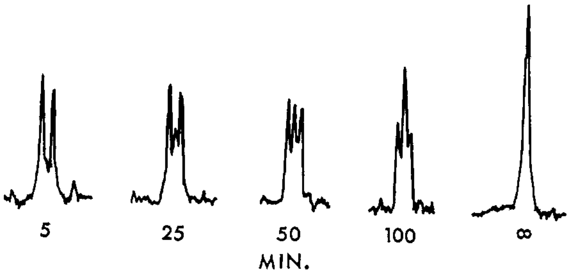


Figure 3. The exchange rate of the α-proton for a deuteron in the DL-[Co(en)$_2$-DL-(ala)]$^{2+}$ ions as followed by the collapse of the methyl doublet to a singlet.

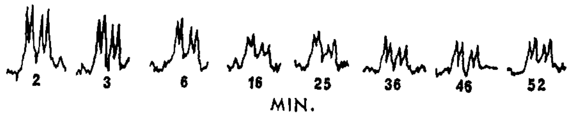
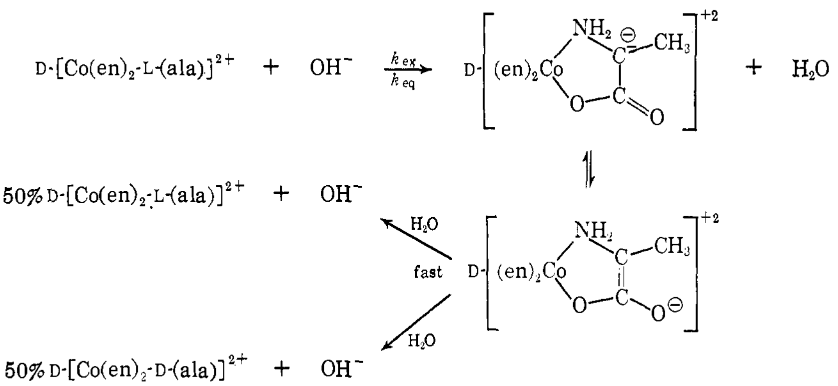


Figure 4. The exchange rate of the α-proton for a deuteron in the DL-[Co(en)$_2$-DL-(val)]$^{2+}$ ions as followed by the collapse of the α-CH doublets.

D-[Co(en)$_2$-L-(val)]Cl$_2$ are reported. The kinetic data were obtained for the alanine system by following the collapse of the methyl doublet signal to a singlet as the α-proton exchanged with D$^+$ (Figure 3), and the plots of log [(peak height)$_t$ − (peak height)$_\infty$] *vs.* time were linear. Unfortunately, no accurate values could be obtained for the rate of exchange of the α-proton in the [Co(en)$_2$-(val)]Cl$_2$ species because the intensity of the doublets is low. However, Figure 4 shows that the signals for the α-hydrogens do diminish and at approximately the same rate for the two diastereoisomeric components D-[Co(en)$_2$-L-(val)]$^{2+}$ and L-[Co(en)$_2$-L-(val)]$^{2+}$. A more accurate initial rate plot was obtained for D-[Co(en)$_2$-L-(val)]Cl$_2$ where only one doublet signal was involved, and the intensity was therefore doubled for the same concentration of complex. A complicating feature of the kinetics for valine was the slow decomposition of this compound in base. Only 3% decomposition of these species is necessary to consume the 0.010 *N* NaOD in the pmr tube. The much lower [complex]/[OH$^-$] ratio in the polarimetric studies allowed the small amount of decomposition to occur without significantly altering the base concentration.

Scheme I

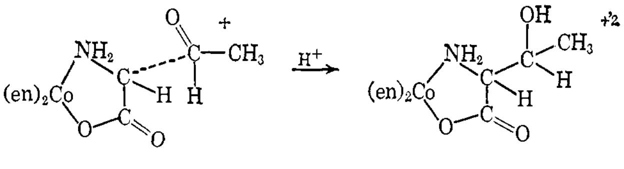


The significant results of these exchanges studies are that the rate of proton exchange is approximately equal to the rate of mutarotation in D$_2$O and that the rate law for proton exchange is the same as that for mutarotation, namely $R = k_D[\mathrm{Co}][\mathrm{OD}^-]$.

Discussion

The rate law for the α-carbon proton exchange in the coordinated amino acid anion is consistent with the nucleophilic attack of OH$^-$ at the proton leaving a coordinated amino acid carbanion. If it is assumed that the carbanion is formed, the kinetic results can be clearly interpreted. The rate constants and activation parameters for both proton exchange and mutarotation at the carbon center show that these processes are synchronous for the alanine complexes and are close and probably equal for the valine compounds. We propose the mechanism in Scheme I to account for these results using the alanine complex as the example. The rate-determining step is the removal of the proton; the carbanion immediately rearranges to a symmetrical form and reacts rapidly ($\sim 10^{10}$ sec^{-1}) with solvent water to regenerate approximately equal amounts of D and L amino acid. Clearly the asymmetric configuration about the Co(III) ion has little effect on the distribution of either D or L organic moieties, and this aspect will be discussed further below.

The results observed in this system parallel those found for purely organic systems where there is an electronegative delocalized center adjacent to and capable of stabilizing the sp^2 state at the formerly asymmetric carbon center.[12] Further evidence for the presence of the carbanion intermediate is deduced from the studies of aldol-type condensations with related complexes. For example, it has been shown that [Co(en)$_2$(gly)]$^{2+}$ condenses with CH$_3$CHO in basic solution[13] and this reaction is consistent with the competition of CH$_3$CHO for the carbanion to produce [Co(en)$_2$(thre)]$^{2+}$. Only a small preference was found in this condensation for the formation of D- and L-threonine, but there was a substantial preference for threonine over the diastereoisomer allothreonine in the reaction. However, this latter observation may reflect only the relative stability of threonine and allothreonine.



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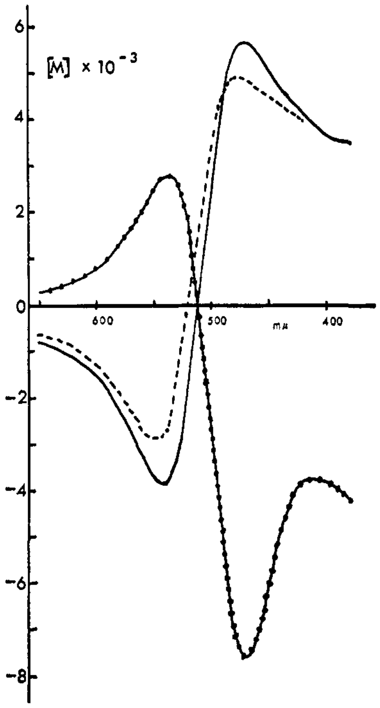

Figure 5. Rotatory dispersion curves for $(+)_{589}$-[Co(en)$_2$-(+)-(val)]I$_2$·H$_2$O (-●-●-●-), $(-)_{589}$-[(Co(en)$_2$-(+)-(val)]I$_2$·H$_2$O (———), and $(-)_{589}$-[Co(en)$_2$(sar)]I$_2$·2H$_2$O (- - - -).

It seems likely that the Co(III) ion activates the coordinated ligand since the condensation does not occur measurably with the free amino acid anion. Part of the activation is probably associated with the positive charge on the complex ion since in a series of glycinato compounds[14] the following rate order was observed for the condensation of acetaldehyde: [Co(en)$_2$(gly)]$^{2+}$ > [Co(gly)$_3$]^0 > [Co(gly)(C$_2$O$_4$)$_2$]$^{2-}$.

The rotatory dispersion (Figure 5) and circular dichroism curves for the $(+)_{589}$-[Co(en)$_2$-L-(+)-(val)]$^{2+}$ and $(-)_{589}$-[Co(en)$_2$-L-(+)-(val)]$^{2+}$ ions correspond with those found for the $(+)_{589}$- and $(-)_{589}$-[Co(en)$_2$(sar)]$^{2+}$ ions,[15] respectively, and are assigned the same configurations. The absolute configurations of the sarcosine complexes were confirmed by an X-ray crystallographic study[16] and they are structurally related to D- and L-[Co(en)$_3$]$^{3+}$, respectively. A similar correspondence was observed for the $(+)_{589}$- and $(-)_{589}$-L-(+)-alaninato complexes, and these ions are also assigned the D and L configurations, respectively. The configurational analysis is also supported by the structural analysis of the [Co(en)$_2$-L-(glutamato)]$^{2+}$ ion whose absolute configuration was assigned from the known configuration of L-glutamic acid.[17]

In Corey and Bailar's analysis of the Co(en)$_3$$^{3+}$ ion for the two extreme conformational forms kkk and k′k′k′ (Figure 3, ref 2), the nonbonded axial NH · · · C (H · · · H) interactions were the most significant in determining the energy difference between the conformational forms, and the ions containing mixed conformations were intermediate in stability between these forms. The analysis implies that if the axial–equatorial character of the substituents on the chelate ring is eliminated, then the energy differences are diminished.

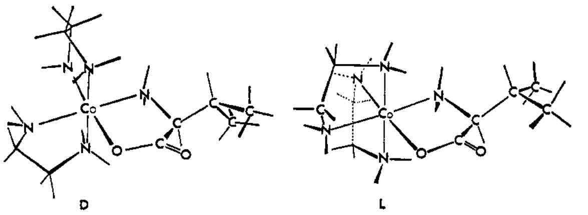

Figure 6. The projections of Dreiding models for D-[Co(en)$_2$-L-(val)]$^{2+}$ and L-[Co(en)$_2$-L-(val)]$^{2+}$ ions.

The effect of the least and most stable Co–en type conformations is probably observed in the Co complexes of (+)-propylenediamine. In this chelate system the methyl group forces the chelate always to adopt the conformer with CH$_3$ equatorial. While the kkk arrangement is most stable for the D configuration, kkk is least stable for the L configuration, and for D-$(+)_{589}$-[Co-L-(+)-(pn)$_3$]$^{3+}$ (kkk) and L-$(-)_{589}$-[Co-L-(+)-(pn)$_3$]$^{3+}$ (kkk) the equilibrium constant is $K_{\mathrm{D/L}}$ = 14.6.[18] For the D- and L-[Co(en)$_2$L-(+)-(pn)]$^{3+}$ ions the conformation arrangement is probably D-[Co(en)$_2$(k)-(+)-(pn)(k)]$^{3+}$ and L-[(Co(en)$_2$(k′)-(+)-(pn)(k)]$^{3+}$. The equilibrium constant D/L is 2.1,[18] which again probably reflects the presence of the single least stable conformer in the L isomer. Similarly, if planar chelates are introduced into the complexes, the stability difference between the D and L forms decreases. For example, almost equal amounts of D- and L-[Co-(−)-(pn)$_2$(C$_2$O$_4$)]$^+$ and [Co-(−)-(pn)(C$_2$O$_4$)$_2$]$^-$ occur at equilibrium.[19]

In the present system the Co(III) amino acid chelate ring is not greatly displaced from planarity if we use the Co(III)–sarcosine ring as a model.[16] Certainly it is much less conformationally pronounced than the Co-(−)-pn chelate. In the D- and L-[Co(en)$_2$-L-amino acid]$^{2+}$ systems therefore we should expect to see this factor reflected in the equilibrium constant for the D and L forms compared with the D- and L-[Co(en)$_2$-L-(+)-(pn)]$^{3+}$ ions.

It is clear from the results for the [Co(en)$_2$-L-(ala)]$^{2+}$ system that the energy difference between the diastereoisomers is negligible. A more interesting result arises from the [Co(en)$_2$(val)]$^{2+}$ system where the D-$(+)_{589}$-[Co(en)$_2$-D-(−)-(val)]$^{2+}$ ion is more stable than L-$(-)_{589}$-[Co(en)$_2$-D-(−)-(val)]$^{2+}$ (K = 1.7, ΔG = −0.30 kcal/mole). This is the inverse of the isomer stability relationship for D- and L-[Co(en)$_2$-L-(+)-(pn)]$^{3+}$ ions since D-$(+)_{589}$-[Co(en)$_2$-D-(−)-(val)]$^{2+}$ has the same structural relationship to the D-[Co(en)$_2$-L-(+)-(pn)]$^{3+}$ ion for the configuration about the Co ion, but the active ligands have a catoptric relationship. The absolute configuration of L-(+)-propylenediamine was derived from L-(+)-alanine and is therefore related to L-(+)-valine.[20]

The projections of the Dreiding stereomodels for the L-valine isomers, Figure 6, do not show how the energy difference might arise and conformational calculations

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give only a small energy difference (0.1–0.3 kcal/mole) between the isomers of the wrong sign. The calculations were carried out using the distances measured from Dreiding scale models for the D configuration about cobalt with the k conformation for both Co–en rings. The amino acid conformation found in the [Co(en)$_2$(sar)]$^{2+}$ ion was used in one calculation (0.3 kcal/mole) while keeping the isopropyl group in its most equatorial position, and in the other the interactions between the amino acid NH$_2$ and the neighboring apical NH groups were minimized (0.1 kcal/mole). These differences arise from the sum of a number of small interactions, and it is conceivable that the equilibrium conformers in solution could be different from those proposed. Also it is possible that slightly different solvation energies for the two ions decide the isomeric stability. Some support for the last possibility might be derived from the fact that the calculations showed no difference between the corresponding alanine and valine isomers.

It would appear that the results support the thesis that planar or near-planar optically active chelates are less effective in determining the degree of stereospecificity in the D and L complexes than those with more pronounced conformational characteristics.

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Nickel(II) Complexes of Glycine Peptides in Aqueous Solution[1,2]

M. K. Kim[3a] and A. E. Martell[3b]

Contribution from the Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois. Received February 11, 1967

Abstract: Nickel(II) complexes of diglycine, triglycine, and tetraglycine in aqueous solution are studied by potentiometric pH, visible spectral, and infrared spectral measurements. Coordination sites of these glycine peptides for the nickel(II) ion are nitrogen atoms of amino and peptide groups and an oxygen atom of the carboxylate group. As with the corresponding Cu(II) complexes, the formation of nickel(II) complexes promotes the dissociation of a proton from each peptide linkage; direct evidence for this reaction is provided by a frequency shift of the infrared absorption of the peptide carbonyl group from 1670 (free ligand) to 1610 cm^{-1} (coordinated ligand). Unlike copper(II) complexes, the displacement of peptide protons by the nickel(II) ion occurs in a single dissociation step, with simultaneous conversion of the paramagnetic octahedral nickel(II) complexes to diamagnetic planar chelates.

In previous studies of copper(II) complexes of glycine peptides[4,5] it was possible to obtain structural information on the chelates formed and equilibrium constants for all microscopic reaction steps, by combining potentiometric pH measurements with infrared and visible spectral studies. Frequency changes of the infrared absorption bands of the peptide carbonyl groups provide the first direct proof of the dissociation of a proton from the peptide linkage in the course of chelate formation.

From a study of potentiometric titration curves, Martin, *et al.*,[6] suggested that reactions of the nickel(II) ion with glycine peptides are similar to those of the copper(II) ion. In the present paper, the methods used for the study of copper(II) complexes, that is, potentiometric pH measurements combined with the infrared and visible spectral studies, are extended to nickel(II) complexes.

Experimental Section

Methods. All the measurements, potentiometric pH, visible spectral, and infrared spectral, were carried out as described previously.[4]

Reagents. The ligands used are the same as those reported previously.[7] Nickel(II) nitrate and chloride were certified reagent chemicals purchased from Fisher Scientific Co., Fair Lawn, N. J.

Results

Potentiometric Titrations and Visible Spectra. Nickel(II)–Diglycine System. Potentiometric titration curves for solutions containing 1:1 and 1:2 molar ratios of nickel(II) to diglycine in 0.10 *M* KNO$_3$ media are shown in Figure 1. About 5–10 min was required to reach equilibrium after each increment of base. Contrary to what had been observed for the interaction of diglycine with copper(II), nickel(II) does not show a strong tendency to coordinate with this ligand, except at relatively high pH precipitation of nickel(II) hydroxide begins. For solutions having a 1:2 molar ratio of metal ion to ligand, the addition of base was accompanied by a relatively small color change (deepening of the blue color), and no inflection was observed in the potentiometric titration curve, indicating further reaction with base.

The reactions taking place involve the formation of simple 1:1 and 1:2 complexes of the mononegative form

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(2) Abstracted in part from material submitted by M. K. Kim to the Faculty of Illinois Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) Department of Chemistry, Texas A & M University, College Station, Texas.

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