Proton Exchange and Inversion at Coordinated *sec*-Amine Centers. Particularly Rapid Inversion at Sterically Strained "Planar" N in Some [Co(cyclen)(S-AlaO)]$^{2+}$ and [Co(Mecyclen)(S-AlaO)]$^{2+}$ Complexes[1]

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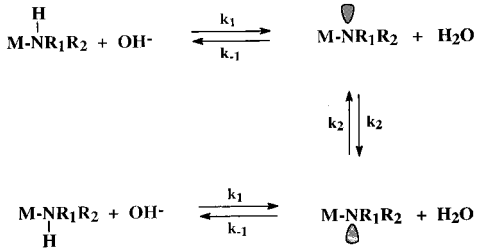
Abstract: It is shown that the *syn*(N),*syn*(O)- isomer (**3**) is the intermediate on the reaction path for interconversion between the *syn*(N),*anti*(O)- (**1**) and *syn*(O),*anti*(N)- (**2**) diastereomers of *syn*(Me)-[Co(Mecyclen)(S-AlaO)]$^{2+}$ and [Co(cyclen)(S-AlaO)]$^{2+}$. ^{1}H-exchange rate constants for the various N*H* protons are reported (k_H/M^{-1} s^{-1}, 25 °C, D_2O) and are correlated with the derived isomerization rate constants (k_N/M^{-1} s^{-1}, 25 °C, H_2O). At equilibrium (25 °C, $I \sim 0.1$ M) the [**1**]:[**2**]:[**3**] ratios are 73:21:6 and 63:32:5, respectively, for the two complexes. Ratios of k_H/k_N show that the two "planar" *sec*-N centers of the coordinated cyclen ligand are particularly susceptible to inversion, with estimated k_2 values for lone pair inversion being between 5×10^6 and 2×10^8 s^{-1} at 25 °C. The effects of long-range electronegative substituents (*trans* carboxylate-O, *trans* amine-N) and CNC bond angle strain on inversion at metal-coordinated amines is discussed.

Introduction

It has long been recognized that inversion barriers for pyramidal nitrogen ($\Delta G_I^{\ddagger}$) result from geometric and electronic factors causing bond angle restrictions.[2] Nelsen et al.[3] have recently quantified this for a series of monocyclic and bicyclic methylamines by comparing $\Delta H_I^{\ddagger}$ data (DNMR measurements) with departures averaged ground-state CNC bond angles made from the 120° angle expected for a trigonal-planar transition state. A reasonably good correlation was found, and differences were discussed. Coordination of an amine to a metal atom often produces a strained environment about the N center, especially when chelate rings are involved. Often CNC angles, rather than being constrained, are extended well beyond the tetrahedral value of 108°. Mirror imaged forms (both asymmetric and nonasymmetric amines) are often distinguished by their disymmetry with respect to other coordinated ligands, particularly in the case of octahedral complexes; i.e., they are diastereoisomeric and are able to be separated, or distinguished, by physical means. Octahedral Co(III) complexes provide a plethora of such examples, but before inversion can take place an electron pair must be generated at the center to be inverted and generally this occurs by H^+ dissociation, cf. Scheme 1, $k_I(\text{obs}) = k_2K_a/K_w = k_1k_2/k_{-1}$[4] (one consequence of this is that coordinated tertiary amines cannot invert). For most Co(III) amines the acidity constant lies outside the measurable range in aqueous solution ($pK_a > 14$). For these proton lability (k_1) is used as a measure of acidity, on the assumption that the reverse reprotonation rate constant is invariant and at the diffusion controlled limit ($k_{-1} \approx 10^{10}$ s^{-1})[4]. This allows the inversion rate constant (k_2) to be found.

Scheme 1. Stepwise Mechanism for Inversion at a Coordinated Amine Center



Recently we reported[5,6] the synthesis and structures of several [Co(Mecyclen)(S-AlaO)]$^{2+}$ and [Co(cyclen)(S-AlaO)]$^{2+}$ complexes. Various diastereomers are possible in these systems, depending on the disposition of hydrogen atoms attached to the two *sec*-N centers lying in the same plane as the chelated amino acid (S-AlaO). These H atoms may be either *syn*- or *anti*- to the amino acid donors. The five accessible [Co(Mecyclen)(S-AlaO)]$^{2+}$ isomers (Figure 1) are designated **1**−**5**, with **1**−**3** and **4** and **5** having *syn*(Me) and *anti*(Me) configurations, respectively. Similarly, three [Co(cyclen)(S-AlaO)]$^{2+}$ isomers are accessible, **1**−**3**, and these have the same stereochemistry as their Mecyclen counterparts but lack the *ap*-N*Me* group. The *ap*-N centers (*ap* = apical) are constrained by the chelate ring system, with substituents (i.e., H, Me) having only one ground state stereochemistry. These centers are unable to invert. Isomer interconversion (i.e., equilibration) in the [Co(Mecyclen)-(S-AlaO)]$^{2+}$ and [Co(cyclen)(S-AlaO)]$^{2+}$ systems is easily achieved in aqueous solution, is OH^- catalyzed, and occurs via deprotonation of, and then inversion about, the "planar" *sec*-N centers. The *syn*(N),*anti*(O)- and *syn*(O),*anti*(N)- isomers have

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(2) (a) Rauk, A.; Allen, L. C.; Mislow, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 400. (b) Lehn, J. M. *Forsch.* **1970**, 311. (c) Lambert, J. B. *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L., Eds.; Wiley: New York, 1971; Vol. 6.

(3) Nelsen, S. F.; Ippoliti, J. T.; Frigo, T. B.; Petillo, P. A. *J. Am. Chem. Soc.* **1989**, *111*, 1776.

(4) Buckingham, D. A.; Sargeson, A. M. *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L., Eds.; Wiley: New York, 1971; Vol. 6.

(5) Buckingham, D. A.; Clark, C. R.; Rogers, A. J., Simpson, J. *Inorg. Chem.* **1995**, *34*, 3646.

(6) Buckingham, D. A.; Clark, C. R.; Rogers, A. J.; Simpson, J. Paper in preparation.

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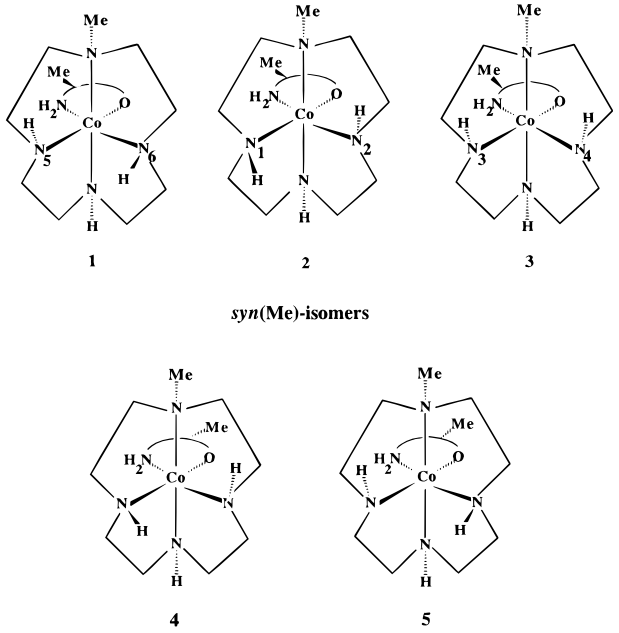


Figure 1. Schematic representations of the five accessible isomers (having either *syn*(Me)- or *anti*(Me)- configurations) in the [Co(Mecyclen)(S-AlaO)]$^{2+}$ system. Isomer **1**: *syn*(Me),*syn*(N),*anti*(O); isomer **2**: *syn*(Me),*syn*(O),*anti*(N); isomer **3**: *syn*(Me),*syn*(N),*syn*(O); isomer **4**: *anti*(Me),*syn*(N),*anti*(O); isomer **5**: *anti*(Me),*syn*(O),*anti*(N). The three accessible [Co(cyclen)(S-AlaO)]$^{2+}$ isomers (**1**, **2**, and **3**) have identical configurations to those above but lack the *ap*-(Me) group. The six N-centers of interest (see text) are designated N_1−N_6.

been found to be the most abundant in the equilibrium mixtures, with the third form, the *syn*(N),*syn*(O)- isomer, being present in much smaller amounts (3−5%).

This collection of isomers provides a rare opportunity, unique as far as we are aware in coordination chemistry, of exploring the ability of different dissymmetric N centers to invert, while maintaining essentially the same molecular framework. The two in-plane N centers have different semistrained environments (as shown by X-ray structures)[5,6] and are in different electronic situations (*cis or trans* to carboxylate-O). Almost nothing is known about the effects of structural strain, or electronic environment, on the ability of *coordinated* N to invert. Also it was of some interest to see if the minor syn(O),syn(N)- isomer was the intermediate between the two major forms or whether it was a side product of only one of them; the latter would imply that the true intermediate was the unknown *anti*(O), *anti*(N)-isomer.

This article then explores the pathways to interconversion of the [Co(Mecyclen)(S-AlaO)]$^{2+}$ and [Co(cyclen)(S-AlaO)]$^{2+}$ isomers and looks at the structural and electronic factors which influence this process. It must be said at the outset that epimerization at the asymmetric S-alanine center, and/or one-ended dissociation and rechelation of the amino acid, does not occur under the pH conditions employed here.[7] Thus, isomer interconversion by processes other than the one described is not possible.

Experimental Section

Preparations. Preparations of salts of the *syn*(O),*anti*(N)-, *syn*-(N),*anti*(O)-, and *syn*(O),*syn*(N))- isomers of [Co(cyclen)(S-AlaO)]$^{2+}$ and *syn*(Me)-[Co(Mecyclen)(S-AlaO)]$^{2+}$ have been reported previously.[5,6]

Kinetic Measurements. Variable temperature (±0.5 °C) ^{1}H NMR spectra were recorded on Varian Gemini 200 or VXR 300 spectrometers using buffered D_2O solutions referenced to 3-(trimethylsilyl)propionic-*2,2,3,3-d*$_4$ acid, sodium salt (TSP). Rates of H/D exchange were obtained by monitoring the decay of amine signals. In a typical experiment ∼12 mg of the Co(III) complex was dissolved in a thermostated buffer solution (0.70 mL), placed in the spectrometer, and allowed to equilibrate (1−5 min). A multiple array experiment was programmed to run at times allowing the collection of a least eight spectra per run (usually between 7−30 min). Peak areas were obtained by integration and corrected relative to the area of a nonexchanging signal. In the case of measurements made using chloroacetate buffer dimethylformamide (∼7 μL) was added to a stock solution of buffer (3 mL) and the signal at 7.92 ppm used as the integration reference. Reactions were followed for at least 2 half-lives, and rate constants were evaluated from linear plots of $\ln(A_t - A_\infty)$ against time. Plots of $\ln(A_t - A_\infty)$ *vs.* time were linear for at least 2 half-lives. A_∞ was assumed to be zero in all experiments except those where overlap of the *trans*(O)-N*H* and *ap*-N*H* signals occurred. In these cases A_∞ was taken as the area of the *ap*-N*H* signal remaining after *ca.* 6 half-lives).

Isomerization of [Co(Mecyclen)(S-AlaO)]$^{2+}$ was monitored in formate or acetate buffered D_2O solutions (25.0 ±0.5 °C, $I = 0.20$ M) by following the growth and/or decay of the appropriate N*Me* signal. Rate constants were obtained from plots of $\ln(A_t - A_\infty)$ or $\ln(A_\infty - A_t)$ *vs.* time, where A_t refers to the area of an N*Me* signal at time *t*, and A_∞ was the peak area at equilibrium. All areas were corrected relative to the total N*Me* peak area.

Rates of isomerization in the [Co(cyclen)(S-AlaO)]$^{2+}$ system were obtained using a Varian 5000 HPLC instrument equipped with a Hewlett Packard 3390A integrator coupled to a Varian 9050 UV/vis detector set at 506 nm. Isomer separation was achieved on a Waters μ-Bondapak C-18 cartridge column contained in a Waters Radial Compression Z-module with use of 25 mM *p*-toluenephosphoric acid ion pairing reagent, which contained 12% methanol and which was adjusted to pH 3.5 (2 mL min^{-1} flow rate). Runs were initiated by adding 6−9 mg of the required isomer as its ClO_4^- salt to 500−600 μL of buffer solution ($I = 0.10$ M) maintained at 25 °C. Aliquots (10 or 15 μL) of the reaction mixture were periodically withdrawn and loaded onto the column via a Waters U6-K injector. The [Co(cyclen)(S-AlaO)]$^{2+}$ isomers were eluted in the order **2** (9 min), **3** (11 min), and **1** (13 min). Reactions were followed for at least 2 half-lives, and rate constants were evaluated from linear plots of $\ln(A_t - A_\infty)$ against time, where A_t was the peak area at time *t*, and A_∞ was the peak area once equilibrium was established. In some cases (longer runs) values of A_∞ were estimated using nonlinear regression methods.

Equilibration Experiments. Isomers **1** and **2** of [Co(Mecyclen)-(S-AlaO)]$^{2+}$ and [Co(cyclen)(S-AlaO)]$^{2+}$ were equilibrated at pD (or pH) ∼ 7 for 5−10 min under the same conditions as those used for the rate measurements ($I = 0.1$, 0.2 M; 25 °C or 60 °C). Following acid quenching (to pH ∼ 2) at various times isomer ratios were found either by ^{1}H-NMR (N*Me* resonance) or reversed phase HPLC separation. Complete equilibration of isomers **1**−**5** for [Co(Mecyclen)(S-AlaO)]$^{2+}$ was achieved using two methods: (1) at 25 °C, pD 10.4 (no buffer), 138 h and (2) at 70 °C in the presence of animal charcoal, 45 min, followed by acid quenching and ^{1}H-NMR measurement. For the latter method longer equilibration times, or higher temperatures, caused extensive *demethylation*[8] with production of [Co(cyclen)(S-AlaO)]$^{2+}$.

Buffers, pH Measurement. Sodium chloroacetate was made by adding 1 M chloroacetic acid to 1 M sodium hydroxide. The mixture was taken to dryness (rotavap.), and the resulting white solid crystallized using the minimum volume of water/methanol and acetone. LR grade sodium acetate and sodium formate were used without further purification. Sodium dimethylphosphate was prepared as described elsewhere.[9] Buffers (0.10 M or 0.20 M, $I = 0.20$ M) were made up in D_2O (3.0 mL), and their acidity was adjusted using DCl (1.0 M). pD was measured using a Radiometer PHM 62 pH meter fitted with G2020B glass and K4040 calomel electrodes and a salt bridge ($NH_4NO_3 = 1.6$ M, $NaNO_3 = 0.20$ M) to separate the test solution from the calomel

(7) At pD 10.8 in D_2O the *anti*(Me)- and *syn*(Me)- isomers of [Co(Mecyclen)(S-AlaO)]$^{2+}$ equilibrate largely without deuteration at α-C*H*; equilibration under this condition thus requires reversible one-ended dissociation of the coordinated amino acid: Buckingham, D. A.; Clark, C. R.; Rogers, A. J. Paper in preparation.

(8) Searle, G. H.; Lincoln, S. F.; Teague, S. G.; Rowe, D. G. *Aust. J. Chem.* **1979**, *32*, 519.

(9) Bunton, C. A.; Mhala, M. M.; Oldham, K. G.; Vernon, C. A. *J. Chem. Soc.* **1960**, 3293.

Table 1. ^{1}H-Exchange Rate Data for [Co(Mecyclen)(S-AlaO)]$^{2+}$ Isomers in D_2O at 25 °C ([Buffer][a] = 0.20 M; I = 0.20 M, $NaClO_4$)

N-*H* proton (ppm)	pD or pD range[e]	10^{12}[OD$^-$]/M or range	10^4k_{obs}/s^{-1} or range	k^f_H/M^{-1} s^{-1}
		Isomer 1		
syn(N) (6.75)	1.30, 2.03[b]	0.424, 0.228	3.0, 17.3	7.4×10^9
anti(O)[g] (7.20)	2.03−3.54(7)[c]	0.23−7.38	2.6−13.2	2.1×10^8
N*H* (*syn*C*Me*) (6.05)	3.54[c]	7.38	∼2.5	∼3.5×10^7
N*H*(*syn*α*CH*) (4.85)	3.87[d]	15.8	1.9	1.1×10^7
*ap*N*H* (6.70)	3.87	15.8	4.5	2.2×10^7
		Isomer 2		
anti (N)[h] (6.80)	1.27−2.04(6)[b]	0.040−0.233	2.1−12.5	5.4×10^9
syn(O) (7.22)	2.04, 3.06[b]	0.233, 2.44	0.22, 2.5	9.7×10^7
N*H*(*syn*α*CH*) (5.75)	3.79[d]	13.1	6.1	4.7×10^7
N*H*(*syn*C*Me*) (4.85)	3.54[c]	7.38	∼7.3	∼1.0×10^8
*ap*N*H* (6.65)	3.79[d]	13.1	2.0	1.5×10^7
		Isomer 3		
syn(N) (6.45)	1.30[b]	0.0442	3.04	7.3×10^9
syn(O) (7.12)	3.12[c]	2.80	3.29	1.2×10^8
		Isomer 4		
syn(N) (6.75)	1.45[b]	0.060	4.1	1.0×10^{10}
anti(O) (7.25)	2.74[c]	1.17	4.1	3.5×10^8
N*H*(*syn*α*CH*) (5.80)	2.74−2.81(3)[c]	1.17−1.48	2.7−3.1	2.3×10^8
N*H*(*syn*C*Me*) (4.50)	3.77[d]	12.5	2.9	2.2×10^7
*ap*N*H* (6.82)	3.31−4.34(3)[d]	4.3−46.5	0.61−6.3	1.3×10^7
		Isomer 5		
anti(N) (6.50)	1.44[d]	0.0586	2.0	3.4×10^9
syn(O) (7.20)	3.04[c]	2.33	2.2	9.5×10^7
N*H*(*syn*α*CH*) (6.05)	4.36[d]	48.7	8.7	1.7×10^7
N*H*(*syn*C*Me*) (5.15)	4.36[d]	48.7	3.8	7.3×10^6
ap N*H* (6.75)	4.36[d]	48.7	5.7	1.1×10^7

[a] In some cases [Buffer] = 0.10 or 0.05 M, to test for general base catalysis; none was found. [b] Dimethylphosphate buffer. [c] Chloroacetate buffer. [d] Formate buffer. [e] For multiple runs, number of determinations is given in parentheses. [f] $k_H = k_{obs}/[OD^-]$; average value for multiple determinations. [g] A temperature-dependence study gave the following data: T/K, 10^4k_{obs}/s^{-1}, pH: 293, 2.3, 3.02; 298, 3.1, 2.88; 303, 4.5, 2.65; 308, 6.0, 2.47. [h] A temperature-dependence study gave the following data; T/K, 10^4k_{obs}/s^{-1}, pH: 288, 1.1, 1.42; 293, 1.7, 1.39; 298, 2.9, 1.33; 298, 2.4, 1.27; 303, 6.6, 1.41; 303, 6.8, 1.41.

electrode. [OH$^-$] was calculated using pK_w (H_2O) = 14.00 at 25 °C. [OD$^-$] was calculated using the empirical formula pD = pH(meter reading) + 0.40[10] and pK_w (D_2O) = 14.81,[11] $\gamma_\pm$ =0.728 (0.20 M), or $\gamma_\pm$ =0.772 (0.10 M)[12] in both D_2O and H_2O. [OD$^-$] at different temperatures was calculated by allowing for the temperature variation of pK_w(D_2O):[13] 15 °C, 15.19; 20 °C, 15.00; 25 °C, 14.81; 30 °C, 14.63; 35 °C, 14.45; 40 °C, 14.29.

Results

^{1}H-Exchange Rate Data. These are given in Tables 1 and 2 and were obtained by following the decay of amine N*H* signals as a function of time by ^{1}H-NMR using dilute DCl solutions or D_2O buffers (I = 0.2 or 0.1 M, $NaClO_4$; 25 °C). In some cases signal overlap occurred,[14] but in this circumstance exchange rates were sufficiently different such that each process could be analyzed separately. Figure 2 gives a more typical example for exchange of the two *ap*-N*H* protons (these are distinguished, *syn*CMe, 6.75 ppm; *syn*αCH, 6.60 ppm) in [Co(cyclen)(S-AlaO)]$^{2+}$ (isomer **1**) at pD 5.0 (DOAc buffer). These data correspond to k_{obs} values of 3.2×10^{-4} and 2.5×10^{-4} s^{-1}, respectively. The rate law, $k_{obs} = k_H[OD^-]$, was followed in all cases where runs at different pD were carried out, and no general base (i.e., buffer) catalysis was found. Values of k_{obs} were reproducible to ±15%, and k_H values listed in the final

(10) Glascoe, P. K.; Long, F. A. *J. Chem. Phys.* **1960**, *64*, 188.
(11) Kingerley, R. W.; LaMer, V. K. *J. Am. Chem Soc.* **1941**, *63*, 3256.
(12) Davies, C. N. *J. Chem. Soc.* **1938**, 2093.
(13) Halpern, B.; Sargeson, A. M.; Turnbull, K. R. *J. Am. Chem. Soc.* **1966**, *88*, 4630.

(14) ^{1}H-NMR spectra in dilute DCl are given in refs 1 and 2. The degree to which signals overlap depends to some extent on ionic strength and pH.

Table 2. ^{1}H-Exchange Rate Data for [Co(cyclen)(S-AlaO)]$^{2+}$ Isomers in D_2O at 25 °C ([Buffer][a] = 0.10 M; I = 0.10 M, $NaClO_4$)

N-*H* proton (ppm)	pD or range[f]	10^{12}[OD$^-$]/M or range	$10^4 k_{obs}$/s^{-1} or range	k_H[g]/M^{-1} s^{-1}
		Isomer 1		
syn(N) (6.55)	1.52,[b] 2.26[b]	0.066, 0.365	1.5, 9.8	2.5×10^9
anti(O) (7.25)	3.14[c]	2.77	1.8	6.6×10^7
*ap*N*H*(*syn*C*Me*) (6.75)	4.91, 5.12[e]	163, 265	2.3, 4.7	1.6×10^6
*ap*N*H*(*syn*α*CH*) (6.60)	4.91, 5.12[e]	163, 265	1.9, 3.7	1.2×10^6
N*H*(*syn*α*CH*) 5.85	4.08[d]	241	6.0	2.5×10^7
N*H*(*syn*C*Me*) (4.95)	5.12[e]	265	1.3	4.8×10^6
		Isomer 2		
anti(N) (6.40)	1.38[b]	0.0481	0.70	1.5×10^9
syn(O) (6.85)	3.08[c]−4.08(3)[d]	2.4−24.1	0.82−10.0	3.9×10^7
*ap*N*H*(*syn*C*Me*) (6.8)	4.96−5.10[e]	183−253	1.5−3.5	1.2×10^6
*ap*N*H*(*syn*αCH) (6.8)	5.10[e]	253	2.3	9.2×10^5
N*H*(*syn*α*CH*) (5.55)	4.08[d]−5.10(4)[e]	24−253	1.4−11.2	5.0×10^6
N*H*(*syn*C*Me*)	4.08[d]−5.10(3)[e]	24−253	0.47−3.6	1.6×10^6
		Isomer 3		
syn(N) (6.90)	1.29[b]	0.0391	2.6	6.6×10^9
syn(O) (6.70)	2.72[c]	1.05	0.61	5.8×10^7

[a] In some cases [Buffer] = 0.20, 0.05 M, to test for general base catalysis; none was found. [b] DCl solution. [c] Chloroacetate buffer. [d] Formate buffer. [e] Acetate buffer. [f] For multiple runs, number of determinations is given in parentheses. [g] $k_H = k_{obs}$/[OD$^-$]; average value for multiple determinations.

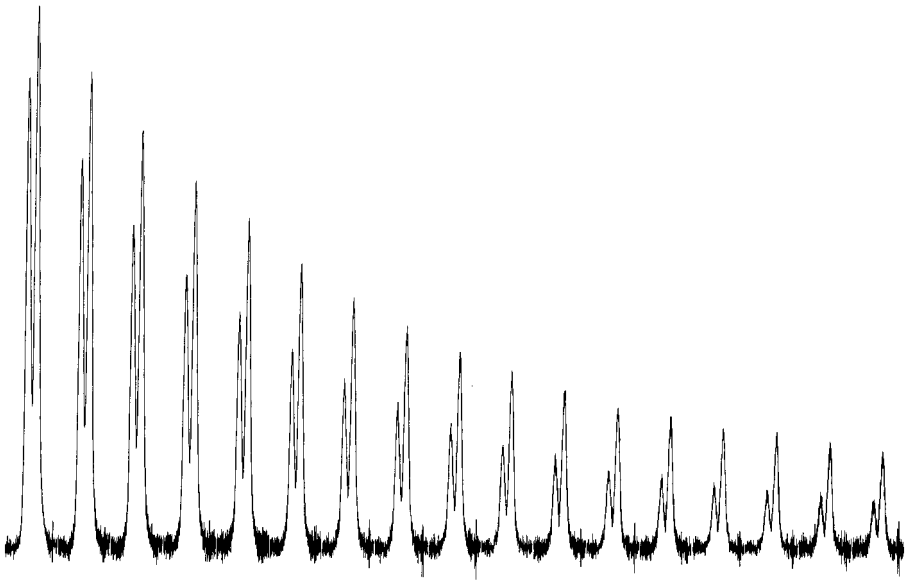


Figure 2. ^{1}H NMR spectra showing changes in the *ap*-N*H* signals (6.75, 6.60 ppm) of *syn*(N),*anti*(O),-[Co(cyclen)(S-AlaO)]$^{2+}$ (isomer **1**) with time. Buffered D_2O solution (DOAc), pD = 5.0, 25 °C, I = 0.1 M. Interval between successive spectra 10.0 min.

columns of Tables 1 and 2 ($k_H = k_{obs}$/[OD$^-$]) are considered accurate to ±25%.

The temperature dependence of the exchange process for the *anti*(O) proton of isomer **1** and for the *anti*(N) proton of isomer **2** in the [Co(Mecyclen)(S-AlaO)]$^{2+}$ system (cf. footnotes to Table 1) gave E_a values of 11.1 ± 1.0 and 8.6 ± 1.0 kcal mol^{-1}, respectively. In order to compare exchange rates for *syn* and *anti* protons *trans* to the **same** donor atom a H-exchange study of the oxalato complex [Co(Mecyclen)($O_2C_2O_2$)]$^+$ was undertaken. Figure S1 gives details of changes occurring in the N*H* region under the pD = 2.81 condition, with the two signals at highest field (6.6, 6.74 ppm) decaying with k_{obs} values of 3.7 × 10^{-4} s^{-1} and 4.6 × 10^{-4} s^{-1}, respectively. These correspond to k_H values of 2.7 × 10^7 M^{-1} s^{-1} and 3.4 × 10^7 M^{-1} s^{-1} (no attempt was made to assign the signals). Thus the orientation (*syn* or *anti*) of these protons does not appear to significantly influence their lability and hence their acidity (*vide infra*). The lowest field signal (7.10 ppm, 2H) can be attributed to *ap*-N*H*, and this proton was again much slower to exchange, k_H = 6.9 × 10^5 M^{-1} s^{-1}.

Isomerization Rates. Isomerization was followed by two techniques: reversed phase HPLC for [Co(cyclen)(S-AlaO)]$^{2+}$

Table 3. Isomerization Rate Data for $[Co(Mecyclen)(S\text{-}AlaO)]^{2+}$ Isomers in D_2O at 25 °C (I = 0.20 M, $NaClO_4$; [Buffer] = 0.20 M)

starting isomer	pD[a]	$10^{12}[OD^-]$/ M or range	$10^4 k_{obs}$/ s^{-1} or range	$k^e_I/M^{-1}\ s^{-1}$
2	3.56(2)[b]	6.73	1.5, 1.2	2.0×10^7 (fast)
3[g]	3.68[c]	10.2	2.0	2.0×10^7 (fast)
2	4.21−5.16(4)[d,f]	34−303	0.29−2.6	8.3×10^5 (slow)
1[h]	5.21[d]	340	2.6	7.8×10^5 (slow)
5	5.22[d]	348	2.6	7.5×10^5 (slow)
4	5.22[d]	348	2.5	7.2×10^5 (slow)

[a] For multiple runs, number of determinations is given in parentheses (often at different pD). [b] Chloroacetate buffer. [c] Formate buffer. [d] Acetate buffer. [e] $k_I = k_{obs}/[OD^-]$; average value. [f] In one run [buffer] = 0.10 M to test for possible general base catalysis; none was found. [g] A temperature dependence study gave the following data; T/K, $10^4 k_{obs}/s^{-1}$, pH: 293, 0.62, 3.53; 298, 2.0, 3.68; 303, 2,9, 3.51; 308, 6.2, 3.56; 308, 7.1, 3.87. [h] A temperature dependence study gave the following data: T/K, $10^4 k_{obs}/s^{-1}$, pH: 298, 0.55, 4.48; 298, 0.54; 4.47; 303, 5.6, 5.23; 303, 5.2, 5.15; 308, 2.4, 4.49; 308, 10.2, 5.21; 313, 5.4, 4.46; 313, 1.7, 3.95.

Table 4. Isomerization Rate Data for $[Co(cyclen)(S\text{-}AlaO)]^{2+}$ Isomers in H_2O at 25 °C (I = 0.10 M, $NaClO_4$; [Buffer] = 0.10 M)

starting isomer	pH[a]	$10^{12}[OH^-]$/ M or range	$10^4 k_{obs}$/ s^{-1} or range	$k^e_I/M^{-1}\ s^{-1}$
3	3.35	29.0	1.6	5.5×10^6 (fast)
2	4.42−5.90(6)	340−7940	0.61−15.4	1.8×10^5 (slow)
1	4.77−5.90(3)	760−7940	1.3−13.6	1.7×10^5 (slow)

[a] For multiple runs, number of determinations is given in parentheses (usually different pH). [b] Formate buffer. [c] Acetate buffer. [d] Mes buffer. [e] $k_I = k_{obs}/[OH^-]$; average value.

in H_2O and ^{1}H-NMR (N*Me* resonance) for $[Co(Mecyclen)(S\text{-}AlaO)]^{2+}$ in D_2O. Both methods involved obtaining peak areas as a function of time. At pH (pD) values above six isomers **1**, **2**, and **3** (both systems) rapidly interconvert, as do isomers **4** and **5** of $[Co(Mecyclen)(S\text{-}AlaO)]^{2+}$. Rate measurements were consequently restricted to more acidic solutions. These data are given in Tables 3 and 4 and again the processes are OH^- (OD^-) catalyzed; viz. $k_{obs} = k_I[OH^-]$ (or $k_I[OD^-]$). Second-order rate constants (k_I values) are given in the final columns of the tables.

Two separate rate processes were identified, $k_{I(fast)}$ and $k_{I(slow)}$. Figure 3A shows changes in the N*Me* region of isomer **3**-$[Co(Mecyclen)(S\text{-}AlaO)]^{2+}$ vs time for reaction at pD 3.68. It can be seen that **2** is formed initially (lowest field signal), with the [**2**]/[**3**] ratio reaching a pseudoequilibrium value (0.29) well before much **1** (highest field signal) is formed. Eventually this **2**/**3** mixture relaxes to come into equilibrium with **1**, and with $k_{I(slow)} \sim 3\%\ k_{I(fast)}$ at this pD. Figure 3B shows this slower process accelerated at higher $[OD^-]$ (pD 5.06), with the final spectrum after 280 min representing the final equilibrium distribution (*vide infra*). Likewise for the $[Co(cyclen)(S\text{-}AlaO)]^{2+}$ inversions. Figure 4A shows HPLC chromatograms for the faster relaxation process **3** ↔ **2** at pH 3.35, and Figure 4B shows (starting with isomer **1**) the relaxation of this species into the **3**/**2** + **1** mixture at higher pH (5.22). For both systems it is clear that $k_{I(fast)}$ represents equilibration of **3** with **2**, while $k_{I(slow)}$ represents equilibration of these species with **1**. The derived second-order rate constants (k_I, Tables 3 and 4) are considered accurate to ±10% and within this error are independent of starting isomer (**4** or **5**, **1** or **2** (both systems)). The temperature dependence for isomerization **3** ↔ **2** and **1** ↔ **3** + **2** in the $[Co(Mecyclen)(S\text{-}AlaO)]^{2+}$ system gave E_a values of 14 ± 1.5 and 15 ± 2 kcal mol^{-1}, respectively (cf. footnotes to Table 3).

Equilibrium Distributions and Energy Differences. The data, Table 5, were obtained from ^{1}H-NMR spectra (N*Me* resonance) or reversed-phase HPLC chromatograms, using samples which had been pre-equilibrated under the conditions given. The equilibrium distributions are pH independent and,

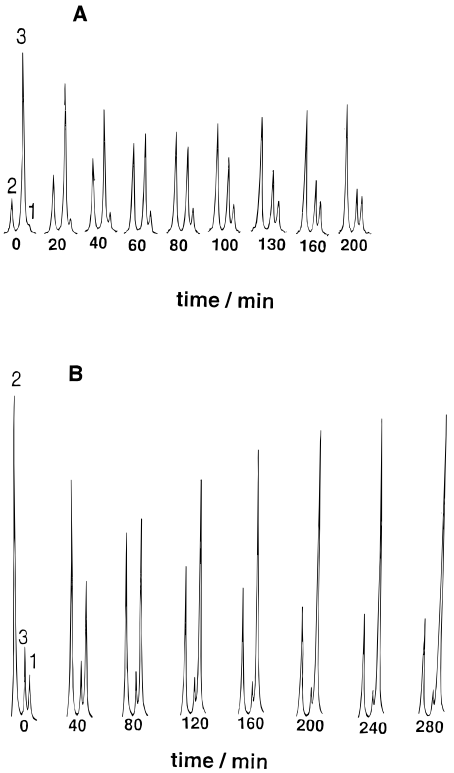


Figure 3. Changes in ^{1}H NMR spectra (N-*Me* region) during the two processes leading to equilibration in the *syn*(Me)-$[Co(Mecyclen)(S\text{-}AlaO)]^{2+}$ system, D_2O solution, 25 °C, I = 0.2 M. A: Isomer **3** at pD = 3.68 corresponding to k_{fast}. B: Isomer **2** at pD = 5.06 corresponding to k_{slow}.

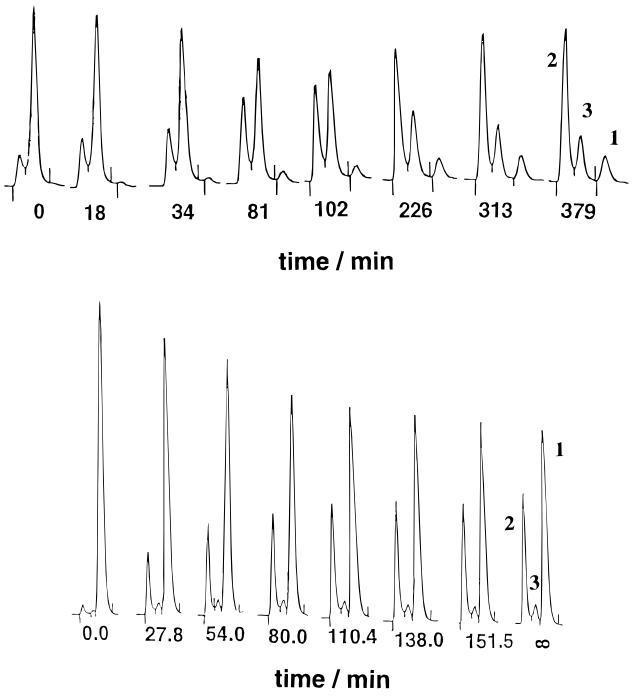


Figure 4. HPLC chromatograms showing the variation in isomer distribution with time during the two processes leading to equilibration in the $[Co(cyclen)(S\text{-}AlaO)]^{2+}$ system, H_2O solution, 25 °C, I = 0.1 M. A: Isomer **3** at pH = 3.35 corresponding to k_{fast}. B: Isomer **1** at pH = 5.22 corresponding to k_{slow}. Species emerge in the order (left to right) **2**, **3**, and **1**. Separation conditions are given in the Experimental Section.

Table 5. Equilibrium Isomer Distributions and Equilibrium Constants: Energies for [Co(Mecyclen)(S-AlaO)]$^{2+}$ and [Co(cyclen)(S-AlaO)]$^{2+}$ Complexes

system/conditions	concn ratio/%					$K_{n/1}$; $\Delta G_{n/1}$[a] (kcal mol^{-1})			
				[Co(Mecyclen)(S-AlaO)]$^{2+}$					
	1	**2**	**3**	**4**	**5**	$n = 2$	**3**	**4**	**5**
pH 7, 25 °C, 5 min	73	21	6			0.29; 0.73	0.082; 1.5		
pD 7, 60 °C, 2 min	71	21	8			0.30; 0.72	0.11; 1.3		
pD 7, 25 °C, 10 min				66	34				0.52; 0.39
pD 10.4, 25 °C, 138h	51	15	4	20	10	0.29; 0.72	0.078; 1.5	0.39; 0.55	0.20; 0.96
activ. C, 70 °C, 45 min	55	16	3.5	17	9	0.29; 0.73	0.064; 1.6	0.31; 0.69	0.16; 1.1
				[Co(cyclen)(S-AlaO)]$^{2+}$					
	1	**2**	**3**			$n = 2$	**3**		
pH 7, 25 °C, 5 min	63	32	5			0.51; 0.40	0.079; 1.5		

[a] Relative to isomer **1** (or relative to isomer **4** for the **4**/**5** system).

as indicated by the [Co(Mecyclen)(S-AlaO)]$^{2+}$ results, are also essentially temperature independent (i.e., enthalpy differences between the three isomers, $\Delta H_{n/1}°$ (n = 2, 3), are essentially zero). Equilibration between the two groups of isomers (*syn*(Me)- and *anti*(Me)- configurations) in the latter system occurs via one-ended dissociation of the S-alaninato ligand at pD 10.8[2] and via the Co(II) complex when activated charcoal is used.[15] Equilibrium constants ($K_{n/1}$; $n = 2-5$) and experimental free energy differences $\Delta G_{n/1}$ (kcal mol^{-1}) for the isomers under the conditions specified are also listed.

Discussion

H-Exchange (Tables 1 and 2). This is very fast for both "planar" amine centers of the coordinated macrocycle. Second-order rate constants (k_H) for exchange at sites *trans* to carboxylate-O, 10^9-10^{10} M^{-1} s^{-1} (25 °C, I = 0.1, 0.2 M), are at, or are very close to, the diffusion limit for deprotonation by OD$^-$ in aqueous solution,[16] eq 1. This suggests a pK_a (N-H ionization) in the vicinity of, or below, that for D_2O (*ca.* 16.5).

$$\text{Co-NHR}_1\text{R}_2 + \text{OD}^- \overset{k_H}{\rightleftharpoons} \text{Co-NR}_1\text{R}_2^- + \text{HOD} \qquad (1)$$

Indeed, for [Co(cyclen)(S-AlaO)]$^{2+}$initial absorbance data (300 nm, obtained within 5 ms) for strongly alkaline aqueous solutions ([OH$^-$] = 0.10−1.0 M) suggests generation of significant amounts of conjugate base. These data[17] analyze to give $K_a = 2.0 \times 10^{-14}$ M (25.0 °C, I = 1.0 M, $NaClO_4$),[15] pK_a = 13.7 for the isomer mixture **1** + **2** + **3** (Table 5). The *sec*-N*H* centers *trans* to carboxylate-O are expected to be more acidic than those *cis* to carboxylate-O (i.e., *trans* to amine N) since exchange at the latter site is about 10× slower ($k_H \sim 10^8$ M^{-1} s^{-1}). This is the usual pattern for Co(III)-acido complexes, with N*H* sites *trans* to an electronegative group invariably being more labile (and hence more acidic) than those *trans* to neutral amine.[18] The new aspect here is that the present N*H* protons appear to be the most acidic yet examined in Co(III)-amine chemistry. The reason for this is suggested to be steric strain about the *sec*-N*H* center, and this will be further examined below, together with the inversion property.

The *ap*-N*H* centers, which are under considerably less strain (*vide infra*) but are otherwise similar, are considerably less labile, $k_H = 10^6-10^7$ M^{-1} s^{-1}. The primary NH_2 protons of the coordinated amino acid are also less labile, $k_H = 10^7-10^8$ M^{-1} s^{-1}. Also, it appears that the N*H* protons of [Co(Mecyclen)(S-AlaO)]$^{2+}$ are, on average, three times more labile than those of [Co(cyclen)(S-AlaO)]$^{2+}$. This again could arise from increased strain due to the methyl substituent, but this is not apparent in the X-ray structural data (*vide infra*, Table 8). However the [Co(Mecyclen)(S-AlaO)]$^{2+}$ ion is more prone to complete loss of the amino acid moiety (at high pH, >12), which suggests a decreased stability. The orientation of the planar N*H* proton has only a small effect on its lability (acidity) as shown by the data for the *syn* and *anti* protons of [Co(cyclen)-($O_2C_2O_2$)]$^+$, both of which are *trans* to carboxylate-O (k_H = 2.7, 3.4 × 10^7 M^{-1} s^{-1}). Other studies[17] agree with this and further suggest that it is the *anti*-N*H* proton which is the more acidic.[19,21] This proton is remote from the electronegative donor atom and hence more likely to be abstracted by OD$^-$.

Table 6. Observed ^{1}H-Exchange (k_H) and Isomerization (k_N) and Estimated Inversion (k_2) Rate Constants for syn(Me)-[Co(Mecyclen)(S-AlaO)]$^{2+}$ and [Co(cyclen)(S-AlaO)]$^{2+}$ Complexes at 25 °C (cf. Scheme 2)

amine center	k_H/ M^{-1} s^{-1}	k_N/ M^{-1} s^{-1}	k_H/k_N ratio	k^c_2/s^{-1}
	syn(Me)-[Co(Mecyclen)(S-AlaO)]$^{2+}$ [a]			
N_1	5.4×10^9	4.4×10^6	1200	8×10^6
N_2	9.6×10^7			
N_3	7.3×10^9	1.56×10^7	470	2×10^7
N_4	1.2×10^8	2.6×10^6	46	2×10^8
N_5	7.4×10^9			
N_6	2.1×10^8	2.2×10^5	950	1×10^7
	[Co(cyclen)(S-AlaO)]$^{2+}$ [b]			
N_1	1.5×10^9	8×10^5	2000	5×10^6
N_2	4.0×10^7			
N_3	6.4×10^9	4.7×10^6	1400	7×10^6
N_4	5.5×10^7	7.5×10^5	70	1×10^8
N_5	2.5×10^9			
N_6	6.6×10^7	6.5×10^4	1000	1×10^7

[a] k_N values are based on the average values $K_{3/2}$ = 0.28, $K_{1/2}$ = 3.48, $k_{fast} = 2.0 \times 10^7$ M^{-1} s^{-1}, $k_{slow} = 8.0 \times 10^5$ M^{-1} s^{-1} (cf. Tables 3 and 5). [b] k_N values are based on $K_{3/2}$ = 0.16, $K_{1/2}$ = 1.97, $k_{fast} = 5.5 \times 10^6$ M^{-1} s^{-1}, $k_{slow} = 1.75 \times 10^5$ M^{-1} s^{-1} (cf. Tables 4 and 5). [c] Rounded to one significant figure.

Isomerization Reactions and Rate Constants. The observed first-order in [OH$^-$] dependence for the **1** ↔ **2** interconversion, a process whereby *both* planar N*H* centers become inverted, means that either **3**, or the unobserved *anti*(N),*anti*(O)-isomer, must be formed as an intermediate with deprotonation and inversion at *one* center being overall rate-determining. Synchronous inversion at both N*H* centers, such as has been

(15) Searle, G. H.; Keene, F. R.; Lincoln, S. F., *Inorg. Chem.* **1978**, *17*, 2362 and earlier references therein.
(16) Bell, R. P. In *The Proton in Chemistry*; Cornell University Press: 1973; Chapter 7.
(17) Buckingham, D. A.; Clark, C. R. Data to be reported.
(18) Tobe, M. L. *Adv. Inorg. Bioinorg. Mech.* **1983**, *2*, 1.
(19) Tobe, M. L.; Sosa, M. E. *J. Chem. Soc., Dalton Trans.* **1985**, 475.
(20) Buckingham, D. A.; Cresswell, P. J.; Dellaca, R. J.; Dwyer, M.; Gainsford, G.J.; Marzilli, L. G.; Maxwell, I. E.; Robinson, W. T.; Sargeson, A. M.; Turnbull, K. R. *J. Am. Chem. Soc.* **1974**, *96*, 1713.
(21) Buckingham, D. A.; Dwyer, M.; Gainsford, G. J.; Jason Ho, V.; Marzilli, L. G.; Robinson, W. T.; Sargeson, A. M.; Turnbull, K. R. *Inorg. Chem.* **1975**, *14*, 1739.

Table 7. Observed Proton Exchange and Inversion Rate Constants and Activation Enthalpies for Metal-Coordinated Amine Systems

complex	k_H/ M^{-1} s^{-1}	k_N/ M^{-1} s^{-1}	k_H/k_N[a]	ΔH_H^* [b]/ kcal mol^{-1}	ΔH_N^* [b]/ kcal mol^{-1}	ref (T/°C)
$[Co(O_2C_2O_2)_2(Meen)]^-$	5×10^4	3×10^2	2×10^2			c
$[Co(acac)_2(Meen)]^+$	9×10^3	6×10^{-2}	2×10^5			*d* (25)
trans-$[Co(NO_2)_2(Meen)_2]^+$	9.3×10^4	1.0	9×10^4	16	28	*e* (25)
$[Co(NH_3)_4(Meen)]^{3+}$	3.0×10^7	1.2×10^2	2.5×10^5	14	24	*f* (34.3)
$[Pt\ en(Meen)]^{2+}$	1.9×10^5	4×10^2	5×10^2			*m* (34)
trans-$[PtCl_2(en)(Meen)]^{2+}$	2×10^{10}	3.3×10^5	6×10^4			*m* (34)
$\Delta(S)[Co(Hbg)_2(sar)]^{2+}$	3.6×10^3	11	3×10^2	11	21	*g* (39.6)
$[Co(NH_3)_4(sar)]^{2+}$	1.2×10^8	1.7×10^4	7×10^3	14	19	*h* (33.3) (30.3)
β_1-RR-$[Co(trien)(glyO)]^{2+}$	8.3×10^8	6.1×10^2	1×10^6			*i* (34,25)
β_1-RS-$[Co(trien)(glyO)]^{2+}$	8.1×10^8	5.0	2×10^6			*i*
β_2-RR-$[Co(trien)(glyO)]^{2+}$	6.0×10^7	3.5×10^2	2×10^5			*j*
β_2-RS-$[Co(trien)(glyO)]^{2+}$	1.8×10^7	35	5×10^5			*j*
$[Co(dien)_2]^{3+}$	1.0×10^8	1.2×10^2	8×10^5	13.5	23.5	*k* (35)
s-$[Co(trenen)N_3]^{2+}$	1.3×10^9	2.9×10^6	4×10^6		23	*l* (34)
syn(Me),*syn*(N),*anti*(O)-$[Co(Mecyclen)(S\text{-}AlaO)]^{2+}$	2.1×10^8	2.2×10^5	1×10^3	9	13	this work
syn(Me),*syn*(O),*anti*(N)-$[Co(Mecyclen)(S\text{-}AlaO)]^{2+}$	5.4×10^9	4.4×10^6	1×10^3	6	12	this work
syn(Me),*syn*(N),*syn*(O)-$[Co(Mecyclen)(S\text{-}AlaO]^{2+}$	7.3×10^9	1.6×10^7	5×10^2			this work
syn(N),*anti*(O)-$[Co(cyclen)(S\text{-}AlaO)]^{2+}$	1.2×10^8	2.6×10^6	5×10^1			this work
syn(O),*anti*(N)-$[Co(cyclen)(S\text{-}AlaO)]^{2+}$	6.6×10^7	6.5×10^4	1×10^3			this work
syn(N),*syn*(O)-$[Co(cyclen)(S\text{-}AlaO)]^{2+}$	1.5×10^9	8×10^5	2×10^3			this work
	6.4×10^9	4.7×10^6	1×10^3			
	5.5×10^7	7.5×10^5	7×10^1			this work

[a] Rounded to one significant figure. [b] Rounded to the nearest kcal mol^{-1}. [c] Ma, G.; Hibino, T.; Kojima, M.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1053. [d] Ma, G.; Kojima, M.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2547. [e] Buckingham, D. A.; Marzilli, L. G.; Sargeson, A. M. *J. Am. Chem. Soc.* **1967**, *89*, 3428. [f] Buckingham, D. A.; Marzilli, L. G.; Sargeson, A. M. **1967**, *89*, 825. [g] Kawaguchi, H.; Matsuki, M.; Ama, T.; Yasui, T. *Bull Chem. Soc. Jpn.* **1986**, *59*, 31. [h] Halpern, B.; Sargeson, A. M.; Turnbull, K. R. *J. Am. Chem. Soc.* **1966**, *88*, 4630. [i] Buckingham, D. A.; Cresswell, P. J.; Dellaca, R. J.; Dwyer, M.; Gainsford, G. J.; Marzilli, L. G.; Maxwell, I. E.; Robinson, W. T.; Sargeson, A. M.; Turnbull, K. R. *J. Am. Chem. Soc.* **1974**, *96*, 1713. [j] Buckingham, D. A.; Dwyer, M.; Gainsford, G. J.; Jason, Ho.V.; Marzilli, L. G.; Robinson, W. T.; Sargeson, A. M.; Turnbull K. R. *Inorg. Chem.* **1975**, *14*, 1739. [k] Searle, G. H.; Keene, F. R. *Inorg. Chem.* **1972**, *11*, 1006. [l] Buckingham, D. A.; Marzilli, P. A.; Sargeson, A. M. *Inorg. Chem.* **1969**, *8*, 1595. [m] Buckingham, D. A.; Marzilli, L. G.; Sargeson, A. M. *J. Am. Chem. Soc.* **1969**, *91*, 5227.

suggested[22] for **1** ↔ **2** isomerization in $[Co(cyclen)(S\text{-}NH_2CH_2\text{-}CH_2CH(CH_3)S)]^{2+}$, is impossible. The early appearance of **3** when starting with **1** or **2**, and the observation that **3** isomerizes *directly* into a combination of both **1** and **2**, confirms **3** as this intermediate. The two relaxation processes, given by Scheme 2, then follow. The faster equilibration involves only **2** and **3**, and values of k_{N1} and k_{N3} can be evaluated from the $k_{I(fast)}$ data, eq 2, and $K_{3/2} = k_{N1}/k_{N3}$ ($= K_{3/1}/K_{2/1}$, cf. Table 5). Likewise for the slower relaxation process, eq 3, where the rate data allows

$$k_{I(fast)} = k_{N1} + k_{N3} \tag{2}$$

estimation of k_{N4} and k_{N6} using $K_{2/1}$ ($= k_{N6}k_{N3}/k_{N1}k_{N4}$), cf. Table

$$k_{I(slow)} = k_{N1}k_{N4}/(k_{N1} + k_{N3}) + k_{N6} \tag{3}$$

5. Table 6 gives these derived rate constants for both systems. It can now be seen that the small amount of **3** present in the equilibrium mixtures results from larger k_{N3}, k_{N4} values compared to k_{N1}, k_{N6}; i.e., deprotonation and inversion at N_3 and N_4 (isomer **3**) is easier than at N_1 (isomer **2**) or N_6 (isomer **1**). The failure to detect the *anti*(N),*anti*(O)- isomers (both systems) must mean that the k_{N2}, k_{N5} rate constants are somewhat smaller again.

Inversion Mechanism. The commonly accepted mechanism[4] for inversion at coordinated N involves deprotonation (k_1) followed by inversion of the lone pair (k_2), cf. Scheme 1. This leads to the following expression for the derived inversion rate constants

$$k_N = k_1k_2/(k_{-1} + k_2) \tag{4}$$

which reduces to

$$k_N = k_1k_2/k_{-1} \tag{5}$$

since reprotonation of the lone pair is, in every case so far examined, preferable to inversion ($k_{-1} > k_2$). The observed proton exchange rate constant k_H is approximately equal to k_1 (a small isotope effect favouring deprotonation by OD^- compared to OH^- is to be expected[23]), and the value of k_{-1} in water (*ca.* 10^{10} s^{-1}) leads to the inversion rate constants (k_2) listed in the final column of Table 6. These represent very fast inversion rates, but the values are not too different from those found for uncoordinated amines with reasonably bulky substituents, e.g., 2.0×10^5 s^{-1} (25 °C) for di(*n*-butyl)methylamine.[24] It appears that coordination to a metal atom does not alter the ability of the lone pair to invert to any large extent. However, it is more usual when dealing with "quaternized" amines of unknown pK_a to compare k_H/k_N values, since these reflect the relative ability of the lone pair to reprotonate and invert, $k_H/k_N = k_{-1}/k_2$. Such values are also listed in Table 6 and are compared with those for other coordinated amines in Table 7. Two points immediately emerge. Firstly, the k_H/k_N ratios for the cyclen and Mecyclen complexes are $\sim 10^3$ smaller than those found for other similarly charged and structurally related amines; i.e., 10^2-10^3 for the present complexes vs 10^5-10^6 for β_1- and β_2-$[Co(trien)(GlyO)]^{2+}$. Secondly, the k_H/k_N ratio for reaction at N_4 (46 and 70; i.e., $< 10^2$) is significantly smaller than the value for reaction at N_1, N_3, and N_6 (by a factor of at least ten).

(22) Kojima, M.; Nakabayashi, K.; Ohba, S.; Okumoto, S.; Saito, Y.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 277.

(23) Bunton, C. A.; Shiner, V. J. *J. Am. Chem. Soc.* **1961**, *83*, 3207.

(24) Dutler, R.; Rauk, A.; Sorensen, T. S. *J. Am. Chem. Soc.* **1987**, *109*, 3224.

Table 8. Comparison of Bond Angles about Some Coordinated *sec*-Amine Centers

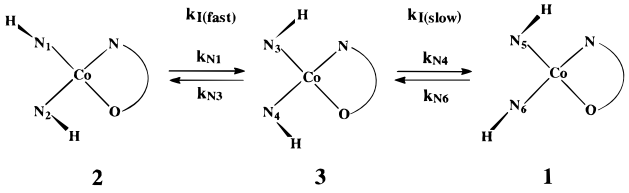
complex	NH center	CNC bond angle (deg)	ref
$[Co(cyclen)(O_2CO)](C1O_4)\cdot H_2O$	*syn*(O)	118.4	*a*
	anti(O)	116.2	
	ap	112.1, 112.7	
$[Co(cyclen)(NO_2)_2]Cl$	*syn*(N)	118.5	*b*
	anti(N)	113.4	
	ap	111.1, 110.9	
$[Co(cyclen)(S\text{-}NH_2CH_2CH_2CH(CH_3)S)]ZnCl_4$	*syn*(S)	120.2	*c*
	anti(N)	115.6	
	ap	110.3, 111.10	
$[Co(cyclen)(acac)](ClO_4)\cdot H_2O$	*syn*(O)	120.2	*d*
	anti(O)	116.3	
	ap	113.8, 109.3	
$[Co(cyclen)(acacaBr)](ClO_4)_2\cdot 0.5H_2O$	*syn*(O)	119.7	*d*
	anti(O)	115.9	
	ap	111.0, 112.1	
syn(N),*anti*(O)-	*syn*(N)	118	*e*
$[Co(cyclen)(S\text{-}AlaO)]I_2\cdot H_2O$	*anti*(O)	113	
	ap	108, 111	
syn(O),*anti*(N)-	*syn*(O)	119.3	*e*
$[Co(cyclen)(S\text{-}AlaO)](ClO_4)_2\cdot H_2O$	*anti*(N)	115.5	
	ap	111.1, 112.3	
syn(N),*syn*(O)-	*syn*(N)	116.8	*e*
$[Co(cyclen)(S\text{-}AlaO)]ZnBr_4$	*syn*(O)	115.9	
	ap	111.6, 112.0	
syn(N),*anti*(O),*syn*(Me)-	*syn*(N)	117.4	*f*
$[Co(Mecyclen)(S\text{-}AlaO)](ClO_4)_2\cdot H_2O$	*anti*(O)	115.2	
	ap	110.8	
syn(N),*anti*(O),*anti*(Me)-	*syn*(N)	117.5	*f*
$[Co(Mecyclen)(S\text{-}AlaO)](ClO_4)_2\cdot H_2O$	*anti*(O)	117.2	
	ap	110.9	
syn(O),*anti*(N),*syn*(Me)-	*syn*(O)	119.3	*f*
$[Co(Mecyclen)(S\text{-}AlaO)]ZnCl_4\cdot H_2O$	*anti*(N)	116.5	
	ap	111.1	
$(RSRS)\text{-}[Co(Et_4cyclen)(S\text{-}AlaO)](ClO_4)_2$	*anti*(O)	118.5	*g*
	anti(N)	117.9	
	ap	116.6,116.3	
$(RSRS)\text{-}[Co(Et_4cyclen)(S\text{-}ThreO)](ClO_4)_2$	*anti*(O)	118.4	*g*
	anti(N)	118.2	
	ap	115.5,116.6	
$(SSSR)\text{-}[Co(Et_4cyclen)(S\text{-}ThreO)](ClO_4)_2$	*anti*(O)	120.5	*g*
	syn(N)	115.4	
	ap	112.6,112.0	
$s\text{-}[Co(trenen)N_3](NO_3)_2\cdot H_2O$		117.4	*h*
$\beta_1(RS)\text{-}[Co(trien)(GlyO)]I_2\cdot 0.5H_2O$	*syn*(N)	117.8	*i*
	ap	114.5	
$\beta_1(RR)\text{-}[Co(trien)(GlyO)]I_2\cdot 0.5H_2O$	*anti*(N)	115.2	*i*
	ap	113.6	
$\beta_2(RS)\text{-}[Co(trien)(GlyO)]Cl_2\cdot H_2O$	*syn*(O)	117($\lambda\lambda\delta$), 114($\delta\lambda\delta$)	
	ap	110($\lambda\lambda\delta$), 117($\delta\lambda\delta$)	*j*
$\beta_2(RR)\text{-}[Co(trien)(GlyO)]Cl_2\cdot H_2O$	*anti*(O)	113.6($\delta\delta\lambda$), 113.0($\lambda\delta\lambda$)	
	ap	111.5($\delta\delta\lambda$), 111.9($\lambda\delta\lambda$)	*j*

[a] Loehlin, J. H.; Fleischer, E. B. *Acta Cryst.* **1976**, *B32*, 3063. [b] Iitaka, J.; Shina, M.; Kimura, E. *Inorg. Chem.* **1974**, *13*, 2886. [c] Kojima, M.; Nakabayashi, K.; Ohba, S.; Okumoto, S.; Saito, Y.; Fujika. J. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 277. [d] Matsumoto, N.; Hirano, A.; Hana, T.; Ohyoshi, A. *J. Chem. Soc., Dalton Trans.* **1983**, 2405. [e] Buckingham, D. A.; Clark, C. R.; Rogers, A. J.; Simpson, J. *Inorg. Chem.* Submitted for publication. [f] Buckingham, D. A.; Clark, C. R.; Rogers, A. J.; Simpson, J. *Inorg. Chem.* **1995**, *34*, 3646. [g] Tsuboyama, S.; Shiga, Y.; Takasyo, Y.; Chijimatsu, T.; Kobayashi, K.; Tsuboyama, K.; Sakurai, T. *J. Chem. Soc., Dalton Trans.* **1992**, 1783. [h] Maxwell, I. E. *Inorg. Chem.* **1971**, *10*, 1782. [i] Buckingham, D. A.; Cresswell, P. J.; Dellaca, R. J.; Dwyer, M.; Gainsford, G. J.; Marzilli, L. G.; Maxwell, I. E.; Robinson, W. T.; Sargeson, A. M.; Turnbull, K. R. *J. Am. Chem. Soc.* **1974**, *96*, 1713. [j] Buckingham, D. A.; Dwyer, M.; Gainsford, G. J.; Jason, Ho. V.; Marzilli, L. G.; Robinson, W. T.; Sargeson, A. M.; Turnbull K. R. *Inorg. Chem.* **1975**, *14*, 1739.

There are two possible reasons for these differences. One is that the rate of lone pair reprotonation (k_{-1}) may not be constant for the weakly basic amido centers considered here and may be appreciably less than the diffusion limit of *ca.* 10^{10} s^{-1}. Alternatively, some centers may be particularly susceptible to inversion. The former possibility is not particularly attractive since, in general, the more acidic amines are not obviously characterized by small k_H/k_N values (Table 7); i.e., there seems to be no correlation between k_H/k_N and pK_a or k_H. Thus the ratio is 6×10^4 for *trans*-$[PtCl_2(en)(Meen)]^{2+}$ ($pK_a = 10.6$), 5×10^2 for $[Pt(en)(Meen)]^{2+}$ ($pK_a > 14$), and 4×10^6 for $[Co(trenen)N_3]^{2+}$ (for which $k_H = 1.3 \times 10^9$ M^{-1} s^{-1})). Some correspondence might have been expected if variation in k_{-1} were responsible. We believe therefore that the differences arise through variation in k_2, with the planar *sec*-N lone pair in the present complexes being more prone to inversion, and with that on N_4 being particularly so (cf. k_2 values, Table 6).

Factors Affecting k_2. The acidity of the coordinated amine appears to be an influencing factor, with those centers *trans* to electronegative donors having smaller inversion rate constants (larger k_H/k_N values) than those *trans* to neutral amines. Thus (cf. Table 7) the very acidic *sec*-N*H* center of *s*-$[Co(trenen)N_3]^{2+}$($k_H = 1.3 \times 10^9$ M^{-1} s^{-1}) also has a large k_H/k_N ratio (4×10^6), and the β_1-$[Co(trien)(GlyO)]^{2+}$ complex in which the

Scheme 2. Representation of Isomerization via Inversion about the Two N−H Centers *Trans* to the Amino Acid Chelate



sec-NH center is trans to carboxylate-O has both larger k_H and k_H/k_N values (by factors of 10) than the structurally very similar β_2-isomer where the exchanging center is trans to NH_2R. Likewise for the present complexes, k_2 at N_1 (8×10^6 s^{-1} and 5×10^6 s^{-1}; Table 6) is somewhat smaller than the value at N_6 (1×10^7 s^{-1}). However a different order has been found by Fujita et al.[25] for a series of $[Co(Meen)(acac\text{-}X)_2]^+$ complexes (X = CH_3, H, Cl, NO_2); increasing electronegativity in X gives rise to *smaller* k_D/k_N values (1×10^5, 1.3×10^5, 1×10^4, 4×10^3 respectively, 34 °C), suggesting larger inversion rates. This is not generally so with organic amines, however,[26] as has been shown recently with a series of X-substituted azabicyclononanes.[27] In the latter case this has been attributed to a decreasing ease of forming the planar cation radical with increasing electron withdrawal. The new feature with coordinated amines is in having the electronegative group far removed from the N center, so that "electronegative" effects rather than direct orbital overlap must be responsible. To test this property further it would be of interest to compare k_2 values with Co(III)/Co(II) reduction potentials for the deprotonated amine conjugate base, since similar trends should be evident.

Possibly just as important as electron density, however, is the structural strain about the amido center caused by the attached chelate rings. The question of the timing of conformational change vs lone pair inversion has been raised previously for coordinated amines[28,29] but with no clear answer. Our recent NMR results (^{1}H, NOE),[5,6,30] however, infer that these cyclen and Mecyclen complexes are less conformationally labile in aqueous solution than their ethylenediamine (en) or triethylenetetramine (trien) counterparts. The present results suggest that bond angle strain about the N center plays an important role, with increased strain lowering the barrier to inversion. Thus the almost tetrahedrally coordinated *ap*-N*H* centers *cannot* invert, whereas the planar N centers have CNC bond angles approaching the planar 120° condition, cf. Table 8. As

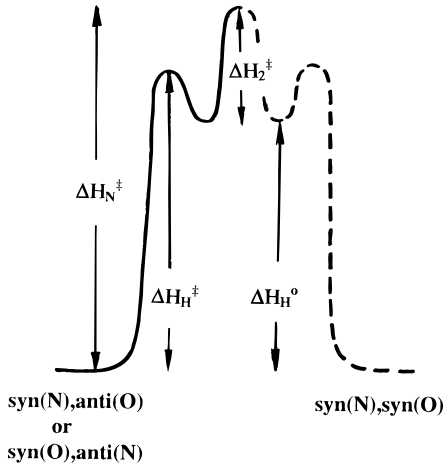


Figure 5. Energy diagram for inversion at a coordinated amine center.

mentioned in the Introduction Nelsen[3] has recently drawn comparisons between $\Delta(\Delta H^{\ddagger})$ for inversion and CNC bond angle for a series of aza-ring systems of increasing size (following earlier work[27,1b,c]), and the correlation seems good. Coordinated amines fit this pattern, with the planar N*H* centers of the Mecyclen and cyclen complexes having much larger k_2 values than the similar centers in the β_1- and β_2-[Co(trien)(GlyO)]$^{2+}$ complexes which lack this overall ring strain. The *syn*-N*H* centers, with the largest CNC bond angles, are particularly prone to invert (cf. isomer **3**). The very large k_2 value at N_4 (*syn*(O)) may result from an additional electrostatic effect whereby the lone pairs on deprotonated N and carboxylate-O interact repulsively. Likewise, that at N_3 (*syn*(N)) may be stabilized by H-bonding to the NH_2 group of the amino acid. Such features require further examination.

Activation Enthalpies. The observed $\Delta H^{\ddagger}$ values for H-exchange (8.6 and 6.1 kcal mol^{-1}) and isomerization (12.5 and 11.5 kcal mol^{-1}) for isomers **1** and **2**, respectively are less than those reported previously for other complexes, cf. Table 6. Although $\Delta H_2^{\ddagger}$ for inversion (cf. Figure 5) is almost certainly greater than $\Delta H_N^{\ddagger} - \Delta H_H^{\ddagger}$ (4−5 kcal mol^{-1}), the absence of known $\Delta H_H°$ for deprotonation makes its exact value unknown (note also that $\Delta H_1° \sim \Delta H_3° \sim \Delta H_2°$).[31] However the relative acidity of these planar amine centers suggests a not too different $\Delta H_2^{\ddagger}$ value. This would be consistent with noncoordinated amines, e.g., $\Delta H_2^{\ddagger} = 6.7$ kcal mol^{-1} for di(*n*-butyl)methylamine ($k_2 = 2.0 \times 10^5$ s^{-1}).[24]

Supporting Information Available: Figure S1 showing ^{1}H NMR spectra during amine proton exchange in $[Co(Mecyclen)(O_2C_2O_2)]^+$ (1 page). See any current masthead page for ordering and Internet access instructions.

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(25) Ma, G.; Kojima, M.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2547.
(26) Rauk, A.; Allen, L. C.; Mistow, K. *Angew. Chem., Int. Ed. Engl.* **1990**, *9*, 400.
(27) Nelsen, S. F.; Petillo, P. A.; Rumach, D. T. *J. Am. Chem. Soc.* **1990**, *112*, 7144.
(28) Buckingham, D. A.; Marzilli, P. A.; Sargeson, A. M. *Inorg. Chem.* **1969**, *8*, 1595.
(29) Searle, G. H.; Keene, F. R. *Inorg. Chem.* **1972**, *11*, 1006.
(30) Buckingham, D. A.; Clark, C. R.; Rogers, A. J. *Inorg. Chim. Acta* **1995**, *240*, 125.

(31) The temperature independence of the **1**/**2**/**3** equilibrium also supports the structural (i.e., $\Delta S^{\ddagger}$) argument for inversion (*vide supra*).