Equilibration of *syn*- and *anti*(Me)-[Co(Mecyclen)(*S*-AlaO)]$^{2+}$ Isomers via One-Ended Dissociation of (*S*)-Alanine

David A. Buckingham,* Charles R. Clark, and Andrew J. Rogers

Department of Chemistry, University of Otago, PO Box 56, Dunedin, New Zealand

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Introduction

Two mechanisms are possible for the recently observed OH^--catalyzed equilibration of the *syn*- and *anti*(Me)-[Co(Mecyclen)-(*S*-AlaO)]$^{2+}$ isomers.[1] The first involves deprotonation of, and then inversion about, the α-C*H* center of the amino acid chelate without Co−ligand bond rupture; c.f. Scheme 1. This type of process occurs for [Co(en)$_2$(*S*-AlaO)]$^{2+}$,[2] and for many other so-called "inert" Co(III)−amino acid complexes.[3] Alternatively, *one-ended* dissociation of the amino acid could occur, followed by re-entry of the dangling end at an opposite octahedral face, Scheme 2. This mechanism is likely with the less robust Co(III) systems such as those used here.[1] Recently it has been found that *complete* dissociation of the amino acid occurs with other *N*-methyl-substituted tetramine complexes (e.g. [Co(1,5*R*,7*R*,11-Me$_4$-2,3,2-tet)(*S*-AlaO)]$^{2+}$)[4] under alkaline conditions and that this takes place without racemization of the amino acid or further disruption of the complex. Clearly, one-ended dissociation of the amino acid chelate is a possible first step in such a process.

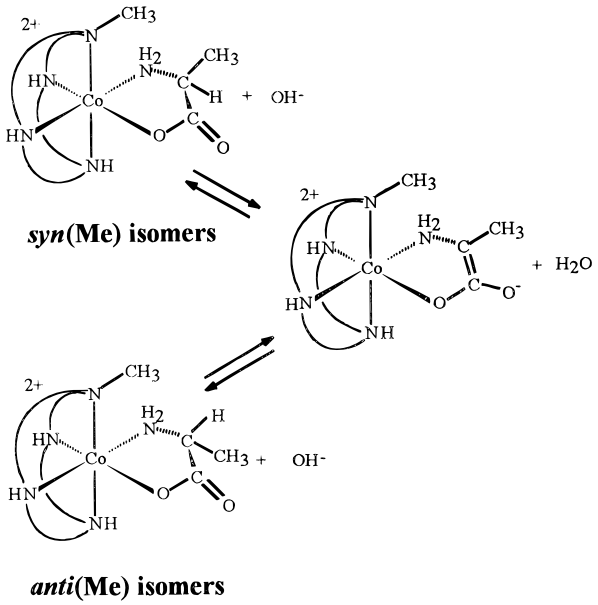
In what follows it will be shown that with [Co(Mecyclen)-(*S*-AlaO)]$^{2+}$ both mechanisms operate but that the one involving one-ended dissociation predominates.

Experimental Section

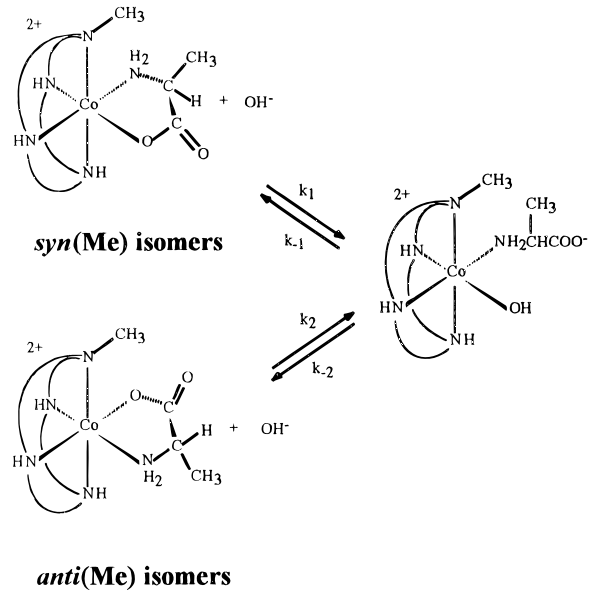
^{1}H-NMR spectra were recorded on a Varian VXRS 300 spectrometer at 25.0 °C using (in the case of the kinetic runs) Teflon-lined 10 mm NMR tubes previously equilibrated with the solvent (alkaline D_2O, no buffer). 3-(Trimethylsilyl)propionic-2,2,3,3-d_4 acid (Na salt) was used as integration standard and reference. Typically *ca*. 20 mg of complex in 0.7 mL solvent was used. Measurement of pD was made using a Radiometer pHM 62 standard pH meter and an Ingold 6030-02 pH electrode designed to fit inside the NMR tube. This system was calibrated for measurement in D_2O solution according to the method of Fife and Bruice,[5] pD = pH meter reading + 0.42. Values of [OD^-] were calculated from pD using $pK_w(D_2O) = 14.81$ [6] and $\gamma_\pm = 0.772$.

Kinetic data were collected by multiple array experiments programmed for 40 min collection times with each being followed by a 20 min delay; pD was measured at the beginning and conclusion of each run.

Scheme 1



Scheme 2



The complexes *anti*(Me),*syn*(N),*anti*(O)-[Co(Mecyclen)(*S*-AlaO)]-$(ClO_4)_2$ and *syn*(Me),*syn*(O),*anti*(N)-[Co(Mecyclen)(*S*-AlaO)]$ZnCl_4$ were prepared as previously described.[7] The latter complex was converted into its Cl^- salt by sorption onto, and then elution from (2 M HCl), a short column of Dowex 50W × 2 cation-exchange resin, followed by rotary evaporation to dryness (40 °C).

Results and Discussion

Figure 1A gives the ^{1}H NMR spectrum of the *syn*(Me),-*syn*(O),*anti*(N)- [Co(Mecyclen)(*S*-AlaO)]$^{2+}$ isomer (designated **2**)[7] in acidified D_2O (pD = 2.2). The signals of interest are the alaninato α-CH*Me* doublet at 1.55 ppm, the α-C*H*Me multiplet at 3.95 ppm (NH_2 coupling also present), and the

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(2) Buckingham, D. A.; Stewart, I.; Sutton, P. A.; *J. Am. Chem. Soc.* **1990**, *112*, 845. Buckingham, D. A.; Marzilli, L. G.; Sargeson, A. M. *J. Am. Chem. Soc.* **1967**, *89*, 5133.
(3) Brubaker, G. R.; Schaefer, D. P. *Inorg. Chem.* **1971**, *10*, 2170. Yamaguchi, M.; Yamamatsu, S.; Furusawa, T.; Yano, S; Sauri, M.; Yosikawa, S. *Inorg. Chem.* **1980**, *19*, 2010.
(4) Yashiro, M.; Yoshikawa, S.; Yano, S. *Inorg. Chem.* **1993**, *32*, 4166. and earlier references given therein.
(5) Fife, T. H.; Bruice, T. C. *J. Phys. Chem.* **1961**, *65*, 1079.
(6) Kingerley, R. W.; LaMer, V. K. *J. Am. Chem. Soc.* **1941**, *63*, 3256.
(7) Buckingham, D. A.; Clark, C. R.; Rogers, A. J.; Simpson, J. *Inorg. Chem.* **1995**, *34*, 3646. This paper also gives the complete structural designation of these isomers.

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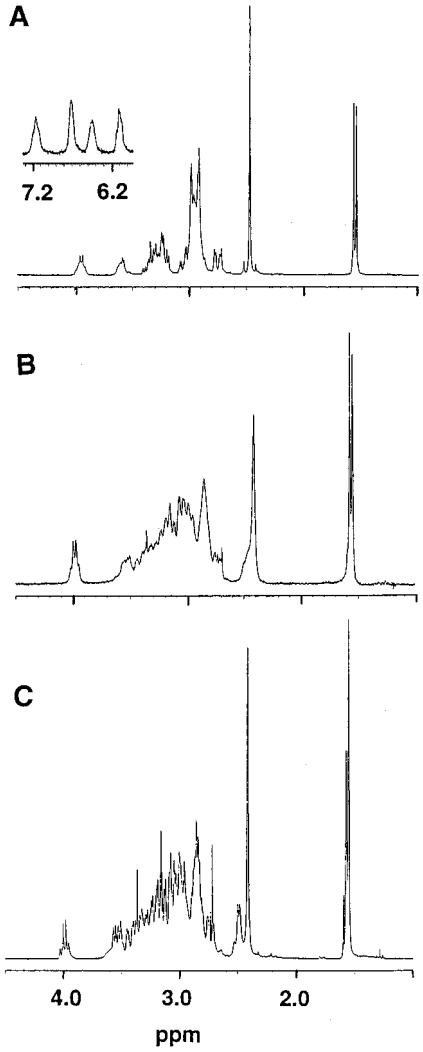

Figure 1. 300 MHz ^{1}H NMR spectra of *syn*(Me),*syn*(O),*anti*(N)-[Co(Mecyclen)(*S*-AlaO)]Cl_2 (isomer **2**; ca. 50 mM D_2O solution): (A) at pD = 2.2; inset shows absorptions for N*H*(*cis* CH), 6.11 ppm; *ap* N*H*, 6.45; N*H*(*syn* O), 6.71; N*H*(*anti* N), 7.16; cf. ref 7; (B) at pD = 10.5 after ca. 5 min and representing the equilibrium mixture of *anti*(Me) isomers **1** + **2** + **3**; (C) after a further 4 days, final pD = 9.93.

*Me*cyclen singlet at 2.47 ppm. At pD 10.52 (no buffer present), Figure 1B, a condition where equilibration of the various *syn*(Me) NH isomers is very rapid ([**1**]:[**2**]:[**3**] = 73:21:6, with **1** and **3** corresponding to the *anti*(O),*syn*(N) and *syn*(O),*syn*(N) isomers, respectively),[1] little change is seen in the CH*Me* resonance (however, better definition shows that this signal now consists of two overlapping doublets), the α-C*H*Me quartet is more clearly defined (N*H*/N*D* exchange), and the *Me*cyclen singlet is now considerably broadened. The latter absorption fails to distinguish the **1**, **2**, and **3** *syn*(Me) isomers, but their separate signals are resolved for acidified samples.[8] Figure 1C gives the spectrum after 4 days reaction (final measured pD = 9.93). The α-CH*Me* signal is now complex, as is the signal in the *Me*cyclen region, but the α-C*H*Me quartet largely remains intact. Acidification of this sample (added DCl) improves resolution and allows five isomers to be distinguished, Figure 2. Structural assignments were made as previously,[1] and the isomer distribution, determined by integration of the five *Me*cyclen singlets, agrees with that reported for a fully equilibrated sample;[1] that is [**1**]:[**2**]:[**3**]:[**4**]:[**5**] = 51:14.5:4.5:20:10, where **4** and **5** correspond to the *anti*(Me),*syn*(N),*anti*(O)- and *anti*(Me),*syn*(O),*anti*(N)-[Co(Mecyclen)(*S*-AlaO)]$^{2+}$ isomers, respectively. It is clear that complete equilibration has occurred in the above experiment and that this has taken place without observable decomposition.

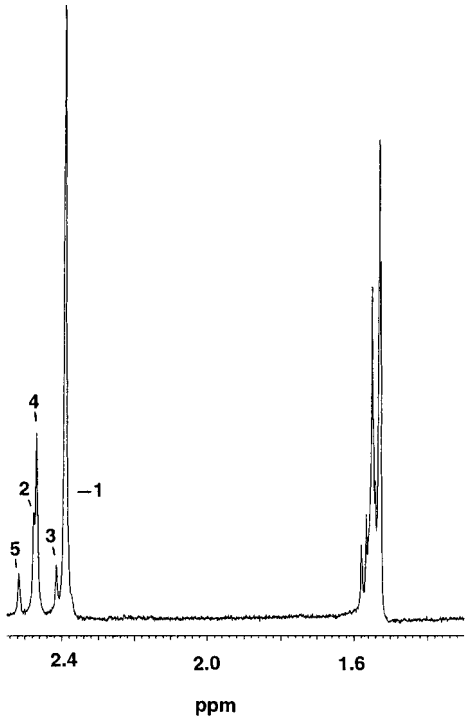

Figure 2. Partial ^{1}H NMR spectrum of the *Me*cyclen region for the solution of Figure 1C following DCl quenching, showing the **1**−**5** isomer distribution.

Figure 3 gives spectra for the *anti*(Me),*syn*(N),*anti*(O)-[Co(Mecyclen)(*S*-AlaO)]$^{2+}$ isomer (designated **4**)[7] after 0, 39 h, and 89 h at pD = 10.82 (no buffer). Changes to the *Me*cyclen signal show that isomerization is virtually complete after 39 h, and the final spectrum, recorded for an acidified sample after 137 h reaction (Figure 4), closely resembles that for isomer **2** at long reaction times (*cf.* Figure 2). A plot of $\ln(P_t - P_\infty)$ vs time for decay of the reactant *Me*cyclen signal at pD = 10.82 (P represents peak height) was found to be linear giving $k_{obs} = 4 \times 10^{-5}$ s^{-1} under this condition (i.e. $t_{1/2} = 5.0$ h). Other qualitative data[9] showed this change to be first-order in [OD^-]; thus k' ($=k_{obs}/[OD^-]$) is *ca.* 0.3 M^{-1} s^{-1}.

Most importantly as regards mechanism is the observation of little decrease in the intensity of the α-C*H*Me signal during these experiments. Thus after 39 h at pD 10.82 ($8t_{1/2}$ for *syn*(Me)/anti(Me) isomerization) integration shows there is 72% of the 3.95 ppm signal remaining (Figure 3B), and after 89 h some 50% remains (Figure 3C). Eventually the absorption is completely lost (2 weeks), but during this time there is no significant change to the rest of the spectrum. The conclusion to be drawn is that the *syn*(Me) ↔ *anti*(Me) interconversion occurs substantially without α-C*H*Me proton exchange. This is possible only if the amino acid chelate opens up at one end and rechelates at another octahedral face with retention of the *S*-configuration; *cf.* Scheme 2. The alternative epimerization mechanism (Scheme 1) would lead to concomitant H/D

(8) If the sample is acidified at this stage, good definition of the **1**−**3** *Me*cyclen singlets is achieved (2.39, 2.47, and 2.41 ppm respectively).

(9) No *syn*(Me) ↔ *anti*(Me) isomerization was observed over many hours for the pH < 5.2 condition (*cf.* ref 1), and in 0.05 M OH^- isomerization was found to be competitive with the complete loss of (*S*)-alanine.

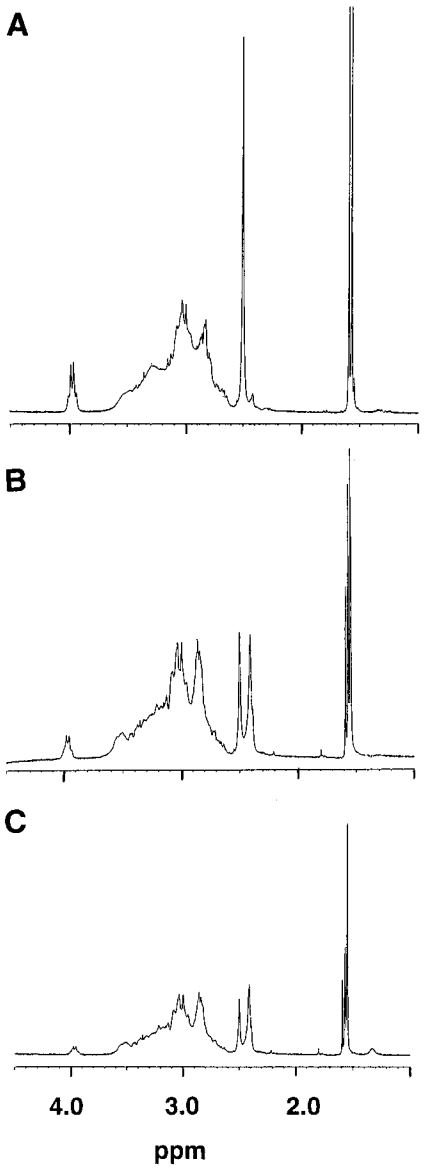

Figure 3. 300 MHz ^{1}H NMR spectra of *anti*(Me),*syn*(N),*anti*(O)-[Co(Mecyclen)(*S*-AlaO)](ClO$_4$)$_2$ (isomer **4**; 50 mM D_2O solution): (A) at pD = 10.82 after *ca*. 5 min representing **4**, **5** isomer distribution; (B) after 39 h; (C) after 89 h.

exchange. The ring-opening process is clearly OD^- catalyzed, and other studies[10] suggest carboxylate-O rather than amine-N

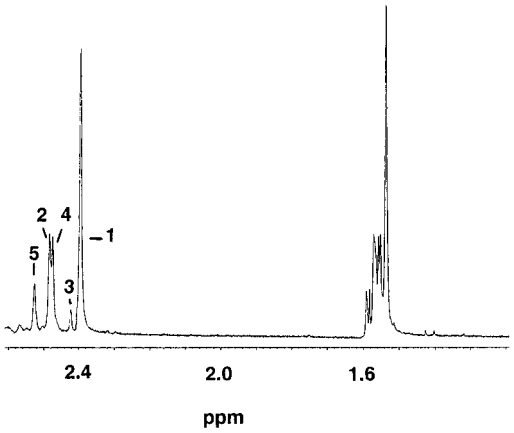

Figure 4. Partial spectrum for the solution represented by Figure 3 after 137 h of reaction (DCl quenched), with the *Me*cyclen region showing the **1**−**5** isomer distribution.

dissociation. The intermediate hydroxo−amine monodentate was not detectable (by visible−UV or ^{1}H NMR spectroscopies) under the pD 10.8 condition and so must be present at very low concentrations, giving k_{-1}, $k_{-2} \gg 10^{-3}$ s^{-1}. This is in agreement with the absence of free amino acid, which would be expected to be produced from the monodentate amino acid complex with a rate constant ≥ 1.0 M^{-1} s^{-1}.[10] Thus ring opening dominates the observed rate with k_1, $k_2 \approx 0.3$ M^{-1} s^{-1}. The eventual loss of the α-C*H*Me signal presumably occurs via the slower OD^--catalyzed epimerization process in the chelate (Scheme 1).

It is of interest to note that monodentate hydrolysis rather than ring opening is rate determining for reaction of unsubstituted [Co(cyclen)(*S*-AlaO)]$^{2+}$ in strongly alkaline solution ([OH^-] = 0.1−1.0 M) and that this process also occurs without racemization in the released amino acid.[11] Presumably the differences between the Mecyclen and cyclen systems arise through a lower *sec* N−*H* acidity for the latter and to reduced angle strain within the octahedral framework.

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(10) Buckingham, D. A.; Clark, C. R.; Rogers A. J. A paper discussing OH^--catalyzed hydrolysis of monodentate ligands in the [Co(cyclen)(NH$_3$)X]$^{3+/2+}$ system (X = NH$_3$, OH$_2$, Cl$^-$, OAc$^-$, N$_3^-$) is in preparation.

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