carbon–carbon bonds. The fact that the positions to be oxidized and activated in **2** with respect to cyclization to **1** are the benzylic carbons of the (2,6-dichlorophenyl)methyl substituents at the 5-position of the dipyrromethene groups suggests that synthetic strategies for converting **2** into **1** would logically be based in large part on the use of selective allylic oxidants. Unfortunately, not only did **2** fail to convert to **1** in reasonable yield under the Rothemund conditions (refluxing freshly distilled 2,4,6-collidine solution exposed to the air) but the use of several allylic oxidants including selenium dioxide or manganese dioxide failed to improve the quantity of metalloporphyrin produced. Free-radical bromination of **2** followed by refluxing the brominated products in 2,4,6-collidine exposed to the air produced a UV–visible chromophore indicative of the presence of **1**. However, subsequent analysis of the products of this reaction demonstrated that they were primarily a mixture of polybrominated derivatives of **1** and **2**. Independently it was shown that **1** could be brominated by NBS. A note by Traylor and Tsuchiya that has recently appeared reporting the production of a zinc complex of octabrominated TDCPP upon bromination of Zn^{II}TDCPP by NBS establishes the susceptibility of at least the β-pyrrole hydrogens of **1** to bromination by this reagent under typical free-radical conditions.[15] Inasmuch as the Fe complex of the octabrominated TDCPP appears to be the most oxidatively resistant metalloporphyrin yet prepared, the possible conversion of **2** into the brominated TDCPP derivatives by the procedures given here warrants further attention.

Acknowledgment. This research was supported by the National Science Foundation (Grant No. CHE-8715322).

Registry No. **1**, 100506-72-7; **1**·3NMP, 112816-27-0; **2**·C_7H_8, 100655-02-5; NBS, 128-08-5; 2,6-dichlorobenzaldehyde, 83-38-5; pyrrole, 109-97-7; *meso*-(2,6-dichlorophenyl)-5-(*o*,*o*'-dichlorobenzyl)dipyrromethene, 112839-60-8.

Supplementary Material Available: For the structure determination of **1**·3NMP, complete table of bond lengths (Table SI), complete table of bond angles (Table SII), and tables of anisotropic temperature factors (Table SIII), hydrogen coordinates and temperature factors (Table SIV), nonbonded distances (Table SV), and torsion angles (Table SVI) (12 pages); a table of observed and calculated structure factors (Table SVII) (27 pages). Ordering information is given on any current masthead page. All the supplementary data for the X-ray crystallographic structure determination of the bis(dipyrromethene) complex of zinc, **2**, have already been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.

Contribution from the Chemistry Department, University College, Australian Defence Force Academy, Campbell, Canberra, ACT, Australia 2600, and Research School of Chemistry, Australian National University, Canberra, ACT, Australia 2600

Chlorination of Bis(ethylenediamine)cobalt(III) Complexes Containing Chelated N,S-Bound (*R*)-Cysteine and Cysteamine: Novel Oxidative Ring Expansion Reactions

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Received May 5, 1987

Exhaustive chlorine oxidation of the sulfur center in the N,S-bonded (*R*)-cysteine and cysteamine complexes $[Co(en)_2(NH_2CH(R)CH_2S)]^{2+}$ leads to a remarkable rearrangement involving an increase in the ring size of the original amino thiolate from five-membered to six-membered, concomitantly with the conversion of S-bonded thiolate to (necessarily) O-bonded sulfonate. For the cysteine derivatives, some linkage isomeric product, $[Co(en)_2(NH_2CH(CH_2SO_3)COO)]^+$, accompanies the formation of the chelated amino sulfonate $[Co(en)_2(NH_2CH(CO_2H)CH_2SO_2O)]^{2+}$. Details of the stereochemistry of these rearrangements are reported and mechanisms proposed. Also reported are studies of H exchange and the hydrolysis and interconversions of linkage isomers, which bear on structural assignments and relative isomer stabilities as well as the mechanisms for base hydrolysis of pentaaminecobalt(III) species.

Introduction

Recent interest in the reactions of coordinated thiols has precipitated several reports on a remarkable range of reactions.[1-9] Metal(III) thiolates can be oxidized to coordinated sulfenate, sulfinate, monothiooxalate, sulfenamide, and disulfide with reagents such as hydrogen peroxide, hexaquacobalt(III), neptunium(VI), and acetic anhydride/dimethyl sulfoxide. We report here yet another oxidation, and one that took an unexpected course.

It was anticipated that Cl_2 oxidation of Λ-$[Co(en)_2((R)$-cys-$N,S)]^{2+}$ (**1**) in water would follow that documented[1] for H_2O_2 (Figure 1), where the sulfenate **3** and ultimately the sulfinate **4** are formed. Similarly, exhaustive oxidation by Cl_2 was expected to give the sulfinate **4**, the sulfur being protected by the cobalt against conversion through to the sulfonate ((*R*)-cysteic acid). Our initial interest was vested in the specificity of the first oxidation step, which was expected to give a mixture of the sulfenate diastereoisomers (**3a**,**b**).[1] These isomers differ only in the chirality of the (optically stable) sulfur center. The problem is discussed in detail elsewhere,[10] and this article will be largely concerned with the second oxidation step with Cl_2.

Results and Discussion

Chlorine Oxidation of $[Co(en)_2((R)$-cys-$N,S)]^{2+}$. Controlled oxidation of **1** in H_2O using *N*-chloro- or *N*-bromosuccinimide (1 equiv) as the source of X^+ gave, as anticipated, the stable chiral sulfenate **3** (Figure 1), the isomer ratio being much higher (>20/1) than that found for H_2O_2 (2.3/1).[1] However, excess Cl_2 rapidly (ca. 5 s, 20 °C) gave a pink solution, rather than yellow-brown **4**, from which two products were readily separated by ion-exchange chromatography on Dowex resin using HCl as the eluant. The first band was an orange 1+ ion (**5**, ca. 20%) and the second a pink 2+ ion (**6**, ca. 80%). Each was crystallized readily as a Cl^-, ClO_4^-, $ZnCl_4^{2-}$, or $S_2O_6^{2-}$ salt. Neither product corresponded to the expected sulfinate **4**. The same two products, in the same

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(5) Gainsford, G. J.; Jackson, W. G.; Sargeson, A. M. *J. Am. Chem. Soc.* **1977**, *99*, 2383.
(6) Woods, M.; Karbwang, J.; Sullivan, J. C.; Deutsch, E. *Inorg. Chem.* **1976**, *15*, 1678.
(7) Jackson, W. G.; Sargeson, A. M.; Tucker, P. A. *J. Chem. Soc., Chem. Commun.* **1977**, 199.
(8) Deutsch, E.; Root, M. J.; Nosco, D. L. In *Advances in Inorganic and Bioinorganic Mechanisms*; Sykes, A. G., Ed.; Academic: New York, 1982; Vol. 1, pp 269-389.
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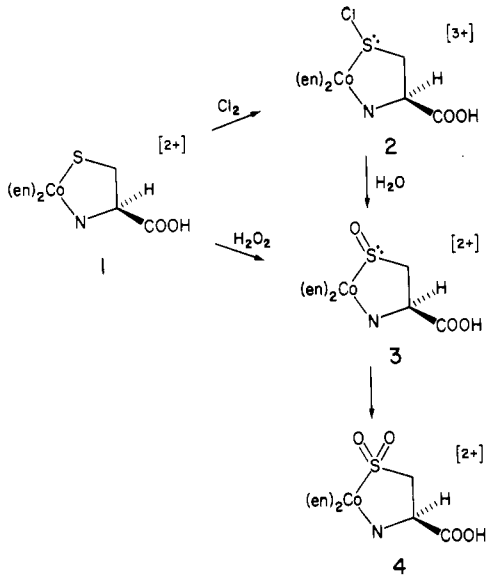

Figure 1. Course of reaction for the hydrogen peroxide and controlled chlorine oxidation of $[Co(en)_2((R)\text{-cys-}N,S)]^{2+}$.

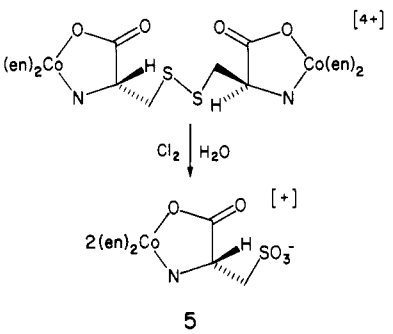

Figure 2. Oxidative cleavage of the (*R*)-cysteine dimers.

proportion, were obtained by starting with **3a** or **3b** rather than **1** (Figure 1), while the sulf*i*nate **4** did not react with Cl_2. Thus it was clear that Cl_2, like H_2O_2 and *N*-chloro or *N*-bromosuccinimide, oxidized **1** first to the diastereoisomers of **3**, but immediately thereafter a new reaction course was evident that did involve the sulf*i*nate complex **4**.

The visible spectrum of the minor product **5** (λ_{max} 487, 347 nm) was characteristic[7] of an N,O-bound amino acid, and together with elemental analyses and ^1H and ^{13}C NMR spectra, the data indicated that the product was $[Co(en)_2((R)\text{-}NH_2CH(CH_2SO_3)CO\mathit{O})]^+$, which contains bound carboxylate and a free sulf*o*nate group. Characterization was secured by the preparation of an identical complex (visible, rotatory dispersion, and ^1H and ^{13}C NMR spectra) by oxidative cleavage (Cl_2) of the bridging disulfide linkage in the dimer, Λ,Λ-$[(en)_2Co((R)\text{-cys-}N,\mathit{O})((R)\text{-cys-}N,\mathit{O})Co(en)_2]^{4+}$ of known structure[7] (Figure 2) and also by direct Cl_2 oxidation of Λ-$[Co(en)_2((R)\text{-cysH-}N,\mathit{O})]^{2+}$.[7]

The other major product of the Cl_2 oxidation reaction, **6**, had a visible spectrum suggesting[11,12] bound sulf*o*nate (λ_{max} 501, 353 nm). The ^1H and ^{13}C NMR spectra and chromatographic characteristics (pH 2–10) of **6** indicated the presence of a free carboxylic acid group (pK_a ca. 3), and hence the product was assigned as a linkage isomer of **5**, namely $[Co(en)_2((R)\text{-}NH_2CH(CO_2)CH_2SO_2\mathit{O})]^{n+}$ (Figure 3). The assignment was confirmed by converting **6** to **5** by heating in dilute $HClO_4$, and the reaction goes to completion (Figure 3). An observation with important mechanistic implications is that **5** and **6** are formed directly from the reaction between **1** and Cl_2, in the ratio of 20/80;

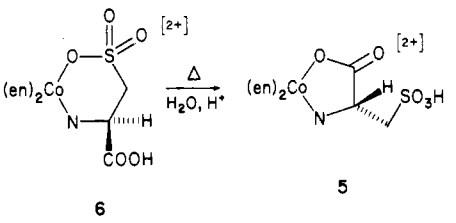

Figure 3. Structures for the linkage isomeric (*R*)-cysteic acid complexes and their interconversion.

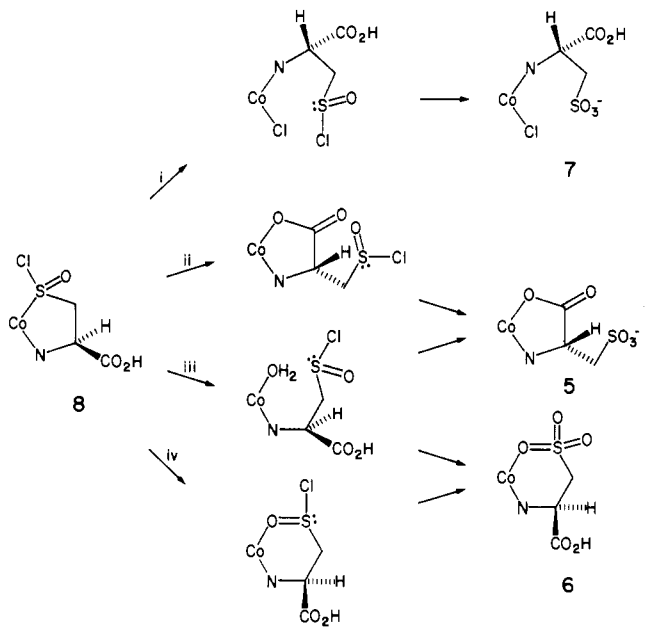

Figure 4. Reaction scheme for the chlorine oxidation of $[Co(en)_2((R)\text{-cys-}N,S)]^{2+}$. Complexes without compound numbers, except **8**, were not actually observed.

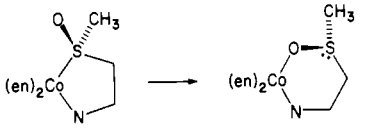

Figure 5. Rearrangement of the S-bound sulfoxide in $[Co(en)_2(NH_2(CH_2)_2S(CH_3)O)]^{3+}$ to give the stable O-bound form.

interconversion between **5** and **6** is very slow on the time scale of the oxidation. Furthermore, all these reactions proceed with retention of chirality at both the cobalt and the methine carbon of the (*R*)-cysteine ligand.

A remarkable feature of the Cl_2 oxidation is the cleavage of the Co–S bond. Even more remarkable is the formation of chelated sulf*o*nate, **6** (Figure 3), a fact that requires the original five-membered ring to expand to a six-membered chelate to accommodate O-bound sulf*o*nate, since sulf*o*nate clearly cannot bind through its saturated sulfur center.

We first reported upon these reactions in 1978,[13] and since then Japanese groups[14,15] (following Adamson et al.[16]) have reported similar rearrangements of Co(III) complexes, containing oxidized cysteamine ($NH_2CH_2CH_2SO_2^-$) and its selenium analogue, which undergo ring-expansion or -contraction reactions of the kind reported here.

Chemically reasonable pathways that stem from **8** (arising from the addition of Cl^+ to the bound S atom of **3**, $[Co(en)_2((R)$-

(11) $[Co(NH_3)_5OSO_2R]^{2+}$ ions absorb at 518 and 350 nm (R = CH_3 and others) and have the same chromophore as **6**.[12]

(12) Buckingham, D. A.; Cresswell, P. J.; Jackson, W. G.; Sargeson, A. M. *Inorg. Chem.* **1981**, *20*, 1647.

(13) Gainsford, G. J.; Jackson, W. G.; Sargeson, A. M. *Abstracts of Papers*, Eighth Coordination and Organometallic Conference, Perth, Australia, 1978; P1. See also ref 9.

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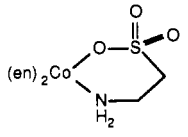
cysO-*N*,*S*)]$^{2+}$, Figure 1) are presented in Figure 4, where subsequent steps involving successive Cl^+ addition and then hydrolysis are omitted. Paths ii and iii involve complete dissociation of Co–S, with capture of solvent water or the pendant carboxylate group. In HCl solution (1 M), capture of Cl^- is also significant (path i), and the violet chloro pentaamine complex **7** has been isolated. The proposed route iii implies attack of coordinated water on carboxylate and sulfenyl halide to give **5** and **6**, respectively, by rapid intramolecular processes. The other possible pathway (iv, Figure 4) implies direct ring expansion, leading ultimately to **6** only. This mode of rearrangement is analogous to that described[17] for the methylation of the S-bound sulfenate ion in $[Co(en)_2(NH_2(CH_2)_2SO)]^{2+}$, where the transient S-bound sulfoxide product rearranges to O-bound sulfoxide, concomitantly with an increase in ring size and without competitive solvent capture or loss of chirality at the chiral sulfur center (Figure 5).

We attempted to confirm some aspects of the proposed mechanism for these rearrangements as follows. Each of the sulf*e*nate diastereoisomers **3a** and **3b** was reacted with 1 equiv of *N*-chlorosuccinimide in an attempt to observe either of the diastereoisomers of the O-bound sulf*i*nate $[Co(en)_2(NH_2(CH_2)_2SO\mathit{O})]^{2+}$ en route to the corresponding sulf*o*nate. Neither was observed; only reactant and sulfonate were obtained. Presumably secondary oxidation is more rapid than the ring-expansion step.

We have no definitive evidence for which mechanistic pathways are dominant, but we note that the competition characteristics observed for other dissociative Co(III) reactions suggest the order $COOH \gg H_2O \approx Cl^-$ for effectiveness as competitors on a mole for mole basis. This consideration leads to the belief that **6** more likely arises by path iv, and **5** by path ii.

Results analogous to those described in this section were obtained by using Δ-$[Co(en)_2((R)\text{-cys-}N,S)]^{2+}$ in lieu of the Λ isomer.

Chlorine Oxidation of $[Co(en)_2(NH_2(CH_2)_2S\text{-}N,S)]^{2+}$. The major product was pink $[Co(en)_2(NH_2(CH_2)_2SO_2O\text{-}N,O)]^{2+}$ (**9**), which differs from **6** only in that it lacks the pendant–COOH group. The complex was isolated as Cl^-, ClO_4^-, I^-, and Cl^-/ClO_4^-



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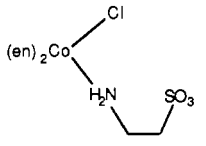

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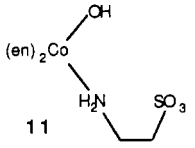
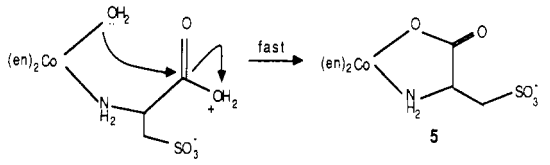


11

salts, and its properties were similar to those of **6**. Two other products were isolated and characterized, red-violet *cis*-$[Co(en)_2Cl(NH_2(CH_2)_2SO_3)]Cl\cdot 0.5CH_3OH$ (**10**; yield ca. 20%), and orange *cis*-$[Co(en)_2(OH_2)(NH_2(CH_2)_2SO_3)]Cl_2$ (**11**; yield ca. 5%). The first complex **10** has a visible spectrum which is similar to that for its cysteine analogue **7** and which is characteristic of the (cis) $Co^{III}N_5Cl$ chromophore. The presence of the uncoordinated $-SO_3^-$ group is apparent from the elution characteristics of the cation on ion-exchange chromatography. It elutes as a 1+ ion, even with strong acid (1 M HCl), consistent with the high acidity of a sulfonic acid group (pK_a ca. 2), enhanced at least 1 order of magnitude by being part of a cationic (2+) cobalt complex. The *cis*-$[Co(en)_2Cl(NH_2(CH_2)_2SO_3)]^+$ ion, **10**, has been synthesized by other routes, e.g. by Cl_2 oxidation of *cis*-$[Co(en)_2Cl(NH_2(CH_2)_2SH)]^{2+}$ (from $POCl_3$/DMF + $[Co(en)_2(S(CH_2)_2NH_2)]^{2+}$) and also, directly, from $PhSO_2Cl/Me_2SO$ + $[Co(en)_2(S(CH_2)_2NH_2)]^{2+}$.[10] Others[18] have reported the synthesis of **10** (but not **9**), by more standard routes commencing with the free sulfonate ligand. The other (minor) product, **11**, presumed to be *cis*-$[Co(en)_2(OH_2)(NH_2(CH_2)_2SO_3)]^{2+}$, could be reversibly deprotonated, and it was chromatographed as a 2+ ion in acid and 1+ ion in base; the attendant changes in visible spectra are also consistent with a coordinated aqua group. In acid solution the pendant sulfonate ion slowly substitutes the aqua group to give the chelate $[Co(en)_2(NH_2(CH_2)_2SO_2O)]^{2+}$, which was shown to be identical with the major product of the Cl_2 oxidation reaction, **9**, and this fact strongly supports the structural assignments.

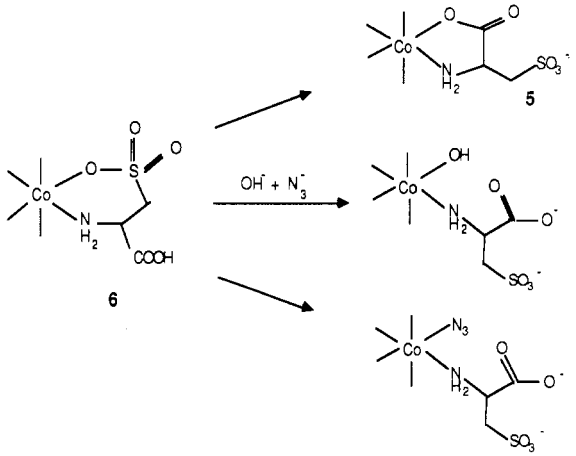
In summary, the oxidation of the cysteamine ($NH_2(CH_2)_2SH$) complex parallels that of the cysteine species in that the main product is the chelated sulfonate (ca. 70–90%). A reaction scheme similar to that shown in Figure 4 should apply, except that path ii, which involves capture of the pendant–COOH group, obviously is not available to the cysteamine complex.

Chemistry of the Oxidation Products. We noted above that the (*R*)-cysteic acid complex **6** slowly converts to **5** on refluxing in H_2O (Figure 3); the reaction proceeds with retention of chirality about cobalt and without mutarotation at the asymmetric methine center (*R*). It seems to us very likely that **6** aquates by first dissociating the sulfonate, and the aqua intermediate then undergoes rapid ring closure:



The retention about cobalt is characteristic of pentaaminecobalt(III) aquation,[9] while rapid intramolecular ring closure of aqua carboxylic acid complexes of this type is well documented.[19]

The transformation **6** → **5** is also base-catalyzed. Indeed, most of the reaction first proceeds to the hydroxo complex, which can be easily separated chromatographically from **5** while under basic conditions. This observation may be interpreted as trapping of the aqua intermediate above by deprotonation at both the –COOH and $Co–OH_2$ functions; subsequent ring closure in species of this kind is known to be slow.[20] On acidification it instantly gives the aqua ion, which then rapidly generates **5** ($t_{1/2} \leq 5$ s, 25 °C), in support of the case made above for intramolecular ring closure. In 1 M NaN_3, some azido complex is also formed in the base-catalyzed reaction, and all these observations are consistent with the normal course of events[9,19,20] for base hydrolysis of complexes of this kind, which proceed via the S_N1cb mechanism:



As expected, the cysteamine analogue undergoes base hydrolysis, and N_3^- competition is observed for 1 M NaN_3. Acid-

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Table I. ^{13}C NMR Data (D_2O) for Known Compounds

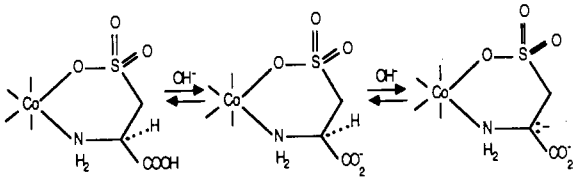
complex	δ, Hz[a]			
	$-CO_2$	$-CH_2NH_2$ (en)	$-CH(NH_2)$, $-CH_2NH_2$	$-CH_2S$
Λ-[Co(en)$_2$((*R*)-cys-*N*,*S*)]$^{2+}$	−1605	309, 320, 328, 344	62.5	523
Δ-[Co(en)$_2$((*R*)-cys-*N*,*S*)]$^{2+}$	−1605	316, 324, 332, 344	50.5	539
[Co(en)$_2$($NH_2(CH_2)_2S$)]$^{2+}$		316, 324, 332, 344	240	575
Λ-[Co(en)$_2$((*R*)-cys-*N*,*O*)]$^{2+}$	−1750	316, 342 (2), 344	105	605
Δ-[Co(en)$_2$((*R*)-cys-*N*,*O*)]$^{2+}$	−1754	324 (3), 336	117	598
Λ,Λ-[Co(en)$_2$((*R*)-cys-*N*,*O*)]$_2^{4+}$	−1752	314, 322, 325, 343	156	419
Δ,Δ-[Co(en)$_2$((*R*)-cys-*N*,*O*)]$_2^{4+}$	−1758	321, 326 (2), 339	162	409
Λ-[Co(en)$_2$((*R*)-cys-O_2-*N*,*S*)]$^{2+}$	−1553	330 (4)	205	33
Δ-[Co(en)$_2$((*R*)-cys-O_2-*N*,*S*)]$^{2+}$	−1582	317, 326, 332, 336	222	11
[Co(en)$_2$($NH_2(CH_2)_2SO_2$-*N*,*S*)]$^{2+}$		326, 331, 335, 337	418	45
cis-[Co(en)$_2$Cl($NH_2(CH_2)_2SH$)]$^{2+}$		323, 324, 329, 333	304	630
Λ-[Co(en)$_2$((*R*)-$NH_2(CH_2)_2SO$-*N*,*S*)]$^{2+}$ [b]		327, 330, 353 (2)	373	208
Λ-[Co(en)$_2$((*S*)-$NH_2(CH_2)_2SO$-*N*,*S*)]$^{2+}$ [c]		331, 337, 338, 345	389	208

[a] Upfield from dioxane, at 15.04 MHz. [b] "Major" sulfenate diastereoisomer; X-ray crystal structure known (refer to text). [c] "Minor" sulfenate diastereoisomer.

ification of the hydroxo product gives the aqua complex **11**, which cannot of course go on to form a carboxylate chelate. However, the chelated sulfonato complex **9** re-forms *slowly* on standing. This path was open to the cysteine analogue but was undercut by the alternative and more rapid ring closure giving the chelated carboxylate **5**.

Finally, we note that **5** and even **6** undergo facile H–D exchange in base (pH >10) at the methine carbon atom. For **5**, this observation is in line with the general behavior of [Co(en)$_2$(amino acidato-*N*,*O*)]$^{2+}$ complexes.[21] Preliminary data indicate that this rate is much faster than is usual, presumably enhanced by the electron-withdrawing sulfonate group.

For the O-bound sulfonato complex, the observation of H–D exchange at the methine center was somewhat surprising because it requires the formation of a dianionic intermediate:



The analogous cysteinato-*N*,*S* ions do not readily exchange their methine proton for this reason,[22] yet it seems the sulfonato group provides the necessary charge delocalization for this to be a facile process.

Proton exchange requires that the methine center racemize because the intermediate is planar at the relevant carbon and, hence, achiral.[21] We have not performed a complete investigation of the base hydrolysis stereochemistry, but we should record that racemization at the methine center in both **5** and **6** is comparable in rate to that of base hydrolysis, which leads to, as is usual,[9] some inversion at the chiral cobalt center as well. Thus, the products of base hydrolysis of either Λ-**6** or Δ-**6** are the equilibrium mixture of the two diastereoisomers of **5** [60% (Λ-(*R*) + Δ-(*S*)), 40% (Δ-(*R*) + Λ-(*S*))], each of which is partly but not fully racemized. Clearly the equilibrium specificity is not pronounced, and this is usual[21,23] for N,O-chelated amino acidato complexes of the bis(ethylenediamine)cobalt(III) moiety.

Finally, it is worthy of comment that a good yield (>60%) of Λ-[Co(en)$_2$((*R*)-$NH_2CH(CH_2SO_3)CO$*O*)]$^+$ is realized for the base hydrolysis of Λ [Co(en)$_2$((*R*)-$NH_2CH(CO_2)CH_2SO_2$*O*)]$^{2+}$. Apart from the fact that the Λ-(*R*) product is much less soluble than its Δ-(*R*) form, this indicates that in large part the chelated amino acid arises from ring closure in the aqua complex, after acidification of the product mixture comprising mostly hydroxo complex. Furthermore, the hydroxo complex must have the same configuration about cobalt as the reactant, and as well it must have the same configuration at the methine carbon (indicating little exchange and, hence, little inversion). It was therefore interesting that Δ-[Co(en)$_2$((*S*)-$NH_2CH(CH_2SO_3)CO$*O*)]$^+$ was isolated (rather than Λ-(*R*) or the racemate), in reasonable yield, following acidification of the products of the base hydrolysis of Δ-[Co(en)$_2$((*R*)-$NH_2CH(CO_2)CH_2SO_2$*O*)]$^{2+}$. Since much of the product arises from the hydroxo complex, it is clear that significant inversion has occurred at the methine carbon of the reactant prior to base hydrolysis; again, there appears to be little inversion about cobalt since the "racemate" (at either or both chiral centers), established as much less soluble, did not crystallize.

Experimental Section

Visible spectra were measured with Cary 118C and Cary 210 spectrophotometers and optical rotations with Perkin-Elmer Model 241 and P22 spectropolarimeters. Proton NMR spectra were obtained with use of Varian T60 and JEOL Minimar (100 MHz) spectrometers, and carbon-13 NMR spectra were measured on a JEOL FX60 instrument. Proton chemical shifts were measured downfield from a Me_4Si reference for Me_2SO-d_6 as solvent and a sodium (trimethylsilyl)propanesulfonate reference for D_2O as solvent. Carbon shifts are reported in hertz upfield from dioxane as the internal standard in D_2O solvent and were recorded at 15.04 MHz; Me_4Si is upfield of dioxane by 1014 Hz (67.4 ppm) at this field strength. Dowex 50W-X2 (200–400 mesh) and Pharmacia SP Sephadex C-25 resins were used in ion-exchange experiments. Chemicals were AnalaR grade or the equivalent. All complexes gave satisfactory analyses for C, H, N, and at least one other element.

[Co(en)$_2$($NH_2(CH_2)_2S$)]$(ClO_4)_2$,[24,25] [Co(en)$_2$($NH_2(CH_2)_2S$)]Cl_2·H_2O, [Co(en)$_2$($NH_2(CH_2)_2SO_2$)]NO_3·ClO_4,[2,3] and Λ- and Δ-[Co(en)$_2$((*R*)-cys-*N*,*S*)]$(ClO_4)_2$·H_2O[22] were synthesized by minor modifications to published methods. The two diastereoisomers of [Co(en)$_2$($NH_2(CH_2)_2SO$)]$^{2+}$ were obtained as [Co(en)$_2$($NH_2(CH_2)_2SO$)]NO_3·ClO_4 (major isomer) and [Co(en)$_2$($NH_2(CH_2)_2SO$)]$(ClO_4)_2$ (minor), respectively, by separate stereoselective procedures.[9,10,17,24] One or both isomers have been described previously.[17,26–28] The major sulfenate diastereoisomers both for Λ- and for Δ-[Co(en)$_2$((*R*)-cysO-*N*,*S*)]$^{+/2+}$ were obtained as the half-protonated double salts [Co(en)$_2$((*R*)-cysO)]ClO_4·[Co(en)$_2$((*R*)-cysO)]$(ClO_4)_2$·H_2O by controlled H_2O_2 oxidation of the parent N,S-bonded (*R*)-cysteinato complexes.[1] The minor diastereoisomers were crystallized from the slightly acidified filtrates from these preparations, as the dithionate salts of the fully protonated cations. Isomeric purity was established by ion-exchange chromatography on Dowex resin (sodium phosphate pH 7 buffer as eluant), under which conditions the diastereoisomers differing only in the chirality at sulfur readily separate.[1,10] The Λ- and Δ-[Co(en)$_2$((*R*)-cysO$_2$-*N*,*S*)]$(ClO_4)_2$

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Table II. Spectroscopic Data for New Compounds (in H_2O Unless Otherwise Noted)

cation	counterions and solvates	λ_{max}, nm (ϵ_{max}, M^{-1} cm^{-1})	λ, nm[a] ([M]^{20}, deg M^{-1} m^{-1})	^{13}C NMR δ, Hz[b]	^{13}C NMR assignt
$[Co(en)_2Cl(NH_2(CH_2)_2SO_3)]^+$	0.5 S_2O_6	526.5 (77.0),		235	$-CH_2SO_3^-$
	Cl, 0.5 CH_3OH[c]	367 (86.7)		(256)[c]	(CH_3OH)[c]
	ClO_4, H_2O			322, 324, 328, 332	$-CH_2NH_2$ (en)
	ClO_4, $HClO_4$[e]			408	$-CH_2NH_2$
$[Co(en)_2(NH_2(CH_2)_2SO_2O)]^{2+}$	Cl_2, 0.5 H_2O	503.5 (84.0),		286	$-CH_2SO_3$
	I_2	357 (71.5)		317, 322, 331, 350	$-CH_2NH_2$ (en)
	2 ClO_4, H_2O			396	$-CH_2NH_2$
	Cl, ClO_4, H_2O				
Λ-$[Co(en)_2((R)$-$NH_2CH(CH_2SO_3)COO)]^+$	Cl, H_2O	485 (100.7),	589 (+1670), 578 (+2100),	−1753	$-CO_2$
	ClO_4	346 (111.0)	546 (+3557), 436 (−4815),	189	$-CH_2SO_3$
	ClO_4, 0.3 $HClO_4$[e]		365 (−4360)	230	−CH
				318, 326, 329, 354	$-CH_2NH_2$ (en)
Δ-$[Co(en)_2((S)$-$NH_2CH(CH_2SO_3)COO)]^+$[d]	Cl, H_2O	486 (101.9),	589 (−1650), 578 (−2080),		
	ClO_4	346 (113.0)	546 (−3560), 436 (+4740),		
	ClO_4, 0.4 $HClO_4$		365 (+4290)		
Δ-$[Co(en)_2((R)$-$NH_2CH(CH_2SO_3)COO)]^+$	Cl, H_2O	485 (101.5),	589 (−1450), 578 (−1850),	−1751	$-CO_2$
	Cl, 0.1 HCl, 2.5 H_2O[e]	346 (110.0)	546 (−3175), 436 (+4130), 365 (+3990)	193	$-CH_2SO_3^-$
				227	−CH
				321, 325, 334, 341	$-CH_2NH_2$ (en)
Λ-$[Co(en)_2((R)$-$NH_2CH(CO_2H)CH_2SO_2O)]^{n+}$	ClO_4[f]	498 (92.6),	589 (+1470), 578 (+1620),	−1585	$-CO_2$
	Cl_2, H_2O	355 (87.1)	546 (+210), 436 (−3130),	188	$-CH_2SO_3$
	1.5 ClO_4, 1.5 H_2O[g]		365 (−3640)	262	−CH
	1.5 Cl, 1.5 H_2O[g]			318, 322, 326, 340	$-CH_2NH_2$ (en)
	1.5 I, 1.5 H_2O[g]				
Δ-$[Co(en)_2((R)$-$NH_2CH(CO_2H)CH_2SO_2O)]^{n+}$	Cl_2, H_2O	499 (84.7),	589 (−597), 578 (−720),	−1578	$-CO_2$
	1.5 ClO_4, 1.5 H_2O[g]	356 (71.3)	546 (−390), 436 (+1840),	193	$-CH_2SO_3$
	S_2O_6, 3 H_2O		365 (+2730)	266	$-CH_2NH_2$
				319, 323, 327, 340	$-CH_2NH_2$ (en)

[a] The wavelengths are the standard sodium and mercury lines. [b] Shifts (D_2O solvent) are upfield from dioxane, measured at 15.04 MHz. [c] Methanol of crystallization. [d] Complex isolated from the reaction between Δ-$[Co(en)_2((R)$-$cysO_3]^{n+}$ and OH^- after acidification (refer to text). [e] Partly protonated on the pendant $-SO_3^-$ group. [f] Deprotonated at the pendant −COOH group; $n = 1$. [g] Half-deprotonated at the pendant −COOH group, $n = 1.5$.

salts were prepared by exhaustive hydrogen peroxide oxidation of the respective parent cysteinato complexes.[1] The SO_4^{2-} and $S_2O_6^{2-}$ salts were also characterized.

The syntheses of the disulfide dimers Λ,Λ- and Δ,Δ-$[Co(en)_2((R)$-cys-$N,O)$-(R)-cys-$N,O)(en)_2Co](ClO_4)_4$ have been given previously.[7]

The free thiol complexes Λ- and Δ-$[Co(en)_2((R)$-cysH-$N,O)]ZnCl_4$ have been described.[7] Details of the synthesis of the cysteamine analogue *cis*-$[Co(en)_2Cl(NH_2(CH_2)_2SH)]ZnCl_4$, from reaction between the chelated thiol and $POCl_3$ in DMF, will be published elsewhere.

Table I records some ^{13}C NMR data for most of the previously known complexes. This provided the clearest method for establishing isomeric purity.

Chlorination Reactions. The following was a typical procedure. Chlorine gas was bubbled through a solution of the parent thiol complex Λ-$[Co(en)_2((R)$-cys-$N,S)]Cl_2\cdot H_2O$ (or the ClO_4^- salt) (10 g) in water (500 mL) for 5 min. The brown solution quickly became orange-red, and after the removal of excess Cl_2 by the passage of N_2 (5 min), the product mixture was diluted to 1 L with water, and sorbed on and eluted (2 M HCl) from Dowex cation-exchange resin. A little of the violet complex Λ-$[Co(en)_2Cl((R)$-$NH_2CH(CO_2H)CH_2SO_3)]^+$ was eluted first, just in front of the orange Λ-$[Co(en)_2((R)$-$NH_2CH(CH_2SO_3)COO)]^+$ species, followed by the major product, pink-orange Λ-$[Co(en)_2((R)$-$NH_2CH(CO_2H)CH_2SO_2O)]^{2+}$. The yield of the violet species was increased somewhat when 0.1–1 M HCl was used instead of water as the chlorinating medium. Each band was rotavaporated (<40 °C) to a small volume, and the product was caused to crystallize by carefully adding equal volumes of methanol and then acetone and cooling.

The above synthesis was repeated with each diastereoisomer of Λ-$[Co(en)_2((R)$-cysO-$N,S)]^{+/2+}$, giving identical product distributions. No reaction was observed when Λ-$[Co(en)_2((R)$-cysO$_2$-$N,S)]^{2+}$ was used as starting material.

The synthesis above was repeated with the Δ isomer in place of Λ-$[Co(en)_2((R)$-cys-$N,S)]Cl_2\cdot H_2O$ (or the ClO_4^- salt). A similar product distribution was observed, but not surprisingly, the individual products had quite different solubility characteristics.

Table II gives the new salts obtained, by using HCl, $HClO_4$, $NaClO_4$, NaI, or $Li_2S_2O_6$ as appropriate as the precipitant, and it includes relevant spectroscopic data. Note that the chelated sulfonate species display a distinct tendency to crystallize as double salts (refer to Table II),[17,29] with half-deprotonation at the pendant −COOH group. Similarly, the N,O-bound cysteic acid species, having a pendant $-SO_3^-$ group, showed some tendency (in strong acid) to crystallize with this group protonated, possibly also as half-protonated double salts. The stoichiometry was controlled by working in the appropriate pH region.

With use of the chelated cysteamine complex as reactant, the above synthesis yielded two major products, *cis*-$[Co(en)_2Cl(NH_2(CH_2)_2SO_3)]^+$ and $[Co(en)_2(NH_2(CH_2)_2SO_2O)]^{2+}$, which were easily separated chromatographically and crystallized as above. A little *cis*-$[Co(en)_2(OH_2)(NH_2(CH_2)_2SO_3)]^{2+}$ was also observed, behaving on the column as a 1+ ion in base and 2+ ion in acid. It slowly ring-closes on standing to generate $[Co(en)_2(NH_2(CH_2)_2SO_2O)]^{2+}$.

Chlorine oxidation carried out as above with the Λ,Λ and Δ,Δ N,O-bound cysteine dimers (Figure 2), or Λ and Δ N,O-bound cysteine monomers, yielded just the one product in each case (Λ-**5** and Δ-**5**, respectively), identical in all respects with authentic specimens. Similarly, Cl_2 oxidation of *cis*-$[Co(en)_2Cl(NH_2(CH_2)_2SH)]ZnCl_4$ gave *cis*-$[Co(en)_2Cl(NH_2(CH_2)_2SO_3)]^+$ cleanly, isolated as above.

Reactions in Base. The pink salt Λ-$[Co(en)_2((R)$-$NH_2CH(CO_2H)CH_2SO_2O)]Cl_2\cdot H_2O$ (2.0 g) in water (10 mL) was treated with 1 M NaOH (10 mL), and after 30 s at 20 °C (the solution now deep pink) the reaction was quenched with HCl (10 mL, 10 M), yielding instantly a clear orange solution. The slow addition of excess acetone resulted in the deposition of fine orange needles (1.3 g). These were recrystallized from water (40 mL) by the addition of HCl (10 M, 10 mL) and acetone (50 mL) and cooling. The product was collected, washed with ethanol and ether, and air-dried (1.2 g). The elemental analysis, molar optical rotations, and ^1H and ^{13}C NMR and visible and UV spectra established that this material was pure Λ-$[Co(en)_2((R)$-$NH_2CH(CH_2SO_3)COO)]Cl\cdot H_2O$.

In separate experiments, reaction of the other diastereoisomer Δ-$[Co(en)_2((R)$-$NH_2CH(CO_2H)CH_2SO_2O)]S_2O_6\cdot 3H_2O$ in aqueous OH^- under conditions similar to those above yielded a seemingly identical product (in lower yield), save for the sign of the molar rotations. In fact, the material proved to be the enantiomeric species Δ-$[Co(en)_2((R)$-$NH_2CH(CH_2SO_3)COO)]Cl\cdot H_2O$, with the configuration retained about cobalt but inverted at the chiral C center (Table II).

The above experiments were repeated but with no acid quenching. Dilution and chromatography from Dowex resin using $NaClO_4$ eluant (1 M; pH 10) revealed a major pink fast-running band, followed by an orange-pink band. The former on acidification yielded the latter, and this former species was clearly the neutral hydroxo complex $[Co(en)_2(OH)((R)$-$NH_2CH(CO_2)CH_2SO_3)]$. The latter was shown to be a nonequilibrium mixture of partly racemized (at cobalt) $[Co(en)_2((R)$-

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$NH_2CH(CH_2SO_3)COO)]^+$ and $[Co(en)_2((S)\text{-}NH_2CH(CH_2SO_3)\text{-}COO)]^+$.

The experiments were again repeated, this time in 1 M NaN_3 containing NaOH (0.5 M). On mild-acid quenching (CH_3COOH) and chromatography using $NaClO_4$ eluant (1 M, pH 3), the presence of the deep purple competition product was clearly evident as a 1+ band on the column.

Controlled Chlorination of $[Co(en)_2(NH_2(CH_2)_2SO)]^{2+}$. Each of the diastereoisomers of $[Co(en)_2(NH_2(CH_2)_2SO)]^{2+}$ was treated in saturated aqueous solution with exactly 1 equiv of *N*-chlorosuccinimide, added very slowly with vigorous stirring. From the product mixture, only starting material, **10** and **11**, could be isolated—there were no significant amounts of either diastereoisomer[14] of $[Co(en)_2(NH_2(CH_2)_2SOO)]^{2+}$.

Proton NMR Spectral Studies. The ^1H NMR spectra (D_2O) of the Λ- and Δ-$[Co(en)_2((R)\text{-}NH_2CH(CO_2H)CH_2SO_2O)]^{2+}$ diastereoisomers are distinct but display the same signal pattern. The CH proton appears as a doublet of doublets, coupled to each of the inequivalent α-methylene protons, while the CH_2 protons are a complex multiplet, characteristic of the AB part of an ABX system.

The ^1H NMR spectra of the $[Co(en)_2((R)\text{-}NH_2CH(CH_2SO_3)COO)]^+$ diastereoisomers are simpler [Λ, δ 3.50 (d, J = 4 Hz, $-CH_2-$), 4.05 (t, J = 4 Hz, $-CH-$); Δ, δ 3.58 (d, J = 4 Hz, $-CH_2-$), 3.98 (t, J = 4 Hz, $-CH-$). At 60-MHz resolution, the CH proton appears as a triplet and the (diastereotopic) CH_2 protons are located at higher field as a doublet. In basic D_2O, the exchange of the CH proton of either isomer is coincident with the appearance of its epimer in the NMR spectrum. The CH triplet is depleted in time but is not replaced by a signal due to the other isomer. However, the CH_2 doublet of one isomer is replaced by the CH_2 singlet of the monodeuteriated epimer, the equilibrium distribution being 60:40 [Λ-(*R*):Λ-(*S*) or Δ-(*S*):Δ-(*R*)], starting with either form. The mutarotation is relatively rapid at pH ca. 12 in CO_3^{2-} media. Isomer assignments were confirmed by adding authentic specimens and noting intensity increases for the relevant signals.

The equilibrium isomer distribution was confirmed by chromatography of the products starting with each isomer in turn. As has been found for many other N,O-chelated amino acid complexes of this kind, Dowex 50W-X2 resin (200–400 mesh; Na^+ form) with a sodium phosphate buffer as eluant was effective in separating the diastereoisomers.

It was observed that CH exchange in the product $[Co(en)_2((R)\text{-}NH_2CH(CH_2SO_3)COO)]^+$ isomers was much faster than the rate of base hydrolysis of the parent chelated sulfonato species, $[Co(en)_2((R)\text{-}NH_2CH(CO_2)CH_2SO_2O)]^+$. Also, it seemed that the $[Co(en)_2((R)\text{-}NH_2CH(CO_2)CH_2SO_2O)]^+$ species underwent some exchange at the methine carbon, and consequently some epimerization, at a rate comparable to that for their base hydrolysis. These observations are in accord with product analyses.

Isomer Interconversions. Aside from the rearrangements described immediately above, the only other reactions to be investigated were the conversions of the two forms (Λ, Δ) of $[Co(en)_2((R)\text{-}NH_2CH(CO_2H)\text{-}CH_2SO_2O)]^{2+}$ to the corresponding forms of $[Co(en)_2((R)\text{-}NH_2CH\text{-}(CH_2SO_3)COO)]^+$. These were carried out by refluxing in 0.01 M $HClO_4$; progress was followed by chromatography on Dowex and monitoring of the two bands (the reactant and one product) by visible spectroscopy and optical rotation measurements. In this way the retention about cobalt was confirmed.

Acknowledgment. We thank the Microanalytical Service of the Australian National University for C, H, N, S, and Cl analyses.

Registry No. Λ-**1**, 62697-05-6; Δ-**1**, 62698-03-7; Λ-**4**, 112835-55-9; Δ-**4**, 112835-54-8; Λ-(*R*)-**5**·Cl, 112791-12-5; Λ-(*R*)-**5**·ClO_4, 112791-14-7; Δ-(*S*)-**5**·Cl, 112713-75-4; Δ-(*S*)-**5**·ClO_4, 112713-65-2; Δ-(*R*)-**5**·Cl, 112835-52-6; Λ-**6**·ClO_4, 112713-77-6; Λ-**6**·Cl·HCl, 112713-82-3; Λ-**6**·ClO_4·0.5$HClO_4$, 112713-79-8; Λ-**6**·Cl·0.5HCl, 112713-80-1; Λ-**6**·I·0.5HI, 112713-81-2; Δ-**6**·Cl·HCl, 112791-19-2; Δ-**6**·ClO_4·0.5$HClO_4$, 112791-18-1; Δ-**6**·HS_2O_6, 112791-16-9; **9**·2Cl, 112713-70-9; **9**·2I, 112713-71-0; **9**·2ClO_4, 112713-73-2; **9**·Cl·ClO_4, 112713-74-3; **10**·0.5S_2O_6, 112713-68-5; **10**·Cl, 76316-84-2; **10**·ClO_4, 112713-69-6; **10**·ClO_4·$HClO_4$, 112713-83-4; $[Co(en)_2(NH_2(CH_2)_2S)]^{2+}$, 42901-32-6; Λ-$[Co(en)_2((R)\text{-cys-}N,O)]^{2+}$, 112791-10-3; Δ-$[Co(en)_2((R)\text{-cys-}N,O)]^{2+}$, 112791-11-4; Λ,Δ-$[Co(en)_2((R)\text{-cys-}N,O)]_2^{4+}$, 112835-51-5; Δ,Δ-$[Co(en)_2((R)\text{-cys-}N,O)]_2^{4+}$, 64085-29-6; $[Co(en)_2(NH_2(CH_2)_2SO_2\text{-}N,S)]^{2+}$, 75249-42-2; *cis*-$[Co(en)_2Cl(NH_2(CH_2)_2SH)]^{2+}$, 112713-66-3; Λ-$[Co(en)_2((R)\text{-}NH_2\text{-}(CH_2)_2SO\text{-}N,S)]^{2+}$, 83917-58-2; Λ-$[Co(en)_2((S)\text{-}NH_2(CH_2)_2SO\text{-}N,\text{-}S)]^{2+}$, 83709-29-9; Cl_2, 7782-50-5; *N*-chlorosuccinimide, 128-09-6; *N*-bromosuccinimide, 128-08-5.

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Molecular Mechanics Analysis of the Influence of Interligand Interactions on Isomer Stabilities and Barriers to Isomer Interconversion in Diammine- and Bis(amine)bis(purine)platinum(II) Complexes

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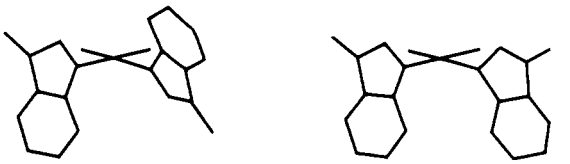
Received September 18, 1987

A molecular mechanics analysis of the factors influencing isomer preferences and ligand rotation barriers in diammine- and bis(amine)bis(purine)platinum(II) complexes shows that the major factor is the nature of the interaction between the ammine or amine ligands and the group in the 6-position of the purine ligands. For complexes of guanine with small ammine or amine ligands, calculated barriers are less than 30 kJ mol^{-1}, and for complexes of adenine, the barriers are greater than 40 kJ mol^{-1}. The difference arises because the oxygen group in the 6-position of guanine hydrogen bonds with an ammine ligand, but the NH_2 group in the 6-position of adenine interacts unfavorably with the ammine. Barriers for complexes of guanine and adenine with tertiary amine ligands are greater than 80 kJ mol^{-1} as a result of highly unfavorable interactions between the group in the 6-position of either guanine or adenine and the bulky amine. In all cases the calculated barriers agree with experimentally determined values. In general, the head-to-tail isomer is more stable than the head-to-head isomer. For $[Pt(NH_3)_2(9\text{-ethylguanine})_2]^{2+}$, which isomer is preferred is determined by the number of intramolecular hydrogen bonds that are assumed to form.

Introduction

The primary interaction between the anticancer drug cisplatin [*cis*-diamminedichloroplatinum(II)] and its putative intracellular target, DNA, is a bifunctional attachment to adjacent guanine residues on one strand.[1] A similar, but less frequent, attachment to adjacent adenine and guanine residues has also been reported.[2] As a consequence, there has been considerable interest[3–16] in

Chart I



HTT HTH

diammine- and bis(amine)bis(purine)platinum(II) (*cis*-$[PtA_2Pu_2]^{x+}$, where A_2 represents two monodentate ammine or

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