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Linkage Isomerism, Structure, and Reactivity Studies of Sulfenamide Complexes of Cobalt(III)

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The S-bonded sulfenamide isomers have been prepared by the known reaction of hydroxylamine-*O*-sulfonate with $(en)_2Co(III)$ thiolate complexes of aminoethanethiol, cysteine, and penicillamine and the cis dithiolate formed by *N*,*N*′-ethylene-di-penicillamine (EDP) and Co(III). It is shown that the sulfenamides undergo linkage isomerization in alkaline solution to produce their respective N-bonded linkage isomers. The addition of acid yields the protonated N-bonded isomers. The structures of $[(en)_2Co(NH_2S(CH_2)_2NH_2)]_2(S_2O_6)_3$ and $[Co((NH_2S)_2EDP)]Br$ have been determined by X-ray crystallography, and the pK_a of $[(en)_2Co(NH_2S(CH_2)_2NH_2)]^{3+}$ has been determined by spectrophotometry. The pH dependencies of the kinetics of the linkage isomerization reactions have been studied and yield pK_a values of the S-bonded isomers. The $(en)_2Co$ systems give only the acid-stable N,N′ isomer at equilibrium, whereas the EDP complex gives a mixture of N,N′ and N,S isomers at pH 7–9.

Introduction

There have been many studies of the oxidation of thiols coordinated to cobalt(III) to form the oxo derivatives sulfenate (R(O)S−M) and sulfinate($R(O)_2S$−M). Probably the most common synthesis has been the reaction of the thiolate complex with hydrogen peroxide. This seems to date back to work by Schubert[1] on the tris(cysteinato)cobalt(III) complex and extends through the synthetic, structural, and kinetic studies of Deutsch and co-workers[2] and Krueger et al.[3] to the recent work of Mascharak and co-workers.[4] More recent work has shown that peroxynitrous acid[5a] and singlet oxygen[5b] are effective oxidizing agents.

With regard to reactivity, the sulfenate and sulfinate complexes of various cobalt(III) amines are generally rather inert toward decomposition in aqueous solution. Adamson et al.[6] first observed that S-bonded sulfinate undergoes photochemical conversion to the O-bonded isomer, which slowly reverts thermally to the S-bonded isomer. Kojima and co-workers[7] have demonstrated similar linkage isomerism in several systems with both sulfenates and sulfinates. Recently, Kovacs et al.[8] have shown that the sulfenate may adopt an η^2-SO bonding mode in a cobalt(III)−imine complex. Lahti and Espenson[9] studied the oxygen atom abstraction from sulfenatocobalt(III) complexes by methyldioxorhenium(V) and evaluated the protonation equilibria of the complexes from the $[H^+]$ dependence of the rate.

The present study is concerned with cobalt(III) complexes of the sulfenamide analogues of the sulfenates. Reynolds et al.[10] showed that these can be prepared easily in aqueous

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solution by the reaction of a thiolate complex with hydroxylamine-*O*-sulfonic acid. The latter reagent is effectively a donor of NH_2^+.[11] Reynolds et al. also studied the kinetics in acidic solution and determined the structure of $[(en)_2Co(S(NH_2)(CH_2)_2NH_2)]^{3+}$ by X-ray crystallography. As derivatives of thiolate complexes, sulfenamides have the advantage of ease of preparation and purification (because of the added positive charge) over sulfenates. It is shown here that these derivatives undergo linkage isomerism in mildly alkaline solutions to become the N-bonded isomer. The only previous N-bonded sulfenamide was reported by Sargeson and coworkers,[12] using a different and much less general route. This group also found that the sulfur of their N-bonded sulfenamide[13] is susceptible to reduction and reaction with nucleophiles. This leads to the possibility of a wide range of new derivatives once the linkage isomerism is characterized.

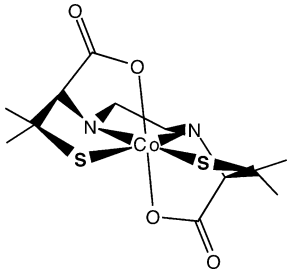
Results

Reactions of Thiolate Complexes with Hydroxylamine-*O*-sulfonic Acid. Previous work[10] has demonstrated that hydroxylamine-*O*-sulfonic acid (HSA) reacts in water, predominantly as the anion, to amidate coordinated thiolates, as shown in eq 1.

$$\left(L_nCo^{III}SR\right)^{z+} + H_2NOSO_3^- \longrightarrow \left(L_nCo^{III}\text{-}S\overset{NH_2}{\underset{R}{<}}\right)^{(z+1)+} + SO_4^{2-} \qquad (1)$$

For the $(en)_2Co^{III}$ derivatives studied here, a limited kinetic study of these reactions was done at pH 6.35−7.37 in 5 mM phosphate buffer at 25 °C and ionic strength 0.10 M ($LiClO_4$) by monitoring the absorbance decrease at 283 nm. Under these pH conditions, the HSA is fully dissociated (pK_a 1.2) into its conjugate base $NH_2OSO_3^-$. The HSA concentration was varied in the range of 0.77 to 5.8 mM, with [Co(III)] = 0.07−0.10 mM, and the rate was found to be first order in HSA and independent of pH. These observations are consistent with the rate law of Reynolds et al.[10] The second-order rate constants for $[Co(en)_2(S(CH_2)_2NH_2)]^{2+}$, $[Co(en)_2(SCH_2CH(CO_2)NH_2)]^+$, and $[Co(en)_2(SC(CH_3)_2CH(CO_2)NH_2)]^+$ were found to be 16, 10, and 2.15 M^{-1} s^{-1}, respectively. The first value is ∼5 times larger than that determined by Reynolds et al., possibly because of differences in ionic strength (1.0 vs 0.1 M) and medium ($HClO_4$ vs phosphate buffer).

To expand the scope of this chemistry, we examined a dithiolate, *N*,*N*′-ethylene-di-penicillamine (EDP). The cobalt(III) complex $Co(EDP)^-$ has the probable structure shown below, although several coordination isomers are possible. The structure shown is based on earlier results of Martell and co-workers[14] on Ga(III) and In(III) complexes of the cysteine analogue, but an amide derivative of Co(III) is shown in this work to have the same arrangement of N- and O-donor atoms.



The reaction of $Co(EDP)^-$ with HSA was studied at higher acidity (0.50 mM H^+ in 0.10 M NaCl) to avoid the linkage isomerization described below and at somewhat higher HSA concentrations (2.0−20.2 mM) because the reaction is biphasic and the slower step is more sluggish than that of the other systems. During the reaction, the absorbance maximum at 291 nm decreases in intensity and shifts to ∼297 nm and then back to ∼290 nm. Absorbance−time data were collected at 280, 290, and 304 nm on a Hewlett-Packard diode array spectrophotometer and analyzed simultaneously by a standard biphasic model to obtain rate constants of 3.6 ± 0.2 and 0.67 ± 0.02 M^{-1} s^{-1}. The kinetic observations and the full characterization of the subsequent isomerization product, described below, indicate that the two reactions are the consecutive amidations of the two coordinated thiolates to produce $Co((SNH_2)_2EDP)^+$.

The S-bonded sulfenamide derivative of $[(en)_2Co(S(NH_2)(CH_2)_2NH_2)]^{3+}$ was fully characterized, including a crystal structure, by Reynolds et al.[10] The analogous derivative of the cysteine complex has been characterized similarly here. The structure of the perchlorate salt is shown in Figure 1, where pertinent bond lengths and angles also are given. As expected, the structures show similar bond lengths and angles for their common functions. For example, the bond lengths in the sulfenamide function are, respectively, Co−S 2.213 and 2.250 Å; S−N 1.638 and 1.659; and S−C 1.789 and 1.782. Similarly, the angles are Co−S−C 98.3 and 97.1°; Co−S−N 109.5 and 112.5°; and S−Co−N (of cysteine) 86.7 and 87.4°.

N-Bonded Sulfenamides of $(en)_2Co^{III}$: Synthesis and Characterization. In general, the conversion of the S-bonded sulfenamide to its N-bonded isomer involves the deprotonation of the S isomer, followed by linkage isomerization, and reprotonation by quenching with acid. For the $(en)_2Co$ systems, the reactions are shown in Scheme 1.

The method has been demonstrated for aminoethanethiol (Y = $(CH_2)_2$), cysteine (Y = $CH_2CH(CO_2)$), and penicillamine (Y = $C(CH_3)_2CH(CO_2)$). Spectrophotometric observations of the reaction in dilute OH^- reveal the same general trends in the 250−450-nm region for these systems. The

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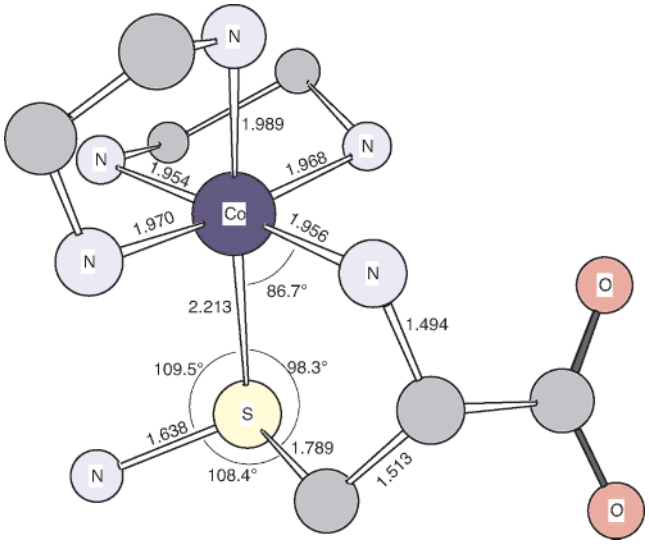
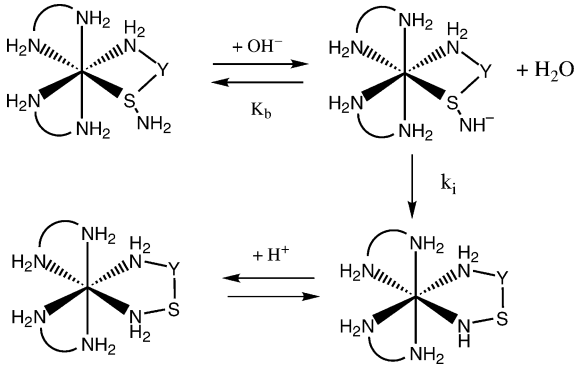


Figure 1. Perspective drawing of $[(en)_2Co(S(NH_2)CH_2CH(CO_2)NH_2)]^{2+}$ based on the crystal structure of $[(en)_2Co(S(NH_2)CH_2CH(CO_2)NH_2)](ClO_4)_2 \cdot H_2O$.

Scheme 1



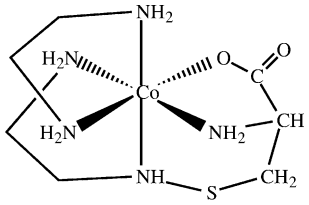
reactant peak at 295 nm decreases in intensity, and a new peak appears at ~350 nm with an isosbestic point at ~325 nm. The product in alkaline solution has a peak at ~350 nm that after quenching in acid shifts to ~330 nm, depending on the quenching time.

Unfortunately, the synthesis is not quite as simple as outlined in Scheme 1, which may be apparent from the procedures described in the Experimental Section that have the appearance of a magic ritual. Optimum yields require careful control of the conditions because of parallel and subsequent reactions. The parallel reaction is a redox pathway that leads to cobalt(II), ammonia, and ethylenediamine for which the products have been identified by cobalt(II) analysis and NMR after acid quenching. This contributes about 10 and 13% during the linkage isomerization of the cysteine and aminoethanethiol derivatives, respectively. If the initial basic solution is not anaerobic, then O_2 reacts with $Co(en)_x^{2+}$ species to give cobalt(III) and probably H_2O_2, which is a problem for long-term storage of solutions of the N-bonded product. The subsequent reaction during the synthesis causes a general loss in absorbance in the 250−450-nm region over 1−2 h and is faster when the $[OH^-]$ is increased from 4.1 to 8.2 mM. This decomposition may involve a nucleophilic attack of OH^- at the sulfur.

Several lines of evidence show that the products of the reactions described above are indeed the N-bonded linkage isomers of the sulfenamides derived from aminoethanethiol (**IA**), cysteine (**IC**), and penicillamine (**IP**), as shown in Chart 1. There is no doubt that the most definitive evidence is the crystal structure of the dithionate salt of **IA**, which is discussed below.

The ^{13}C NMR of the CH_2S group shows a characteristic change in the chemical shift from ~30 ppm in the thiolate to ~50 ppm in the S-bonded isomer and back to 33−35 ppm in the N-bonded isomer. The chemical shifts of the CH_2 groups in the ^1H NMR are much less diagnostic and can be difficult to unravel because of the resonances from the methylenes of the ethylenediamine.

Two features of the electronic spectrum differentiate the N-bonded sulfenamide from the S-bonded isomer and the thiolate starting material. The first is the loss of the intense band in the 280−300-nm region, as shown in Figure 2 for the aminoethanethiol system. This difference is consistent with the assignment of the band in the latter complexes to S → Co(III) ligand-to-metal charge transfer. The N-bonded isomer lacks a Co−S bond. The second difference is the appearance of a new, less intense charge-transfer band at 330 nm. Such a band seems typical of Co−X−S chromophores (X = NH_2 or O). In the O-bonded sulfinate of Adamson et al.,[6] this band is at 326 nm (ϵ 4.1 × 10^3 M^{-1} cm^{-1}), and in the N-bonded sulfenamide of Sargeson and co-workers[12] (**II**), it is at 345 nm ($\epsilon = 2.59 \times 10^3$ M^{-1} cm^{-1}). The latter complex was prepared by Sargeson and co-workers by a unique series of rearrangement and condensation reactions from N,S-bonded $Co(en)_2$(cysteinato)$^{2+}$ reacting with acetic anhydride in DMSO.

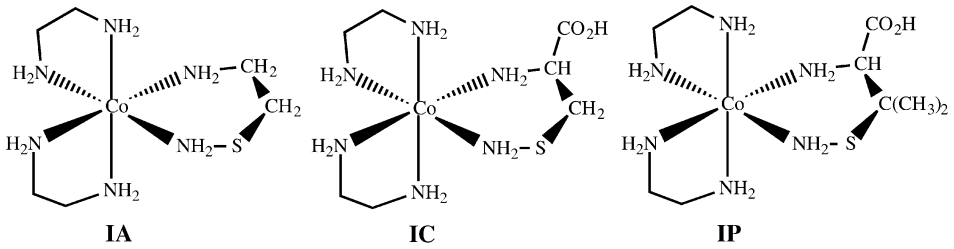


II

The N-bonded isomer has been most unequivocally identified by the crystal structure of the dithionate salt of **IA**, shown in Figure 3. The sulfenamide of aminoethanethiol is coordinated through two N atoms to give a six-membered chelate ring. The structural features may be compared to that of **II**, the only other N-bonded sulfenamide of cobalt(III). Although structurally more constrained, as part of a tridentate chelate, the Co−N(S) bond length in **II** (1.984 Å) is similar to that in **IA** (1.995 Å), and the other Co−N bonds are normal for Co(III)−en systems in both complexes. However, the bonds to sulfur are notably shorter in **IA** than in **II**: S−N 1.657 versus 1.756 Å; S−C 1.752 versus 1.803 Å. The structure of the Co(EDP) analogue, described below, sheds more light on this feature.

Linkage Isomerization Kinetics of $(en)_2$Co-sulfenamides. The rate of linkage isomerization for the $(en)_2Co$ systems has been determined by stopped-flow spectropho-

Chart 1



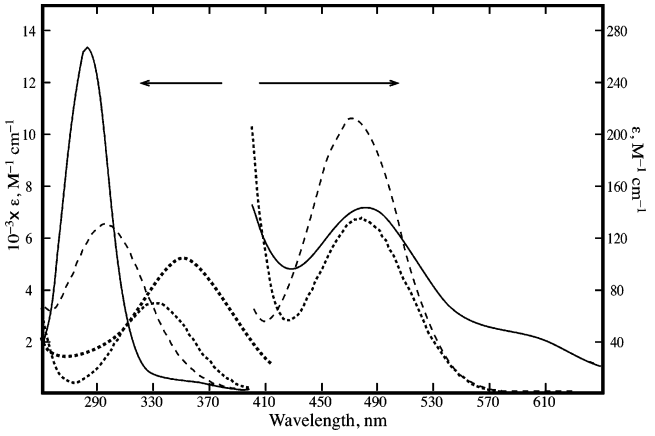


Figure 2. Electronic spectra of $(en)_2Co(S(CH_2)_2NH_2)^{2+}$ in 0.01 M $HClO_4$ (−); $(en)_2Co(S(NH_2)(CH_2)_2NH_2)^{3+}$ in 0.01 M $HClO_4$ (− − −); $(en)_2Co((NH_2)S(CH_2)_2NH_2)^{3+}$ in 0.01 M $HClO_4$ (---); $(en)_2Co((NH)S(CH_2)_2NH_2)^{2+}$ in pH 11.1 CAPS buffer (···).

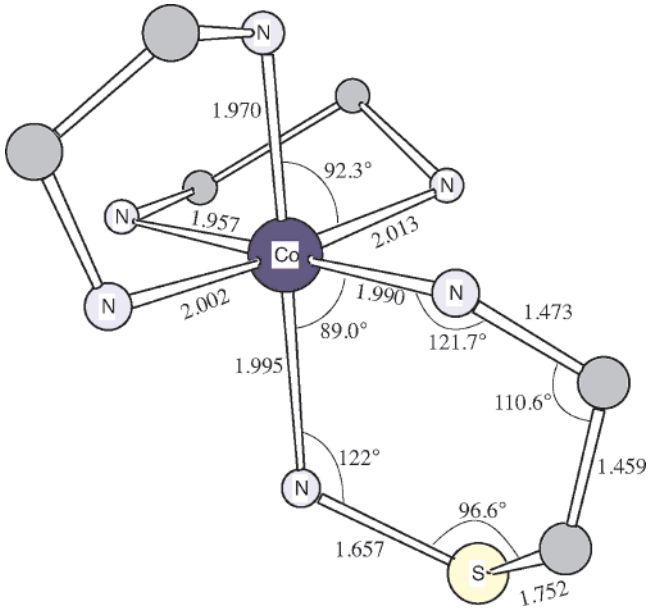


Figure 3. Perspective drawing of $[(en)_2Co(NH_2S(CH_2)_2NH_2)]^{3+}$ based on the crystal structure of $[(en)_2Co(NH_2S(CH_2)_2NH_2)](S_2O_6)_{1.5}\cdot 2.5H_2O$.

tometry. The reactant has an absorbance maximum in the 290-nm region, but a new peak at ~390 nm appears as the $[OH^-]$ increases and becomes dominant for $[OH^-] > 0.01$ M. This is consistent with the rapidly maintained deprotonation equilibrium defined by K_b in Scheme 1. The product spectrum also is dependent on the pH, with the maximum at ~330 nm shifting to ~350 nm as the pH increases. This is consistent with the deprotonation of the $Co-NH_2-S$ moiety in the product. This equilibrium has been

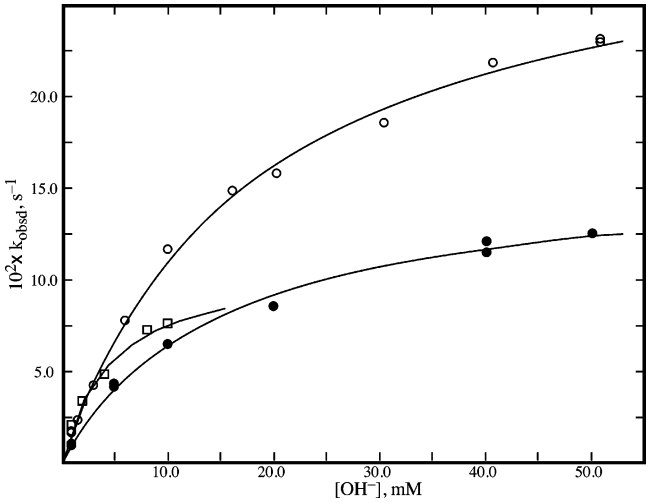


Figure 4. Dependence of the rate constant for linkage isomerization on $[OH^-]$ for $(en)_2Co(S(NH_2)CH_2CH(CO_2)NH_2)^{2+}$ (○); $(en)_2Co(S(NH_2)C(CH_3)_2CH(CO_2)NH_2)^{2+}$ (●); $(en)_2Co(S(NH_2)(CH_2)_2NH_2)^{3+}$ (□).

studied independently for the product from **IA** as described below.

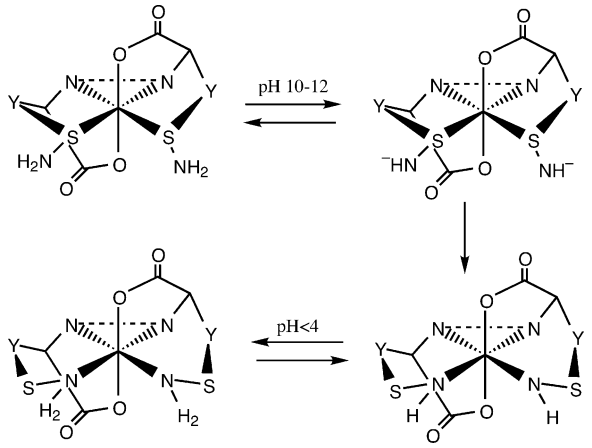
The observed pseudo-first-order rate constants ($[OH^-] \gg [Co(III)]$) show saturation behavior as the $[OH^-]$ is increased, as shown in Figure 4, and are consistent with eq 2.

$$k_{obsd} = \frac{a[OH^-]}{1 + b[OH^-]} = \frac{k_i K_b [OH^-]}{K_b + [OH^-]} \qquad (2)$$

The expression on the right is derived from Scheme 1, where K_b and k_i are defined, assuming that the K_b step is a rapidly maintained equilibrium and that the k_i step is rate-controlling. The results for **IC**, **IA**, and **IP** are given in Supporting Information Tables S1−S3. For **IC**, $k_i = 17.0 \pm 0.3$ M^{-1} s^{-1} and $K_b = 18.2 \pm 0.7 \times 10^{-3}$ M, and the corresponding values are 23.7 ± 1.2 M^{-1} s^{-1} and $4.6 \pm 0.5 \times 10^{-3}$ M for **IA** and 10.7 ± 0.3 M^{-1} s^{-1} and $15.1 \pm 0.8 \times 10^{-3}$ M for **IP**. The curves in Figure 4 are drawn using these parameters. The K_b values can be combined with K_w (10^{-14} M^2) to obtain the pK_a values of 12.3, 11.7, and 12.2, respectively. Overall, the k_i values show minor variations with the substituents on the thiolate ligand.

Acid Dissociation Constant of $Co(en)_2(NH_2SCH_2CH_2NH_2)^{3+}$. Because this N-bonded isomer is moderately stable in alkaline solution, it has been possible to determine its pK_a by spectrophotometry. Nevertheless, it was necessary to add a stock solution of the complex in acetate buffer to an equal volume of a 0.02 M buffer solution, previously adjusted to the desired pH, and then run the spectrum

Scheme 2



immediately on a Hewlett-Packard diode array spectrophotometer. As the pH is increased, the peak for the acidic form at 330 nm appears to shift as the more intense peak of the basic form starts to appear at 350 nm. The absorbance change is about 3.5 times larger at 350 nm, so this wavelength was used to determine the pK_a from measurements at 8 pH values in the range of pH 5.0 to 10.5.

The results were fit by least squares to eq 3

$$A = \frac{(\epsilon_{HA}[H^+] + \epsilon_A K_a)[Co(III)]_{tot}}{(K_a + [H^+])} \qquad (3)$$

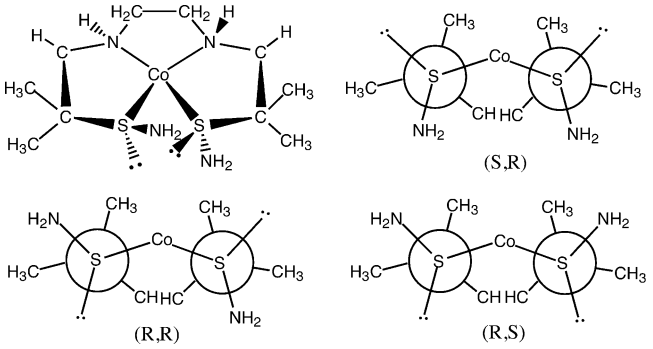
where A is the absorbance measured in a 1.00-cm path length cell, ϵ_{HA} and ϵ_A are the molar absorptivities of the acidic and basic forms, respectively, $[Co(III)]_{tot}$ is the total complex ion concentration, and K_a is the equilibrium constant for proton dissociation from the complex.

The analysis gave $K_a = (2.62 \pm 0.14) \times 10^{-9}$ M (pK_a 8.58) with ϵ_{HA} and ϵ_A values of $(2.43 \pm 0.02) \times 10^3$ and $(5.03 \pm 0.03) \times 10^3$ M^{-1} cm^{-1}, respectively. The pK_a for **IA** is similar to the value of 9.3 reported for **II**, and it seems that the Co(III)$-NH_2S-$ unit is rather weakly acidic.

N-Bonded Sulfenamides of Co(EDP)$^-$: Synthesis and Characterization. For Co(EDP)$^-$, analogous reactions have been observed, as shown in Scheme 2 for Y = $C(CH_3)_2$. Scheme 2 is representative of the synthetic procedure but is somewhat simplified in that at intermediate pH values (6−9) mixtures of (N,N′), (S,N), and (S,S′) isomers and various protonated forms are present.

This system is substantially more complicated than the $(en)_2Co$ analogue for several reasons. The deprotonated N-bonded isomer, $Co((NHS)_2EDP)^-$, forms in the usual way in alkaline solution (pH ≥ 10, NaOH or HPO_4^{2-}/PO_4^{3-} buffer), and acidification of this solution produces the expected protonated N-bonded isomer, $Co((NH_2S)_2EDP)^+$, as the dominant product, but the acidified solution is always contaminated with some mixed-linkage isomer, $Co((NH_2S)(SNH_2)EDP)^+$. The latter appears to result from some reverse-linkage isomerization during the acid quenching operation. Even with the rapid addition of acid to the alkaline solution or vice versa and vigorous stirring, the acidified product contained ∼15% of the mixed-linkage isomer. This

Chart 2



was quantified from the integrated intensities of the ^{1}H NMR spectra of the product solutions when it was important for subsequent use of the solutions, such as in the analysis of the electronic spectra. Nonetheless, it was possible to obtain the solid bromide salt of the N,N′ isomer, which was used to determine the electronic and ^{1}H NMR spectra of the pure N,N′ isomer.

The ^{1}H NMR spectra were crucial to unravelling this system, and the chemical shift details are tabulated in the Supporting Information. It should be noted that samples from D- and DL-penicillamine have identical spectra. The spectrum of the N,N′ isomer is straightforward, but the spectra of the S,S′ and N,S isomers reveal a mixture of conformers, as described below. These spectra have been useful in establishing that there is no detectable S,S′ isomer present at equilibrium and giving a measure of the amounts of N,N′ and N,S isomers in equilibrium.

For the N,N′ isomer, there are two CH_3 resonances of equal intensity because of the normal exo and endo positions in the six-membered chelate ring. The CH_2 region shows two complex multiplets in acidic solution, but in the equilibrium mixture at pH 7.3, these collapse to doublets (J = 8.5 Hz). This suggests that the multiplicity is due, in part, to coupling to the NH protons and that the coupling is lost because of fast proton exchange at pH 7.3. This was confirmed by decoupling experiments on acidic solutions of the N,N′ isomer, which revealed that irradiation of NH at 7.078 ppm causes the CH_2 multiplets to collapse to doublets (J(CH) = 8.5 Hz). The irradiation of one CH_2 multiplet collapsed the other to a doublet (J(NH) = 4 Hz). Then, the broad, asymmetric doublets centered at 6.58 and 7.00 ppm (J(HH) ≈ 11 Hz) must be assigned to nonequivalent protons on the $-SNH_2$ groups of the N,N′ isomer. As expected, irradiation at 6.58 ppm collapsed the resonance at 7.00 ppm to a singlet. The ^{13}C spectrum shows all of the expected features.

The situation is more complex for the S,S′ isomer because of the slow inversion of the $S-NH_2$ groups. This is illustrated in Chart 2, which shows a simplified picture of one conformer and projections along the S−C bond for the three nonequivalent forms. We note that the conformation of the NH groups is essentially locked by the coordinated $-CO_2^-$ (not shown) attached to the CH group.

The simplified structure on the left in Chart 2 and the projection along the S−C bond below the structure have the S atoms with the R conformation on the left and on the right

and will give four CH_3-resonances. If this is designated the (R,R) conformer, then the inversion of the left S atom will give the (S,R) conformer, which will give two CH_3 resonances, as will the (R,S) conformer. The spectrum shows the expected eight CH_3 resonances, with six of very similar integrated intensity and two of equal intensity but with $^1/_3$ to $^1/_5$ of the intensity of any one of the other six. This intensity pattern is consistent with either the (S,R) or (R,S) conformer being less favorable and constituting about 5%, whereas its opposite is about 32%, and the (R,R) conformer, shown in Chart 2, is dominant at about 63% of the total. The CH region shows the four resonances expected from the above analysis, with three of essentially equal intensity and one of much lower intensity. Again, the intensity pattern is consistent with ~60% of the (R,R) conformer and ~32 and ~8% for the other two, respectively. The conformer distribution is in reasonable agreement with that obtained from the CH_3 resonances. The CH_2 region of the S,S′ isomer shows four complex multiplets.

In the low-field region, there are three broad but distinct resonances of similar intensity at 7.92, 8.04, and 8.30 ppm and a weaker shoulder at ~8.33 ppm. The chemical shifts and breadths clearly indicate that they are N-bound H's. Selective decoupling to the CH_2 resonances shows that at least the three more intense NH_x resonances are each coupled to two CH_2 resonances, and therefore appear to be NH protons of the backbone rather than SNH_2 protons. Although the decoupling simplifies the low-field resonances, they remain broad with residual coupling, and it is possible that the SNH_2 protons are simply obscured by the others.

The ^{13}C spectrum of the S,S′ isomer in the CH_3 region shows six resonances of similar intensity and two much weaker resonances, as expected from the ^1H spectrum. Otherwise, the ^{13}C spectrum shows three distinct resonances for each type of carbon (CH_2, C(S), CH, and CO_2).

A similar analysis for the N,S isomer, in which the two halves of the species are nonequivalent, predicts two sets of four CH_3 resonances. Although this isomer has been obtained only as an equilibrium mixture with the N,N′ isomer at pH 7.26, the two strong CH_3 resonances of the latter are clearly distinguisable from eight weaker resonances of the N,S isomer. The CH_3 region of the spectrum was deconvoluted to obtain integrals for all 10 resonances. This showed that the mixture contains 59% N,N′ isomer and that the two forms of the N,S isomer are present in a ratio of ~2:1.

The CH region of the equilibrium mixture can be analyzed similarly. The N,N′ isomer has one resonance, whereas the N,S isomer has the expected two sets of two resonances. The stronger set is at 3.76 and 3.53 ppm, and the weaker set is at 3.65 and 3.62 ppm. The integration of these resonances gives 57% N,N′ isomer, in good agreement with the value from the integration of the CH_3 region.

The electronic spectra of the three isomers are shown in Figure 5. The spectrum of the N,S isomer has been generated from that of an equilibrium mixture at pH 7.26 and that of the N,N′ isomer, with the condition, from the NMR results, that the mixture is 58% of the latter isomer. These spectra show the features expected from simpler $(en)_2Co$ systems.

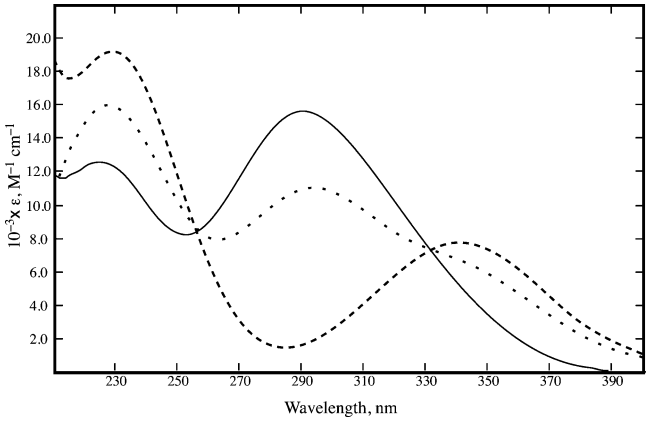


Figure 5. Electronic spectra, as molar extinction coefficient (ϵ) versus wavelength, of (- - -) $Co((NH_2S)_2EDP)$ (N,N′ isomer); (—) $Co((SNH_2)_2EDP)$ (S,S′ isomer); (· · ·) $Co((SNH_2)(NH_2S)EDP)$ (N,S isomer).

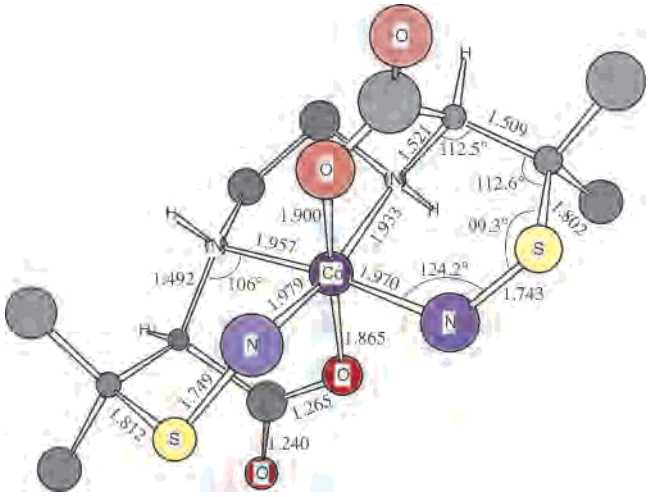


Figure 6. Perspective drawing of the structure of $Co((NH_2S)_2EDP)$ based on the crystal structure of $[Co(\kappa^6\text{-}\{H_2NSC(CH_3)_2CH(CO_2)NHCH_2\}_2][Br]\cdot 1.5H_2O\cdot 0.5EtOH$.

A perspective drawing of $Co((NH_2S)_2EDP)^+$ based on the crystal structure is shown in Figure 6 and may be compared to that of $(en)_2Co(NH_2S(CH_2)_2NH_2)^{3+}$ (**IA**) in Figure 3. Within the six-membered sulfenamide chelate ring there appear to be two significant differences. The S−N bond length is 1.743 Å in $Co((NH_2S)_2EDP)^+$, similar to that in **II** but longer than the 1.657 Å in **IA**. The bond angle at the primary amine N is similar to that at the sulfenamide N in **IA** (~122°), but the corresponding angle at the secondary amine N is 106° in $Co((NH_2S)_2EDP)^+$. This may be rationalized as a constraint caused by the coordinated $-CO_2^-$ attached to the chelated ring in the latter and also present in **II**.

Kinetics of Linkage Isomerization of $Co((SNH_2)_2EDP)^+$ and $Co((NH_2S)_2EDP)^+$. In the EDP systems, it was possible to study the linkage isomerization starting from either the S,S′-bonded $Co((SNH_2)_2EDP)^+$ or from the N,N′-bonded $Co((NH_2S)_2EDP)^+$. These reactions have been studied in several buffers (MES, phosphate, bicine, and CAPS) as well as up to 12 mM OH^- for the S,S′ isomer. The pH range is more limited for the N,N′ isomer because the equilibrium is almost completely toward this form for pH > 9.5. The absorbance−time profiles appear to be first order under all con-

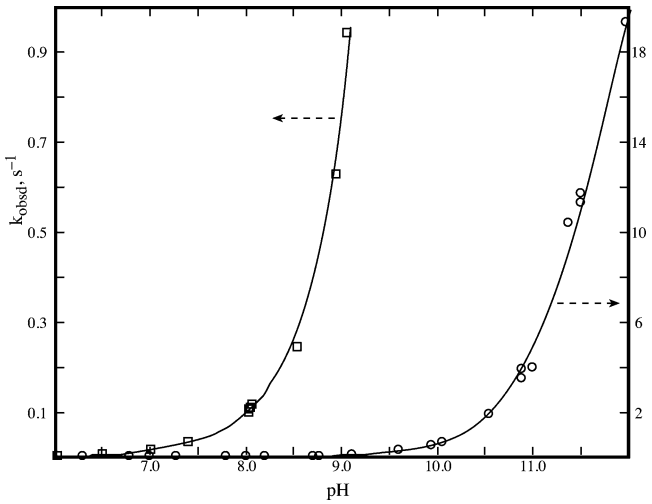


Figure 7. Dependence of the isomerization rate constant on pH for Co(EDP) systems: N,N′ isomer (□); S,S′ isomer (○).

ditions, and the pH dependence of the rate constant is shown in Figure 7. For both reactions, the rate constants increase with increasing pH, but the rate constants for the N,N′ isomer are always larger and the dramatic change with pH is apparent at much lower pH.

The kinetic results have been analyzed in terms of the reactions in Scheme 3, where only the reacting ligand groups bonded to Co(III) are shown. The vertical proton equilibria are based on the observations of the simpler monoamide ethylenediamine systems. Reactions of the fully protonated forms of either isomer are not included because of the observed stability of these systems for pH < 3.

We note that the microdissociation constants for the mixed linkage isomer are related to the overall acid dissociation constants by $K_{B1} = K_{SB1} + K_{NB1}$ and $K_{B2}^{-1} = K_{NB2}^{-1} + K_{SB2}^{-1}$ and that there are detailed balancing relationships between the rate constants and the second acid dissociation constants.

The linkage isomerization steps in Scheme 3 suggest that the reactions should be biphasic, but as already noted, only simple first-order absorbance−time profiles are observed. Initially, the system was analyzed by a biphasic model, and this showed that the simple appearance of the kinetics was due to two factors. One is that the N,N′ isomer-to-N,S isomer conversion is always at least 6 times faster than the other step, and the other is that the S,S′ isomer-to-N,S isomer reaction is essentially irreversible. This has been noted from the NMR observations, which show that there is no detectable S,S′ isomer present at equilibrium. As a result, the two reactions are treated as independent in the following analysis because this is much simpler to describe and has been shown to be quantitatively consistent with a full biphasic analysis.

The reaction of the S,S′ isomer is relatively simple because the reaction is irreversible. k_{21} and k_{20} in Scheme 3 can be ignored, and the observed pseudo-first-order rate constant is given by eq 4.

$$k_{obsd} = \frac{k_{-21}K_{C1}[H^+] + k_{-20}K_{C1}K_{C2}}{[H^+]^2 + K_{C1}[H^+] + K_{C1}K_{C2}} \quad (4)$$

Least-squares analysis gave values for $k_{-21}K_{C1}$, $k_{-20}K_{C1}K_{C2}$, K_{C1}, and $K_{C1}K_{C2}$ of $(1.92 \pm 0.11) \times 10^{-10}$, $(3.76 \pm 1.1) \times 10^{-19}$, $(6.38 \pm 1.7) \times 10^{-9}$, and $(1.25 \pm 0.44) \times 10^{-20}$, respectively. The specific rate constants are $k_{-21} = 0.03$ and $k_{-20} = 30\ s^{-1}$ with pK_{C1} 8.2 and pK_{C2} 11.7. The curve in Figure 7 is calculated from these parameters, and the results and specific conditions are given in Supporting Information in Table S4.

The situation is more complex for the reaction of the N,N′ isomer because both the forward and reverse reactions must be included and this brings in the proton equilibria of the N,S isomer. The values of k_{obsd} increase smoothly with increasing pH and are consistent with eq 5.

$$k_{obsd} = \frac{(k_{11T})[H^+] + (k_{10T})}{[H^+]([H^+] + K_{N1})} \quad (5)$$

A least-squares analysis of the data gives $k_{11T} = (1.51 \pm 0.07) \times 10^{-9}$, $k_{10T} = (1.57 \pm 0.57) \times 10^{-17}$, and $K_{N1} = (2.25 \pm 0.7) \times 10^{-8}$ (p$K_{N1} = 7.65$). The curve in Figure 7 is calculated from these parameters, and the experimental data are given in Table S5 of the Supporting Information.

In terms of Scheme 3, the pseudo-first-order rate constant is given by eq 6.

$$k_{obsd} = \frac{k_{11}K_{A1}[H^+] + k_{10}K_{A1}K_{A2}}{[H^+]^2 + K_{A1}[H^+] + K_{A1}K_{A2}} + \frac{k_{-11}K_{SB1}[H^+] + k_{-10}K_{B1}K_{B2}}{[H^+]^2 + K_{B1}[H^+] + K_{B1}K_{B2}} \quad (6)$$

The experimental rate law (eq 5) must be some approximate form of eq 6. The experimental conditions of pH ≤ 9 suggest that $[H^+] \gg K_{A2}$ and K_{B2} so that the third term in the denominator of each fraction in eq 6 can be dropped. The acidities of the aminoethanethiol derivatives (Table 1) and the proximity of the ionizing group to Co(III) suggest that $K_{NB1} > K_{SB1}$ so that $K_{B1} \approx K_{NB1}$. Because both refer to the ionization of a $CoNH_2S$ group, it also seems probable that $K_{A1} \approx K_{B1}$ ($= K_{N1}$). Then, eq 6 simplifies to eq 7 with the same form as eq 5.

$$k_{obsd} = \frac{(k_{11}K_{A1} + k_{-11}K_{SB1})[H^+] + (k_{10}K_{A1}K_{A2} + k_{-10}K_{B1}K_{B2})}{[H^+]^2 + K_{N1}[H^+]} \quad (7)$$

By combining the above analysis with the equilibrium composition determined by NMR, it is possible to obtain approximate specific rate constants for the linkage isomerization. The NMR study gives the equilibrium ratio of N,S to N,N′ isomers as ∼0.7, which equals the ratio of kinetic coefficients $k_{11}K_{A1}/k_{-11}K_{SB1}$ and $k_{10}K_{A1}K_{A2}/k_{-10}K_{B1}K_{B2}$ in eq 7. Because the sum of the terms in the first ratio equals k_{11T}, $k_{11}K_{A1} = 0.89 \times 10^{-9}$. Then, if $K_{A1} \approx K_{N1}$, one obtains $k_{11} \approx 0.04\ s^{-1}$. A similar analysis of the second ratio and k_{10T}, along with the condition that $K_{A2} \leq 10^{-10}$ is consistent with the derivation of eq 6, gives $k_{10} \geq 0.46\ s^{-1}$.

Scheme 3

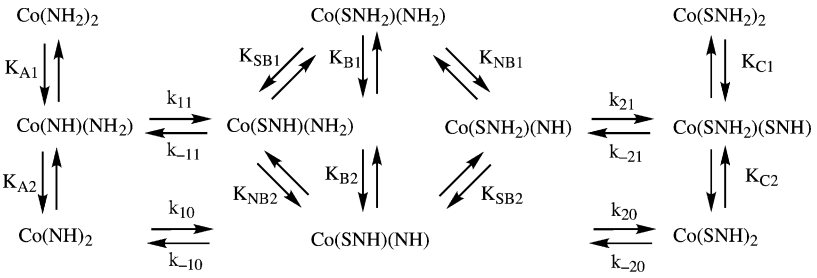


Table 1. Summary of Isomerization Kinetics and Acidity Results

complex ion	isomerization rate constant, s^{-1} [a]	pK_a
$(en)_2Co(S(NH_2)(CH_2)_2NH_2)^{3+}$	23.7	11.7
$(en)_2Co(NH_2SCH_2)_2NH_2)^{3+}$		8.58
$(en)_2Co(S(NH_2)CH_2CH(CO_2)NH_2)^{2+}$	17.0	12.3
$(en)_2Co(S(NH_2)C(CH_3)_2CH(CO_2)NH_2)^{2+}$	10.7	12.2
$Co((SNH_2)_2EDP)^+$	0.03, 30.0[b]	8.2, 11.7[c]
$Co((NH_2S)_2EDP)^+$	~0.04, ≥0.46[b]	7.65[d]

[a] At 25 °C in 0.10 M ionic strength. [b] Rate constants for the second isomerization step. [c] pK_a for ionization of the second proton. [d] On the basis of the assumption that $K_{A1} \approx K_{B1} \approx K_{NB1}$ as described in the text.

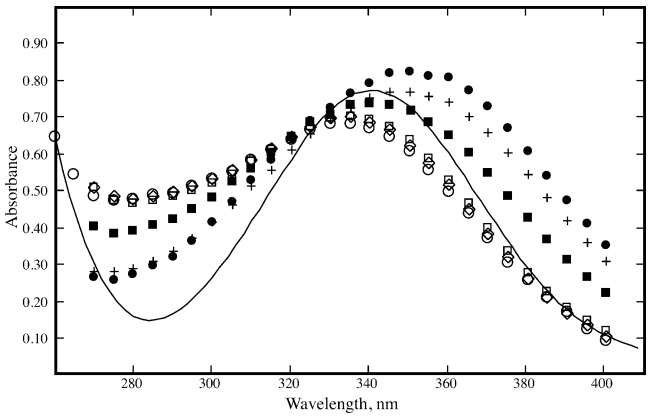


Figure 8. Absorbance changes due to isomerization and pH change: (−) N,N′ isomer at pH 4; equilibrium mixtures at pH 7.00 (◇), 7.26 (○), 8.0 (□), 9.3 (■), 10.0 (+) and 10.7 (●).

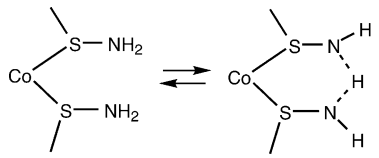
The electronic spectra of the equilibrium mixtures do not provide very definitive information on the composition because of the numerous potential chromophores (Scheme 3) and their inevitable similarity. However, the representative spectra at various pH values in Figure 8 are consistent with the kinetic and NMR results. The spectra are relatively invariant between pH 7 and 8.5, but above pH 9, there is a decrease in absorbance in the 280-nm region, and an increase in absorbance and shift to longer wavelengths in the 340- to 360-nm region. The invariance for pH < 8.5 is consistent with eq 6, and the variation at higher pH suggests that the condition $[H^+] \gg K_{A2}$ and K_{B2} is no longer true; that is, significant ionization of the second proton of the N,N′ isomer starts to occur.

Discussion

For all of the systems studied here, the reaction of the thiolate complex with hydroxylamine-*O*-sulfonic acid is a facile process in aqueous solution and yields the corresponding S-bonded sulfenamide derivatives. The kinetic observations show that the modifications of the thiolate ligand and nonreacting ligand set cause rather modest changes in reactivity that can be rationalized on the basis of steric effects of the CH_3 substituents. Thus, the penicillamine derivatives of $(en)_2Co^{III}$ and $Co(EDP)^-$ react about 5 times more slowly than the others. The second step in the amidation of $Co(EDP)^-$ is 5.4 times slower than the first, which may be attributed to probability and the steric effect of the NH_2 that was added.

At least for Co(III) systems, it appears that the linkage isomerism of the S-bonded sulfenamides is a general reaction. The process requires mildly basic conditions; therefore, the product must be moderately stable in basic solution. Because this condition is marginally true for the ~1-min reaction time of the present systems, we developed detailed synthetic procedures to minimize this problem.

The kinetic and acid dissociation behavior parameters are summarized in Table 1. The S-bonded sulfenamides of $(en)_2Co$ are all very weak acids, as is the monodeprotonated derivative of Co(EDP) (pK_a 11.7−12.3). However, the first proton dissociation of $Co((SNH_2)_2EDP)^+$ appears anomalous with pK_a 8.2. This may be rationalized by intramolecular hydrogen bonding in the monodeprotonated species, as shown in eq 8.



(8)

The much greater acidity of $Co((SNH_2)_2EDP)^+$ has the effect of making the isomerization occur at much lower pH values than for the $(en)_2Co$ analogues. As a consequence, the former were studied at pH 6−12, whereas the latter were observed only in ≥1 mM OH^-. Analogous hydrogen bonding may explain the somewhat greater acidity of $Co((NH_2S)_2EDP)^+$ compared to that of $(en)_2Co(NH_2S(CH_2)_2NH_2)^{3+}$.

The rate constants for the isomerization of the $(en)_2Co$ systems are relatively independent of the nature of the parent thiolate ligand, and the equilibria lie far toward the N-bonded isomer, presumably driven by the strength of the Co−N interaction. The Co(EDP) system is different in that there is a mixture of N,N′ and N,S isomers at equilibrium for the fully protonated species; the N,N′ isomer is fully formed only when the $Co-NH_2$ groups are fully deprotonated. In addition, the rate constant for the first step of the isomerization in either direction is ~500 times smaller than that for the

$(en)_2Co$ systems, whereas the rate constant for the second step with the S,S′ isomer is much larger and in the same range as those for the $(en)_2Co$ systems. The slow first step may be attributed to movement constraints caused by the fact that the sulfenamide part of the chelate ring is coordinated through two groups, and the faster second step may be caused by the conjugate base activation through the ionized Co−NH−S− group.

In summary, it has been shown that S-bonded sulfenamides in mildly alkaline solution can undergo linkage isomerism to the N-bonded form. This general reaction allows extensions of earlier work[12,13] for the one example of this class of compounds where it was found that the exposed S(0) can undergo further reactions with electrophiles or nucleophiles and opens the way to a wider range of derivatives of metal thiolates[15] and S clusters.[16] In addition, the N-bonded isomer forms its conjugate base under mild conditions, which may serve to labilize the metal center for ancillary ligand substitution.

Experimental Section

Materials. Hydroxylamine-*O*-sulfonic acid (Aldrich) was stored over P_2O_5 and analyzed by iodimetry on the basis of the study by Krueger and co-workers.[11] Acidic solutions are subject to hydrolysis, but neutralized solutions can be conveniently stored under refrigeration for several days without serious deterioration. It was observed that solutions in HEPES buffer decompose much more rapidly than those in MES or phosphate.

Caution! Perchlorate salts of metal complexes with organic ligands are potentially explosive! They should be handled with great care and in small amounts.

Tables of electronic spectra (absorbance maxima and molar extinction coefficients) and NMR spectra (^1H and ^{13}C chemical shifts) are given in the Supporting Information.

$[(en)_2Co(S(CH_2)_2NH_2)](ClO_4)_2$ was prepared by the method of Reynolds et al.[10] $[(en)_2Co(SCH_2CH(CO_2)NH_2)](ClO_4)$ was prepared from L-cystine, initially by the method of Sloan and Krueger[17] but mainly by that of Freeman et al.,[18] which gave a better yield and quality of product. Both substances were characterized by their ^1H NMR spectra and by the comparison of their electronic spectra to published results.

$[(en)_2Co(SC(CH_3)_2CH(CO_2H)NH_2]Cl_2\cdot 0.5H_2O\cdot 1.25$ i-PrOH was prepared by slight modifications of the method of Freeman et al. DL-Penicillamine disulfide (0.025 mol) was generated in situ as described by Freeman et al. The solution was deoxygenated, and then deoxygenated solutions of ethylenediamine (0.124 mol) and $CoCl_2\cdot 6H_2O$ (0.05 mol) were added. After reacting overnight at ambient temperature, the brown solution was adjusted to pH 2.2 with 1 M HCl, diluted with 0.01 M HCl, and loaded on a column of Dowex 50W-X2(H^+) resin. The column was eluted with increasing concentrations of HCl, and the product was eluted in 1.0 and 2.0 M HCl. The eluate was reduced to a small volume under vacuum, and then 20 volumes of 2-propanol were added to precipitate the product as a purplish-brown powder. The ^1H NMR confirmed the identity of the product and suggested that it contained a greater proportion of the Λ isomer by comparison to published results and also showed the presence of 2-propanol. Anal. Calcd for $CoC_{12.75}H_{37}N_5O_{3.75}Cl_2$: C, 31.75; N, 14.52; H, 7.73. Found: C, 31.57; N, 14.31; H, 7.79.

$[(en)_2Co(S(NH_2)C(CH_3)_2CH(CO_2)NH_2)](Cl)_2\cdot 1.5H_2O$ (**IP**) was prepared by dissolving 2.0 g (2.07 mmol) of the above product and 0.65 g (2.66 mmol) of $BaCl_2\cdot 2H_2O$ in 2.50 mL of water and adding 4.8 mL of a 0.553 M solution of HSA (2.65 mmol) adjusted to pH 2.88 by addition of 1.0 M NaOH. After 15 min, the mixture was centrifuged to separate the $BaSO_4$ from the reddish-brown solution. The solution was brought to pH 2.76 by the addition of solid $NaHCO_3$ and cooled in an ice bath overnight. The burnt-orange powdered product was collected by filtration, washed with methanol and ether, and dried in a vacuum desiccator to yield 0.325 g of product (36%). An additional 0.133 g was collected similarly after storage in an ice bath for 3 days. Anal. Calcd for $CoC_9H_{30}N_6SO_{3.5}Cl_2$: C, 24.55; N, 19.09; H, 6.87. Found: C, 24.71; N, 18.84; H, 6.87.

$[(en)_2Co(NH_2SC(CH_3)_2CH(CO_2)NH_2)](Br)_2\cdot 2H_2O$ was prepared by dissolving 0.269 g (0.61 mmol) of the above product in 70 mL of water and dividing the solution equally into 10 vials. Then 0.80 mL of 0.10 M NaOH was added rapidly to each vial while stirring vigorously, and after 90 s, the reaction was quenched by adding 0.32 mL of 0.50 M HCl. The solutions of the product were combined and reduced to ∼6 mL by evaporation of the solvent under vacuum. Then 0.9 g of LiBr was added, and after overnight storage in a refrigerator, the product was collected by filtration, washed with methanol and ether, and air dried. This product (0.24 g) was recrystallized by dissolving 0.16 g in 4.0 mL of water, centrifuging to remove undissolve material, adding 0.20 g of LiBr, and cooling as before. The product was collected and washed as before to obtain 0.10 g of a dull orange powder. Analysis suggested that this is a mixture of protonated and unprotonated forms, but the material was used for NMR characterization. In a modified procedure, 12 mg of crude product was dissolved in 0.40 mL of water, and 5.0 mg of lithium acetate dihydrate was added to bring the pH to 4.5−5. Then 86 mg of LiBr was added, and refrigeration for 2 days gave nearly quantitative precipitation of the product as small crystals. Anal. Calcd for $CoC_9H_{31}N_6SO_4Br_2$: C, 20.08; N, 15.62; H, 5.81. Found C, 20.13; N; 15.17; H, 5.65.

$[(en)_2Co(S(NH_2)CH_2CH(CO_2)NH_2)](ClO_4)_2\cdot H_2O$ was prepared by reacting $[(en)_2Co(SCH_2CH(CO_2)NH_2)](ClO_4)$ (2.0 g, 5.0 mmol) in 95 mL of water at 40−45 °C with hydroxylamine-*O*-sulfonic acid (0.68 g, 6.0 mmol) for 2−3 min. The cysteine complex dissolves as the reaction proceeds. The warm solution was filtered and cooled to ambient temperature, and then 5.5 mL of 1.0 M $Ba(ClO_4)_2$ was added and $BaSO_4$ was removed by filtration. To the filtrate we added 35 g of $LiClO_4$ and 225 mL of 95% ethanol, and the solution was cooled to −5 °C. The product, a curry-colored powder, was collected by filtration, washed with ethanol and ether, and air dried. Yield 2.6 g (83%). This product is pure but is a mixture of the forms with the protonated and unprotonated carboxylate group. Recrystallization from either water or 1 M $HClO_4$ yields the pure unprotonated or protonated form, respectively. Cinnamon-colored crystals of the unprotonated form were characterized by X-ray crystallography as $[(en)_2Co(S(NH_2)CH_2CH(CO_2)NH_2)](ClO_4)_2\cdot H_2O$. Anal. Calcd for $CoC_7H_{25}N_6O_{11}SCl_2$: C, 15.83; N, 15.82; H, 4.74. Found: C, 15.92; N, 15.54; H, 4.75.

$[(en)_2Co(S(NH_2)(CH_2)_2NH_2)](ClO_4)_3\cdot H_2O$ was prepared from $[(en)_2Co(S(CH_2)_2NH_2)](ClO_4)_2$ by the same method as for the cysteine analogue, except that a precipitate did not form when

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ethanol was added. The ethanol solution was concentrated under vacuum to ~80 mL and then cooled at −5 °C to yield a mustard-colored powder. The solid was collected by filtration, washed with ether, and air dried. Yield 66%. Anal. Calcd for $CoC_6H_{26}N_6O_{13}SCl_3$: C, 12.26; N, 14.30; H, 4.46; S 5.46. Found: C, 12.35; N, 14.03; H, 4.41; S 5.22. The electronic spectrum is in excellent agreement with literature results,[10] where the crystal structure also is reported.

$[(en)_2Co(NH_2S(CH_2)_2NH_2)]^{3+}$ (**IA**) was prepared by dissolving 0.055 g of $[(en)_2Co(S(NH_2)(CH_2)_2NH_2)](ClO_4)_3 \cdot H_2O$ in 12.9 mL of water and then dividing the solution into three equal portions. A stirring bar was added to each solution, and then each was closed with a serum cap and deoxygenated with Ar. To each solution we added 0.49 mL of 0.10 M NaOH. The reaction was allowed to proceed for 80 s and then quenched by injecting 0.21 mL of 0.50 M $HClO_4$. Close adherence to the procedure and rapid mixing during the addition of reagents are critical to minimize side reactions and product decomposition. Anaerobic conditions greatly improve the stability of the product solutions. Scaling up the method, in terms of concentrations or volumes, has been found to be detrimental, and it is important to avoid a large excess of NaOH.

$[(en)_2Co(NH_2S(CH_2)_2NH_2)]Br_3 \cdot H_2O$ was prepared by pooling the three volumes of product solution from above and concentrating under vacuum to ~2 mL. Then 0.1 g of LiBr and 3 mL of ethanol were added, and after cooling in a refrigerator, the solution yielded reddish-orange crystals that appeared suitable for X-ray analysis but proved to be disordered. A higher yield of product, in the form of an orange powder, can be obtained by using more LiBr and ethanol and cooling to −5 °C in the freezing compartment of a refrigerator. Yield of orange powder 55%. Anal. Calcd for $CoC_6H_{26}N_6OSBr_3$: C, 13.62; N, 15.89; H, 4.95; S 6.06. Found: C, 13.59; N, 15.42; H, 4.84; S, 5.68.

$[(en)_2Co(NH_2S(CH_2)_2NH_2)](S_2O_6)_{1.5} \cdot 2.5H_2O$ was prepared by dissolving 11 mg of the bromide salt in 0.69 mL of water containing 0.25 M $Na_2S_2O_6$ and 1 mM $HClO_4$. The solution was transferred to an NMR tube, and 1.5 mL of ethanol was layered on the top. During 2 days of cooling in a refrigerator, orange-amber crystals of the product were deposited. These proved suitable for X-ray analysis.

$[(en)_2Co(NH_2SCH_2CH(CO_2)NH_2)]^{2+}$ (**IC**) was prepared by a procedure directly analogous to that for **IA**. However, it has not been possible to obtain a pure solid product, although a number of counterions and cosolvents have been tried. The cation has been characterized by its electronic and NMR spectra.

5,5-Dimethythiazolidine-4-carboxylic acid was prepared by the reaction of D,L-penicillamine (10 g in 150 mL of water) with formaldehyde (7.8 mL of 40% in 150 mL of 95% ethanol) for 15 h at ambient temperature. Large shiny-white crystals were collected by filtration and washed with ether. An additonal 3 mL of 40% formaldehyde was added, and the reaction was allowed to continue for 24 h and was then cooled to −5 °C for 48 h before collecting a second crop of product as before. The overall yield was 8.22 g (76%). The melting point (211−213 °C, decomp) agrees with that of Süs.[19] If D-penicillamine is used, then the product is much more soluble. The solution was evaporated almost to dryness, and the product was recrystallized from hot methanol. This product has a melting point of 200−203 °C. The 300-MHz ^{1}H NMR in D_2O shows peaks at δ 1.40 (s, CH_3), 1.65 (s, CH_3), 3.98 (s, CH), and 4.42 (d, CH_2), in reasonable agreement with the reports of Samanen et al.[20] and Dilbeck et al.[21] For the D isomer, the corresponding peaks are at 1.43, 1.68, 4.01 and 4.48 ppm, respectively. Anal. Calcd for $C_6H_{11}NO_2S$: C, 44.70; N, 8.69; H, 6.88. Found: C, 44.49; N, 8.63; H, 6.86.

N,*N*′-Ethylene-di-DL-penicillamine (**EDP**) was prepared by sodium metal reduction of 5,5-dimethythiazolidine-4-carboxylic acid in liquid ammonia, following the procedure of Blondeau et al.[22] Preliminary studies revealed that this material contained what is believed to be 2−3% *N*-methylpenicillamine; the product was purified by dissolving it in water by the addition of NaOH and then reprecipitating by the addition of aqueous HCl to pH 3−4. The 300-MHz ^{1}H NMR in 0.5 M DCl/D_2O shows peaks at δ 1.49 (s, CH_3), 1.67 (s, CH_3), 3.75 (m, CH_2CH_2), and 4.22 (s, CH). The ^{13}C NMR in 0.44 M DCl/D_2O (vs dioxane, 67.4 ppm) shows peaks at δ 27.66 (CH_3), 31.41 (CH_3), 44.78 (CH_2N), 44.93 (CS), 72.15 (CH), and 169.07 (CO_2H). All of the peaks, except that at 44.93 ppm, appeared as pairs separated by 3−8 Hz, and the reported shifts are the average for each pair. This doubling suggests that the product is a mixture of DD, DL and LL forms, as expected because the amino acid reactant was racemic. This was confirmed for the product of a synthesis starting with D-penicillamine, for which the ^{13}C peaks are at 27.69, 31.43, 44.79, 44.82. 72.12, and 169.15 ppm. The NMR spectra agree with those reported by Okamoto et al.,[23] who used a quite different synthesis and appears to have run the spectra under slightly alkaline conditions, on the basis of the pH dependence of the shifts for the cysteine analogue reported by Li et al.[14] Anal. Calcd for $C_{12}H_{24}N_2O_4S_2 \cdot 2H_2O$: C, 39.98; N, 7.77; H, 7.83. Found: C, 40.78; N, 7.78; H, 8.05.

$Co(EDP)^-$ has been prepared in solution by reacting equimolar amounts of $Co(OH_2)_4(O_2CCH_3)_2$ and EDP in water at pH 7−7.5 under anaerobic conditions. The solution was then transferred to a flask containing a stoichiometric amount of $Co(sep)Cl_3$ under an argon atmosphere, and the redox reaction was allowed to proceed for ~30 min. The product solution was transferred to a short, deoxygenated column of Dowex 50W-X8 (Na^+) to remove $Co(sep)^{2+}$. The eluate solution, typically containing 0.5−1 mM $Co(EDP)^-$, was collected in air. It is necessary to remove the $Co(sep)^{2+}$ because it is oxidized by dioxygen, and the H_2O_2 produced oxidizes the thiolate function of the EDP ligand. This also is a problem if O_2 is used as the oxidant for $Co^{II}(EDP)$. The anionic nature of the $Co^{III}(EDP)$ complex has been confirmed by noting that the complex does not bind to cation resins but does bind to the anion resin Dowex 1-X8 (Cl^-). Tests with Ellman's reagent (5,5′-dithiobis(2-nitrobenzoic acid)) revealed 2−3% free thiol from crude EDP and ~0.25% from purified EDP. The ^{13}C NMR in H_2O (12% D_2O) (vs dioxane, 67.4 ppm) shows peaks at δ 32.14 (CH_3), 33.62 (CH_3), 48.78 (CS), 53.01 (CH_2N), 80.38 (CH), and 183.56 (CO_2^-). This agrees with the spectrum reported by Okamoto et al.,[23] except that all signals are upfield by ~1.75 ppm, presumably because of the use of different reference compounds.

The sulfenamide derivative of $Co(EDP)^-$ can be prepared by the reaction of a solution of $Co(EDP)^-$ (~1 mM), prepared as described above, with 0.05 M HSA in ≥0.05 M H^+ for 10 min and then separating the product by ion exchange as described below. The sulfenamide derivative was prepared more directly on the 10 mM scale by reacting an anaerobic solution of equivalent amounts of $Co(ClO_4)_2 \cdot 6H_2O$ and EDP with $Co(NH_3)_5OH_2(ClO_4)_3$. The latter oxidant has the advantage that the cobalt(II) products are not

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Table 2. Summary of Crystallographic Data

	$[(en)_2Co\{S(NH_2)CH_2-CH(CO_2)NH_2\}][ClO_4]_2\cdot H_2O$	$[(en)_2Co(H_2NS-(CH_2)_2NH_2)][S_2O_6]_{1.5}\cdot 2.5H_2O$	$[Co(\kappa^6\text{-}\{H_2NSC(CH_3)_2-CH(CO_2)NHCH_2\}_2][Br]\cdot 1.5H_2O\cdot 0.5EtOH$
empirical formula	$C_7H_{25}Cl_2CoN_6O_{11}S$	$C_6H_{29}CoN_6O_{11.5}S_4$	$C_{13}H_{30}BrCoN_4O_6S_2$
molecular mass	531.22	556.52	541.37
temp (K)	213	193	193
cryst syst	monoclinic	triclinic	monoclinic
space group	$P2_1$ (no. 4)	$P\bar{1}$ (no. 2)	Cc (no. 9)
a (Å)	8.4908(4)	8.4431(14)	16.552(4)
b (Å)	14.1916(5)	8.9608(15)	11.927(3)
c (Å)	8.4937(4)	15.652(3)	12.639(3)
α (deg)		84.216(4)	
β (deg)	113.513(4)	77.067(3)	114.011(4)
γ (deg)		64.888	
V (Å^3)	938.49(7)	1045.1(3)	2279.1(9)
Z	2	2	4
ρ_{calcd} (g cm^{-3})	1.880	1.769	1.578
cryst size (mm^3)	0.44 × 0.31 × 0.07	0.34 × 0.13 × 0.05	0.70 × 0.04 × 0.03
collecn 2θ limit (deg)	115.0	49.98	52.90
wavelength (Å)	1.54178	0.71073	0.71073
reflns collected	2741	5346	4584
indep reflns	2443	3607	3527
final R indices[a]			
R_1 [$F_0^2 \geq 2\sigma(F_0^2)$]	0.0415	0.079	0.0627
wR_2 [$F_0^2 \geq -3\sigma(F_0^2)$]	0.1148	0.2376	0.1537

[a] $R_1 = \sum||F_0| - |F_c||/|F_0|$; $wR_2 = [\sum w(F_0^2 - F_c^2)^2/\sum w(F_0^4)]^{1/2}$.

oxidized by O_2 in acidic solution. Once the oxidation was complete, the solution was opened to air, made 0.05 M in HSA with ~0.06 M H^+, and allowed to react for 10 min. The product was purified by ion-exchange chromatography on Dowex 50W-X2(H^+), keeping the eluant at pH 2−3. Any neutral monoamide species and anionic starting material pass through the column, and the amide form is eluted with 0.1−0.2 M H^+. The amidated $Co(EDP)^-$ complex, initially in the S-bonded form, undergoes linkage isomerization to the N-bonded form(s) at a rate that is synthetically problematic for pH ≥ 6 and yields mixtures of isomers for pH 6−9.5. Therefore, the S-bonded isomer must be kept in acidic solution (pH < 4), and the N-bonded isomer, formed at pH > 9.5 inevitably yields some N,S isomer when it is quenched with acid to pH < 4.

Crystals for the structure determination of the N,N′ isomer were prepared by evaporating the ion-exchange eluate to dryness, dissolving the product in a minimum amount of 95% ethanol, and then adding an equal volume of ether. After several days at ~−5 °C, this yielded thin reddish-purple rods of the bromide salt suitable for the structure determination.

pK_a Determination of IA. A 3.00 × 10^{-4} M aqueous solution of **IA** was prepared, and 1.50-mL aliquots of this were mixed with an equal volume of buffer solution. The spectrum was recorded immediately on a Hewlett-Packard 8451 diode array spectrophotometer, and then the pH of the solution was measured. The buffers (0.02 M) were acetate (pH 5.0); HEPES (pH 7.5), BICINE (pH 8−9), and CAPS (pH 9.4−10.5). The change in absorbance at 350 nm was used to determine the pK_a.

Instrumentation. Electronic spectra were measured on Cary 219 and Hewlett-Packard 8451 diode array spectrophotometers. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM 300 and Varian 500 spectrometers in D_2O or H_2O as required, with internal standards of sodium trimethylsilylpropanesulfonate for ^{1}H and dioxane (δ 67.4) for ^{13}C. Details of the electronic and NMR spectra are tabulated in the Supporting Information.

Stopped-flow studies used a Tritech Dynamics model IIA system, with the data collection and analysis as described previously,[24] and an Applied Photophysics instrument using the manufacturer's collection and analysis software.

X-ray Structures. The crystal data are collected in Table 2.

(a) $[Co(en)_2\{S(NH_2)CH_2CH(CO_2)NH_2\}][ClO_4]_2\cdot H_2O$ was obtained as cinnamon-colored crystals from slow cooling of an aqueous solution of the compound. Data were collected on a Siemens P4/RA diffractometer using Cu Kα radiation at −60 °C.[25] The data were corrected for absorption through use of Gaussian integration (indexing of crystal faces). The structure was solved using direct methods (SHELXS-86),[26] and refinement was completed using the program SHELXL-93.[27] Hydrogen atoms were assigned positions on the basis of the geometries of their attached carbon atoms and were given thermal parameters 20% greater than those of the attached carbons.

(b) $[(en)_2Co(H_2NS(CH_2)_2NH_2)][S_2O_6]_{1.5}\cdot 2.5H_2O$ was obtained as orange-amber crystals from a solution of the bromide salt in 0.25 M $Na_2S_2O_6$ and 1 mM $HClO_4$ with ethanol layered over the water. Data were collected on a Bruker P4/RA/SMART 1000 CCD diffractometer using Mo Kα radiation at −80 °C. The data were corrected for absorption through use of the SADABS procedure. The structure was solved using direct methods (SIR-97),[28] and refinement was completed using the program SHELXL-93. Hydrogen atom positions were generated as in part a.

(c) $[Co(\kappa^6\text{-}\{H_2NSC(CH_3)_2CH(CO_2)NHCH_2\}_2][Br]\cdot 1.5H_2O\cdot 0.5EtOH$ was obtained as thin reddish-purple rods by cooling a

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1:1 95% ethanol/ether solution. Data were collected on a Bruker P4/RA/SMART 1000 CCD diffractometer using Mo Kα radiation at −80 °C. The data were corrected for absorption through use of the SADABS procedure. The structure was solved using direct methods (DIRDIF),[29] and refinement was completed using the program SHELXL-93. Hydrogen atom positions were generated as in (a).

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Supporting Information Available: X-ray crystallographic details of the three compounds in CIF format, observed and calculated rate constants for linkage isomerization, electronic spectra (absorbance maxima and molar extinction coefficients), and NMR spectra (^{1}H and ^{13}C chemical shifts). This material is available free of charge via the Internet at http://pubs.acs.org.

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