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Reaction of Thiols with N-Bonded Sulfenamide Complexes of Cobalt(III): Steric Effect and Reaction Pathway

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The products and kinetics of the reaction of several thiols (RSH = 2-aminoethanethiol, cysteine, penicillamine, cysteine ethyl ester) with N-bonded sulfenamide complexes ($[Co(en)_2(NH_2S(CH_2)_2NH_2]^{3+}$ (**IA**), $[Co(en)_2(NH_2SCH_2CH(CO_2H)NH_2]^{3+}$ (**IC**), $[Co(en)_2(NH_2SC(CH_3)_2CH(CO_2H)NH_2]^{3+}$ (**IP**)) have been studied. The reaction proceeds by nucleophilic attack at sulfur with cleavage of the N–S bond to form a disulfide and leave a coordinated NH_3 ligand. The kinetics (pH 4–10) reveal that the deprotonated thiol, RS^-, is the reactive nucleophile and that the N-deprotonated sulfenamide complex is unreactive. The reactions of **IP** are $\sim 10^4$ times slower than those of **IA** or **IC**, and the reasons and consequences of this large steric effect are discussed. It is concluded, on the basis of these and other observations from the literature, that there will be substantial steric retardation to nucleophilic attack at two-coordinate sulfur in a $R–C(CH_3)_2–S–X–R'$ unit because of the regiospecificity of the reaction. The acid dissociation constants of **IP** and the X-ray structure of its bromide salt also are reported.

Introduction

In a previous study,[1] it was discovered that S-bonded sulfenamide derivatives of several cobalt(III) complexes, made by reaction of hydroxylamine sulfonate ($H_2NOSO_3^-$) with the parent thiolate complexes,[2] undergo linkage isomerism in weakly alkaline solution (pH 8−10) to the N-bonded isomer. The only previously reported N-bonded sulfenamide was made by Gainsford et al.[3] using a unique series of rearrangement and condensation reactions of N,S-bonded Co(en)$_2$(cysteinato)$^{2+}$. The amidation-isomerization route is much more general and may be useful in the broad area of metal−thiolate chemistry.

Jackson, Sargeson, and co-workers also found[4] that the sulfur in their N-bonded sulfenamide is susceptible to reduction and reaction with nucleophiles. The present study concerns the reactions of several N-bonded sulfenamides with a range of thiols. The sulfenamides studied are $(en)_2Co^{III}$ complexes derived from 2-aminoethanethiol (AET, common name cysteamine), cysteine (Cyst), and penicillamine (Pen), which are shown in Chart 1 as **IA**, **IC**, and **IP**, respectively. For these, the isomerization is essentially irreversible,[1] giving the N-bonded isomer shown.

The structures of **IA** (and its S-bonded parent) already have been reported.[1] The protonated N-isomers of **IA**, **IC**, and **IP** are red and have a charge-transfer band at ~330 nm ($\epsilon \approx 3.5 \times 10^3$ M^{-1} cm^{-1}). It also was found by Gainsford et al.[3] and confirmed[1] for the systems in Chart 1 that the S−NH$_2$ groups in the N-bonded isomers are weakly acidic with pK_a's in the 7−9 region, and this ionization causes a change to a brown-red color as the band shifts to ~350 nm ($\epsilon \approx 5.0 \times 10^3$ M^{-1} cm^{-1}). Information on the products and kinetics of the reaction of **IA**, **IC**, and **IP** with thiols are reported here, along with the structure of the bromide salt of **IP**.

As well as providing quantitative reactivity results, the observations here have important implications for the long-standing problem of the regiospecificity of substitution reactions at two-coordinate sulfur. As noted recently by Bachrach and Mulhearn,[5] these reactions are inferred to proceed by backside attack, based essentially on the analysis

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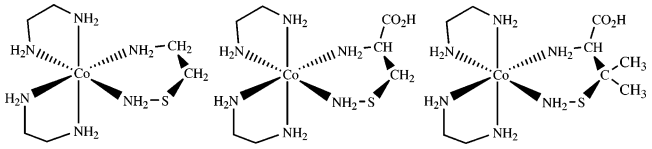
Chart 1



IA **IC** **IP**

by Dunitz and co-workers[6] of preferred orientations of substituents in crystal structures. Earlier, Pryor and Smith[7] had noted the much greater reactivity at sulfur as compared to that at carbon, and they concluded that this could be explained by backside attack to give a metastable intermediate which could be stabilized by the ability of sulfur to expand its octet. Theoretical treatments,[8] mainly on thiolate−disulfide exchange models, have focused on the question of whether nucleophilic reactions at two-coordinate sulfur occur by a concerted S_N2 or by addition−elimination with an intermediate. More recent theory[9] has included some solvent water molecules in the model, and, with the usual theoretical codicils, the results suggest that solvation favors a trend toward the concerted pathway. In all cases, backside attack on two-coordinate sulfur is favored, and this is strongly supported by the experimental observation here that **IP** is much less reactive than **IA** or **IC**.

Results

Synthesis and Characterization of N-Bonded Sulfenamide Complexes. These complexes are synthesized by reaction of the S-bonded isomer in mildly alkaline solution (pH 9−12) as reported previously.[1] In the present study, the X-ray structure and acid dissociation constants of **IP** have been determined.

Table 1 summarizes the crystallographic information for the bromide salt of **IP**, $[(en)_2(NH_2SC(CH_3)_2CH(CO_2)NH_2](Br)_2 \cdot 2H_2O$. This salt was made from racemic penicillamine, and the unit cell contains four Co(III) units derived from each of the enantiomers of penicillamine and the Δ and Λ forms of $Co(en)_2$. A perspective view and some structural parameters for one unit are shown in Figure 1, but the parameters are essentially the same for the other, except for inversion at the CH center. Full details are given in the Supporting Information. The bond lengths and angles are generally within normal ranges and are analogous to those previously found[1] for **IA**. The structure is discussed below in more detail because of its relevance to the kinetic observations.

The acid dissociation constants of $[(en)_2(NH_2SC(CH_3)_2CH(CO_2H)NH_2]^{3+}$ (**IP**) have been determined by potentiometric titration and spectrophotometry. An acidic solution

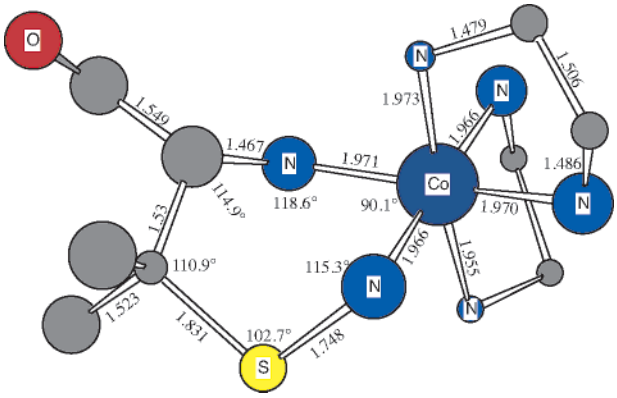


Figure 1. Perspective drawing based on the X-ray crystal structure of the bromide salt of $[(en)_2Co(NH_2SC(CH_3)_2CH(CO_2)NH_2)]^{2+}$ (**IP**). Interatomic distances and angles are for complex 2 (one of the two crystallographically independent species) and are essentially equivalent to those in complex 1 (see CIF in Supporting Information).

Table 1. Summary of Crystallographic Data

	$[(en)_2(NH_2SC(CH_3)_2CH(CO_2)NH_2](Br)_2 \cdot 3.5H_2O$
empirical formula	$C_9H_{34}Br_2CoN_6O_{5.5}S$
molecular mass	565.23
temp (K)	193
cryst syst	triclinic
space group	$P\bar{1}$ (No. 2)
a (Å)	12.4937(12)
b (Å)	12.9888(13)
c (Å)	14.2417(14)
α (deg)	100.938(2)
β (deg)	91.761(2)
γ (deg)	111.092(2)
V (Å^3)	2104.7(4)
Z	4
ρ_{calcd} (g cm^{-3})	1.784
cryst size (mm^3)	0.26 × 0.17 × 0.05
collecn 2θ limit (deg)	52.84
wavelength (Å)	0.71073
reflns collected	11 241
indep reflns	8189
final R indices[a]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0519
wR_2 [$F_o^2 \geq -3\sigma(F_o^2)$]	0.1159

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

(pH 2) of the complex in 0.10 M $LiClO_4$ was titrated with incremental amounts of 0.0100 M NaOH. Due to hydrolytic instability above pH 8, only the ionization constant of the carboxylic acid function could be reliably determined and gave $K_O = 2.21 \times 10^{-3}$ M ($pK_O = 2.66$, 22 °C). Spectrophotometric measurements could be done more rapidly by adding an aliquot of the complex to a 0.01 M solution of buffer (acetate, MES, HEPES, or BICINE) adjusted to the desired pH values. Both complex and buffer were in 0.10 M $LiClO_4$. Each spectrum was recorded at 5 s intervals on an HP 8451A spectrophotometer, and absorbances (extrapolated to time of mixing) at 330 and 350 nm were used to determine the ionization constant of the $CoNH_2S$ function, K_N. Least-squares analysis of the data at the two wavelengths gave pK_N values of 7.34 ± 0.06 and 7.29 ± 0.04, respectively.

Reaction of N-Bonded Sulfenamides with Thiols: Products and Stoichiometry. In a typical experiment, it is found that mixing solutions of $Co(en)_2(NH_2S(CH_2)_2NH_2)^{3+}$ (**IA**)

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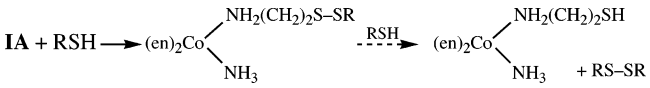
Scheme 1



and penicillamine at pH 6.1 produces an immediate bleaching of the color, and the product spectrum shows that the reactant peak at 330 nm has disappeared, and only a much lower intensity band remains at 473 nm ($\epsilon = 1.0 \times 10^2$ M^{-1} cm^{-1}). Studies with varying ratios of Co(III) to penicillamine in the range of 0.5−2.0 reveal that the absorbance change at 330 nm is consistent with a 1:1 stoichiometry for the reactants. It should be noted that the S-bonded isomers do not react with thiols on a time scale that is competitive with the S- to N-bonded linkage isomerism.

The amidation of the thiolate has the formal effect of oxidizing S(−II) to S(0), and linkage isomerism leaves an S(0) which is activated toward nucleophilic attack by the Co(III)−NH_2 substituent. Therefore, it seems most probable that the thiol reacts at the S(0) with formation of a disulfide and cleavage of the N−S bond, as shown by the first reaction in Scheme 1. The second reaction shows the possible thiol−disulfide exchange that could occur in the presence of excess thiol.

The kinetic study described below shows that these reactions may occur on the stopped-flow time-scale at near neutral pH and are much faster than the decomposition of the sulfenamide complex under the same conditions. This eliminates the possible pathway to the disulfide through hydrolytic cleavage of the Co−N bond followed by reaction with thiol at the free end of the sulfenamide ligand.

The organic disulfide product was characterized by ^{1}H NMR for the reaction at pH 6.3 of **IA** with 1 equiv of aminoethanethiol. The reaction solution was acidified, and then the Co(III) was reduced with aqueous Cr(II). The Co(II) was removed as the anthranilate and the Cr(III) as the hydroxide at pH 7.6. The ^{1}H NMR spectrum at pH 6.3 and in 0.01 M $HClO_4$ (see Supporting Information) showed all of the features of cystamine (the disulfide of AET) by comparison to an authentic sample. The acidic solution also showed the features expected for NH_4^+ and H_2en^{2+}. An analogous product analysis has been done for the reaction of **IP** with cysteine, and the ^{1}H NMR spectrum at pH 2 confirmed the formation of the mixed disulfide of penicillamine and cysteine (see Supporting Information).

The product of the reaction of 2.9×10^{-3} M **IA** with 2.9×10^{-2} M D-penicillamine at pH 5.5 (0.024 M MES buffer) was separated from the excess penicillamine by elution from a Sephadex-SP C25 column with 0.25−0.4 M $NaClO_4$ in 1.0×10^{-3} M $HClO_4$. A test of the product solution with Ellman's reagent (5,5′-dithiobis(2-nitrobenzoic acid)) indicated that no free thiol groups are present. Therefore, cleavage of the disulfide (the second reaction in Scheme 1) did not occur. The ^{1}H NMR spectrum showed the features expected for AET and penicillamine (see Supporting Information), showing that they are attached to the Co(III) complex. Based on spectra of $(en)_2Co^{III}(NH_3)(X)$ species,[10] the resonance at 3.51 is assigned to $CoNH_3$, while four

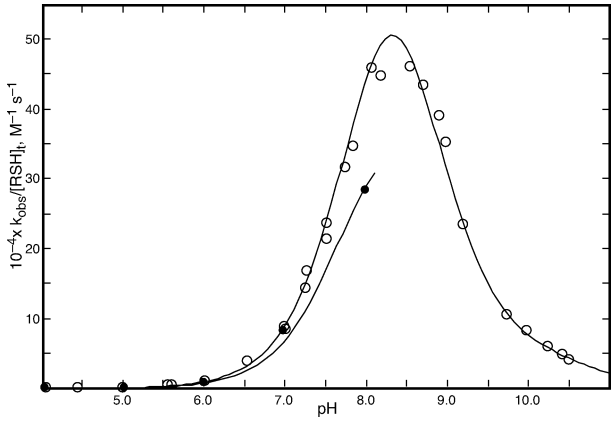


Figure 2. Variation of $k_{obs}/[RSH]_t$ with pH, where RSH is 2-aminoethanethiol (○) or D,L-penicillamine (●), reacting with $[(en)_2Co(NH_2SCH_2CH(CO_2)NH_2)]^{2+}$ (**IC**).

resonances at 4.92, 5.14, 5.38, and 5.44 ppm are assigned to the nonequivalent $CoNH_2CH_2$ and NH_3^+ of penicillamine. The last two resonances are of equal intensity, but the first two overlap with the solvent water so that integration cannot distinguish which are the equivalent *trans*-NH_2 groups from en.

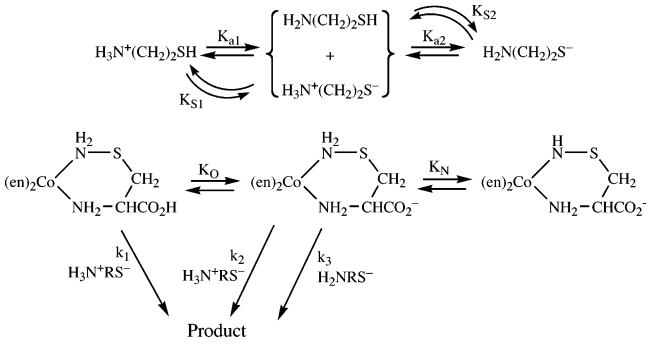
Chemical reactions also have been used to confirm that the product does not have an H_2O ligand. The band at 473 nm in the penicillamine product is unchanged in phosphate buffers between pH 4.45 and 8.05. A coordinated H_2O ligand would be expected to undergo hydrolysis over this pH range and affect the spectrum in a manner analogous to $Co(NH_3)_5(OH_2)^{3+}$. In addition, the small first-order rate constant of 5.4×10^{-5} M^{-1} s^{-1} for the reduction of the product of **IA** with penicillamine by Cr(II) ([Cr(II)] = 0.019 M; $[H^+]$ = 0.14 M; $[Cl^-]$ = 0.13 M; μ = 0.25 M) is much closer to values of 4.9×10^{-5} and 1.1×10^{-5} M^{-1} s^{-1} predicted for $Co(NH_3)_6^{3+}$ and $Co(en)_3^{3+}$,[11] respectively, than to 0.42 M^{-1} s^{-1} predicted for $Co(NH_3)_5(OH_2)^{3+}$.[12] The much larger rate constant for the latter results from the bridged electron transfer through the hydrolyzed aqua ligand. It seems that no such ligand is present in the product in Scheme 1. The product of aminoethanethiol with **IA** also is reduced by Cr(II) under the same conditions with a small rate constant of 5.6×10^{-5} M^{-1} s^{-1}.

Reaction Kinetics. The kinetics of several representative reactions have been studied as a function of thiol concentration and pH, always with the thiol concentration (∼1−20 mM) in excess over Co(III) (≥0.1 mM). Full details are given in the Supporting Information.

The reaction of the N-bonded cysteine sulfenamide complex (**IC**) with 2-aminoethanethiol (AET) has been studied as a function of pH (4.0−10.5) and AET concentration (0.75−1.5 mM) at 21 °C in 0.10 M $LiClO_4$. The rate is first-order in total AET concentration, $[AET]_t$, and shows a classical bell-shaped dependence on pH (see Figure 2).

These observations can be understood in terms of the species shown in Scheme 2, with the reactive species being the AET deprotonated at S and the $CoNH_2S$- species. The conjugate base of the latter must be much less reactive to account for the decrease in rate above pH ≈ 8.2. Scheme 2

Scheme 2



shows horizontal equilibria, which are considered as rapidly maintained, and three rate-controlling pathways to the product. For the kinetic conditions of $[Thiol]_t \gg [Co(III)]_t$, the predicted pseudo-first-order rate constant is given by eq 1.

$$k_{obs} = \frac{(k_1K_{S1}[H^+]^3 + k_2K_{S1}K_O[H^+]^2 + k_3K_{a1}K_{a2}K_O[H^+]^3)[Thiol]_t}{([H^+]^2 + K_O[H^+] + K_OK_N)([H^+]^2 + K_{a1}[H^+] + K_{a1}K_{a2})} \quad (1)$$

To analyze the pH dependence, it is necessary to know the macro (K_{a1},K_{a2}) and micro (K_{S1},K_{S2}) acid dissociation constants of the aminothiols used. After a survey of the available data which are in reasonable agreement, with a few exceptions, it was determined that the earliest values of Benesch and Benesch[13] are most suitable for the present purposes because the temperature and ionic strength are closest, and three of the aminothiols used here were also studied by Benesch and Benesch. For the fourth, penicillamine, the values of Martin and Wilson[14] have been used. These values are given in Table 1.

It is reasonable to assume that K_O for **IC** is similar to the value determined here for **IP**, and the analysis is not sensitive to this assumption because, even at the lowest pH of the kinetic study, $[H^+] \ll K_O$. The first term in the denominator of eq 2 is then $\sim K_O([H^+] + K_N)$ so that K_O does not affect the $[H^+]$ dependence of k_{obs}, and K_O cannot be determined from these data. With this simplification and in more generic terms, the rate law has the form given by eq 2.

$$k_{obs} = \frac{(\alpha[H^+]^3 + \beta[H^+]^2 + \gamma[H^+])[Thiol]_t}{([H^+] + K_N)([H^+]^2 + K_{a1}[H^+] + K_{a1}K_{a2})} \quad (2)$$

where $\alpha = k_1K_{S1}/K_O$, $\beta = k_2K_{S1}$, and $\gamma = k_3K_{a1}K_{a2}$.

With K_{a1} and K_{a2} fixed, this model gives an excellent fit of the data for **IC** reacting with AET, as can be seen from the calculated curve in Figure 2. Least-squares analysis gives $pK_N = 8.23 \pm 0.03$ and values of α, β, and γ summarized in Table 3. It should be noted that α is marginally defined because this pathway makes a small contribution for pH > 4.

Table 2. Acid Dissociation Constants of Thiols and Cobalt(III) Complexes

species	pK_{a1}[a]	pK_{a2}[a]	pK_{S1}[b]	pK_{S2}[b]	pK_O[c]	pK_N[d]
cysteine[e]	8.36	10.53	8.53	10.03		
2-aminoethanethiol[e]	8.35	10.8	8.35	10.8		
penicillamine[f]	7.95	10.45	8.05	10.35		
cysteine ethyl ester[e]	6.69	9.17	7.45	8.41		
IP					2.66[g]	7.31[h]
IC						8.23 ± 0.03[i]
IA						8.58[j]

[a] Mixed macro acid dissociation constants. [b] Micro acid dissociation constants for −SH group defined in Scheme 1. [c] Mixed acid dissociation constant for $-CO_2H$. [d] Mixed acid dissociation constant of $-SNH_2Co$. [e] Reference 12. [f] Reference 13. [g] This work, determined by pH titration. [h] This work, determined by spectrophotometry. [i] This work, determined from pH dependence of rate. [j] Reference 1.

After minor changes, Scheme 2 also can describe the reaction of **IC** with penicillamine. The kinetic results are consistent with the pH and $[Thiol]_t$ dependence predicted by eq 2. However, the more limited pH range (4−8) required K_N to be fixed at the value determined for the reaction with AET while fitting the data, and only the β term contributes significantly. The data and calculated curve are shown in Figure 2.

Similarly, the reactions of **IA** with several thiols (AET, D,L-penicillamine, L-cysteine, and L-cysteine ethyl ester) were studied in the pH 5.4−6.8 range, with K_N fixed at the previously determined value.[1] Because **IA** has no carboxylate group, there is no contribution from the α term in eq 2, and the γ term is insignificant for pH < 7, so that only the β term is required to fit the data. The least-squares best-fit parameters for these systems also are given in Table 3, and curves calculated from these parameters are shown in Figure 3.

It came as a surprise to find that the reactions of **IP** with AET, D-penicillamine, and L-cysteine are much slower than those of **IC** or **IA**. While the latter were studied by stopped-flow, the reactions of **IP** are easily followed by conventional spectrophotometry. These reactions were studied in detail to assess the source of this kinetic difference. Because **IP** is racemic, its enantiomers could have different reactivity with D-penicillamine and L-cysteine. A detailed analysis of the absorbance−time curves found that the ratio of rate constants for the enantiomers is ≤2 and the curves could not be realistically differentiated from a simple exponential decay.

The dependence of k_{obs} on pH for these reactions of **IP** was found to be consistent with the rate law given by eq 2. The AET and penicillamine systems were studied over a wide enough pH range to allow a determination of K_N from the kinetic data. For **IP**, the values of pK_N obtained were 7.22 ± 0.03 and 7.24 ± 0.05, respectively, in excellent agreement with each other and with the average value of 7.31 obtained from spectrophotometry, as described above. The data and calculated curves are shown in Figure 4. The results of least-squares analyses are given in Table 3, where it can be seen that the kinetic coefficients for **IP** are much smaller than those for **IC** or **IA**.

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(11) Przystas, T. J.; Sutin, N. *J. Am. Chem. Soc.* **1973**, *95*, 5545.
(12) Toppen, D. L.; Linck, R. G. *Inorg. Chem.* **1971**, *10*, 2635.
(13) Benesch, R. E.; Benesch, R. *J. Am. Chem. Soc.* **1955**, *77*, 5877; $\mu \approx$ 0.1 M, 23°.
(14) Martin, R. B.; Wilson, E. W. *Arch. Biochem. Biophys.* **1971**, *142*, 445; μ = 0.15 M, 25°.

Table 3. Kinetic Results for the Reaction of N-Bonded Sulfenamide Complexes of $Co^{III}(en)_2$ with Thiols at 21 °C in 0.10 M $LiClO_4$

					k,[c] M^{-1} s^{-1}		
complex	thiol[a]	α[b]	$10^2 \times \beta$[b]	$10^{12} \times \gamma$[b]	k_1	k_2	k_3
IC	L-Cyst	20 ± 11	1.01 ± 0.03	1.4 ± 0.2	9.7×10^6	2.3×10^6	19×10^6
IC	D,L-Pen		0.84 ± 0.06	0.18 ± 0.16		0.91×10^6	(45×10^6)
IA	L-Cyst		1.88 ± 0.05			6.4×10^6	
IA	AET		0.840 ± 0.014			1.9×10^6	
IA	D,L-Pen		0.780 ± 0.009			0.88×10^6	
IA	L-CystEt		2.57 ± 0.01			0.73×10^6	
IP	L-Cyst		$(2.55 \pm 0.07) \times 10^{-4}$			8.6×10^2	
IP	AET	$(8.3 \pm 1) \times 10^{-3}$	$(1.34 \pm 0.03) \times 10^{-4}$	$(5.3 \pm 4) \times 10^{-4}$	4.1×10^3	3.0×10^2	(8×10^4)
IP	D,L-Pen	$(6.0 \pm 4) \times 10^{-3}$	$(3.40 \pm 0.15) \times 10^{-5}$	$(8 \pm 2) \times 10^{-4}$	1.5×10^3	38	2×10^3

[a] L-Cyst = L-cysteine; D,L-Pen = D,L-penicillamine; AET = 2-aminoethanethiol; L-CystEt = L-cysteine ethyl ester; see Supporting Information for details of pH, buffer, and thiol concentrations. [b] Composite kinetic parameters defined in eq 3. [c] Specific rate constants defined in Scheme 1.

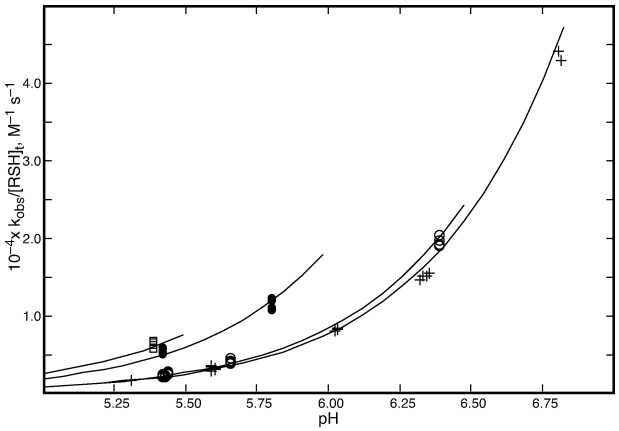

Figure 3. Variation of $k_{obs}/[RSH]_t$ with pH, where RSH is 2-aminoethanethiol (○), D,L-penicillamine (+), L-cysteine (●), or L-cysteine ethyl ester (□), reacting with $[(en)_2Co(NH_2SCH_2CH_2NH_2)]^{3+}$ (**IA**).

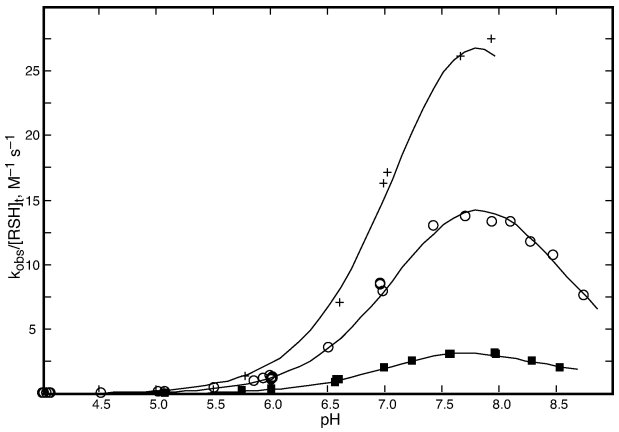

Figure 4. Variation of $k_{obs}/[RSH]_t$ with pH, where RSH is 2-aminoethanethiol (○), D,L-penicillamine (■), or L-cysteine (+), reacting with $[(en)_2Co(NH_2SC(CH_3)_2CH(CO_2)NH_2)]^{2+}$ (**IP**).

Discussion

The spectroscopic and chemical properties of the products show that these reactions proceed as given in eq 1. The rates of the reactions are first-order in the thiol concentration, and the pH dependence shows that the thiol reacts via its thiolate form (RS^-) with the N-protonated form of the coordinated sulfenamide ($CoNH_2SR'$), as shown in Scheme 2.

The variation of k_2 (Table 3) with the thiol for a particular Co(III) complex follows a consistent pattern of cysteine > 2-aminoethanethiol > penicillamine > cysteine ethyl ester. Similar variations can be seen for k_1 and k_3, although fewer values are available. This order of reactivity is expected from the basicity of the thiolate, as judged from the pK_{S1} values (Table 2). Such correlations have often been observed in studies of thiolate reactivity with various organic substrates.[15] It also is observed that $k_3 > k_2$ for a given thiol, and this is consistent with the greater basicity of H_2NRS^- as compared to $^+H_3NRS^-$, based on the fact that $pK_{S2} > pK_{S1}$ (Table 2). The observation that $k_1 > k_2$ suggests, as expected, that protonation of the carboxylate group on the sulfenamide assists nucleophilic attack at the $-SNH_2$ function.

The closest analogue of the reactions studied here for which quantitative reactivity data are avaliable seems to be that of 1-butanethiol with *N*,*N*-dimethyl-*o*-nitrobenzenesulfenamide studied by Kice and Kutateladze.[16] The latter was studied in $MeOH/CH_3CN$ under acidic conditions (3−12 mM CF_3SO_3H) and is acid catalyzed due to protonation of the sulfenamide, with the neutral thiol as the nucleophile. The specific rate constant for $O_2NC_6H_4S(NH(CH_3)_2)^+$is $\sim 10^3$ M^{-1} s^{-1} at 25 °C. In the present case, the $(en)_2Co^{III}$ unit is serving the activating effect of the proton in the former, and the near neutral conditions allow the more reactive thiolate to be the dominant nucleophile. However, even under much more acidic conditions ($[H^+] = 6.7 \times 10^{-3}$ to 0.10 M in 0.12 M HCl/LiCl), the reaction of $Co(en)_2(NH_2S(CH_2)_2NH_2)^{3+}$ with AET shows a simple inverse dependence on $[H^+]$ with $\beta = 0.85 \times 10^{-2}$ s^{-1} in agreement with the value at pH 5.4−6.4. There is no indication from the rate law for reaction of $HS(CH_2)_2NH_3^+$ with **IA**.

The most remarkable feature of the kinetics is that the coordinated sulfenamide derived from penicillamine (**IP**) is $\sim 10^4$ times less reactive than the cysteine analogue (**IC**), which in turn has reactivities similar to the 2-aminoethanethiol derivative (**IA**). The inductive effect of the replacement of two β-H's in **IC** by two β-CH_3's in **IP** is expected to cause a <10-fold reduction in rate (based on substitutions at carbon), so the observed effect must be largely a steric one.

(15) Freter, R.; Pohl, E. R.; Wilson, J. M.; Hupe, D. J. *J. Org. Chem.* **1979**, *44*, 1771. Szajewski, R. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 2011. Reuben, D. M. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1976**, *98*, 114. Patel, H. M. S.; Williams, D. L. H. *J. Chem. Soc., Perkin Trans. 2* **1990**, 37. Toteva, M. M.; Richard, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 11073. DeCollo, T. V.; Lees, W. J. *J. Org. Chem.* **2001**, *66*, 4244.

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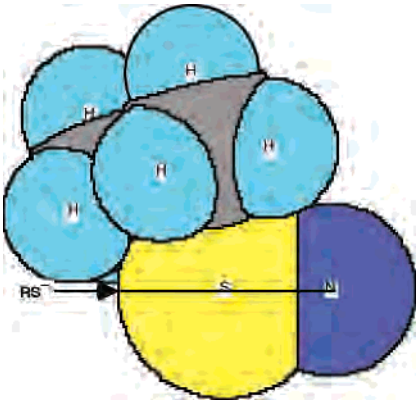

Figure 5. Space-filling model of the $(H_3C)_2CSNH_2$ portion of **IP**, indicating the steric crowding for nucleophilic attack on the backside of the S−N bond.

Yet what is the source of the steric problem in **IP**? The answer seems to lie with the strong regiospecificity for nucleophilic attack at two-coordinate sulfur. The structure of **IP** in Figure 1 suggests that the S-atom is quite exposed and does not appear sterically encumbered. However, the lone pairs on the S-atom are not shown in Figure 1 and will be below and pointing out of and behind, respectively, the C−S−N plane. Because the RS^- nucleophile is unlikely to approach the sulfenamide S in the direction of the lone pairs, it is left with two avenues, either between the lone pairs (i.e., from below in Figure 1) or from the left, opposite to the S−N bond. The latter is the classical, backside-attack pathway for S_N2 substitution at C, which leads to so-called Walden inversion. In the present system, this is the only pathway that has any steric problem with the methyl groups, and the large steric effect of these groups seems to establish this as the pathway for the nucleophilic attack at S studied here.

The extent of the steric problem caused by the methyl groups is shown in Figure 5, which is a space-filling model of the reaction center, derived from the structure in Figure 1. It is apparent that a nucleophile of the size of RS^- will have considerable steric difficulty while approaching the sulfenamide S from the direction opposite the S−N bond. Overall, these observations are consistent with the theoretical treatments[8,9] of nucleophilic attack at two-coordinate sulfur and provide the first experimental support for this long-held belief. The lack of reactivity of thiols with the S-bonded isomers may be attributed to an analgous steric effect due to substituents on the β-carbon in the sulfenamide chelate ring.

It might be argued that the thiol-sulfenamide reaction studied here has some unique requirement or that locking the electrophile into a chelate ring imposes some special problem. The explanation proposed here does not invoke any special effects and suggests that any sulfur in an $R-C(CH_3)_2-S-X-R'$ unit should be exceptionally resistant to nucleophilic attack. There are no sulfenamide precedents to test this prediction, but the reaction has a formal analogy to the much studied thiol−disulfide exchange (X = S). Singh and Whitesides[17] studied steric effects for thiol−disulfide exchange, but $-CH_3$ groups were in the β-position ($-CH_2-CH_2S-$ vs $-C(CH_3)_2CH_2S-$), and they only observed about a 3-fold reduction in rate. In a more qualitative vain, Gorin and co-workers[18] observed that the exchange of *tert*-butyl disulfide with 1-butanethiol was exceptionally sluggish and did not reach equilibrium after 100 days at 60 °C in ethanol, with sodium methoxide as catalyst.

Of more relevance to the current study is the work of Theriault and Rabenstein[19] on the reactions of penicillamine and cysteine and their disulfides. The reaction of penicillamine with cystine at pH 5−8 was found to reach equilibrium on the time-scale of minutes and gives a specific rate constant of 18 M^{-1} s^{-1} for reaction with the thiolate form of penicillamine. Yet the reaction of cysteine with penicillamine disulfide requires hours to reach equilibrium at pH 10.4−12.4, and only initial rates were measured. Our analysis of the four data points gives specific rate constants of $\sim 2.3 \times 10^{-5}$ and $\sim 5 \times 10^{-6}$ M^{-1} s^{-1} for the thiolate forms of cysteine with the amino group protonated and deprotonated, respectively. The original authors suggested that the latter is less reactive because of the less favorable charges on the two reactants. Clearly, penicillamine disulfide is much less reactive than its cysteine analogue, as would be expected from the steric effect explanation proposed here for the sulfenamides.

As a final example of the low reactivity of a penicillamine containing disulfide, we should note the experiment here in which $(en)_2(NH_3)Co(AETS-SPen)^{2+}$ failed to react with excess penicillamine to give penicillamine disulfide (second reaction in Scheme 1). This is consistent with very low reactivity at the −SPen center of the disulfide complex. Reaction may be occurring at the AETS− end, but this just gives exchange rather than a new product.

In summary, it has been found that the large steric effect for nucleophilic attack at a coordinated sulfenamide is best explained by a strong preference for backside attack at two-coordinate sulfur. Examples from previous work suggest this also is true for nucleophilic attack at sulfur in disulfide bonds and may be a general feature for two-coordinate sulfur.

Experimental Section

Materials. The N-bonded sulfenamides of bis(ethylenediamine)-cobalt(III) derived from 2-aminoethanethiol (**IA**), cysteine (**IC**), and penicillamine (**IP**) were prepared as described previously.[1] The free thiols, 2-aminoethanethiol hydrochloride, cysteine hydrochloride hydrate, penicillamine and cysteine ethyl ester hydrochloride, and the disulfide cystamine dihydrochloride, were used as supplied (Aldrich). Solutions of these thiols were freshly prepared on the day of usage. The buffers, sodium acetate trihydrate (BDH), MES (4-morpholineethanesulfonic acid monohydrate), HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), Bicine (*N*,*N*-bis-(2-hydroxyethyl)glycine), TEEN (*N*,*N*,*N*′,*N*′-tetraethylethylenediamine), and CAPS (3-cyclohexylamino-1-propanesulfonic acid), were used as supplied (Aldrich).

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(18) Dalman, G.; McDermed, J.; Gorin, G. *J. Org. Chem.* **1964**, *29*, 1480.
(19) Theriault, Y.; Rabenstein, D. L. *Can. J. Chem.* **1985**, *63*, 2225.

Kinetic Methods. All reactions were monitored at 330 nm, except for a few at 350 nm to check for consistency. Because all of the thiols, except penicillamine, were hydrochloride salts, LiCl (2−20 mM) was added in several runs for reaction of **IA** with penicillamine and was found to have no kinetic effect. The stopped-flow studies involved mixing equal volumes of solutions of the thiol in 0.10 M $LiClO_4$ and 0.01 M buffer, adjusted to the desired pH, with the Co(III) complex in 0.10 M $LiClO_4$. Slower reactions were monitored on the diode array system by adding a small volume of the Co(III) solution from a syringe to a solution of thiol and buffer in a spectrophotometer cell. In all cases, the pH of the reaction solution was measured at the end of the reaction.

Instrumentation. Electronic spectra were recorded on Cary 219 and Hewlett-Packard 8451A Diode Array spectrophotometers. The pH was determined on a Corning 125 m with a combination glass electrode, calibrated with standard buffers of pH 4.00, 7.00, and 9.00. The stopped-flow studies were done on an Applied Photophysics SX 117MV system, using the manufacturer's collection and analysis software. The NMR spectra were recorded on a Varian 500 spectrometer in H_2O/D_2O as required, with sodium trimethylsilylpropanesulfonate (DSS) as an internal standard.

X-ray Structure. The crystal data are collected in Table 1. A 12 mg sample of $[(en)_2(NH_2SC(CH_3)_2CH(CO_2)NH_2](Br)_2 \cdot 2H_2O$ was dissolved in 0.4 mL of water, and 5.0 mg of $Li(O_2CCH_3) \cdot 2H_2O$ was added. A total of 86.5 mg of LiBr was then added over the course of 2 days. This resulted in quantitative deposition of the product as small crystals, which proved suitable for X-ray structure determination. The data were collected on a Bruker Platform/SMART 1000 CCD diffractometer using Mo Kα radiation at −80 °C.[20] The data were corrected for absorption through use of the Gaussian integration (face-indexed) procedure. The structure was solved using direct methods (SHELX-86),[21] and refinement was completed using the program SHELX-93.[22] 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.

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Supporting Information Available: X-ray crystallographic details in CIF format, ^{1}H NMR spectra (chemical shifts), and observed and calculated rate constants for reactions with thiols. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Programs for diffractometer operation, data collection, data reduction, and absorption correction were those supplied by Bruker.

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(22) Sheldrick, G. M. *SHELXL-93*; Program for crystal structure determination. University of Göttingen: Germany, 1993. Refinement on F_o^2 for all reflections (all of these having $F_o^2 \geq -3\sigma(F_o^2)$). Weighted *R*-factors wR_2 and all goodnesses of fit *S* are based on F_o^2; conventional *R*-factors R_1 are based on F_o, with F_o set to zero for negative F_o^2. The observed criterion of $F_o^2 > 2\sigma(F_o^2)$ is used only for calculating R_1 and is not relevant to the choice of reflections for refinement. *R*-factors based on F_o^2 are statistically about twice as large as those based on F_o, and *R*-factors based on all data will be even larger.