Figure 7 also contains data for three compounds synthesized from 4-substituted-2,6-dimethylanilines, namely, the bis(pyrrole-2-carboxaldiminato)copper(II) species with Br, H, and CH_3 as the (phenyl) 4′-substituent, for which the $E_{1/2}$ values are –0.81, –0.87, and –0.89, respectively. The potentials are all more negative (by ca. 100 mV) than for the species without methyl groups ortho to the aniline nitrogen, and this lowering of $E_{1/2}$ must be partially accounted for by the electron-releasing effect of these ortho methyl groups, in agreement with the ESR results.

Results of the type presented here further demonstrate that the redox potential of a copper(II) site is quite sensitive to the electrostatic inductive effects of substituents at centers remote from the metal ion. Similar dependence of redox potential on ligand substituents has been demonstrated recently by Bossu et al.[8] for the peptide-ligated copper(III)–copper(II) couple. Clearly, the $E°$ of a Cu^{II}–Cu^{I} couple bound, for example, at the active site of a copper protein can, in effect, be "fine tuned" to the optimum value required for catalytic activity by both stereochemical and inductive effects. Tetrahedral distortion of a square copper(II) system systematically moves the reduction potential to more positive values,[3] while again, with a given set of donor atoms, the reduction potential will change according to the α substituent of a coordinated peptide and to the presence of interactions of the ligands with charged groups. The replacement of the proton by zinc(II) on an imidazole coordinated to the copper(II) in bovine superoxide dismutase provides an extreme example of the latter as a remote aromatic substitution in a copper protein structure.[23]

The lack of sensitivity of the ESR spectra to substitutions which markedly affect the potential of the Cu^{II}–Cu^{I} couple is noteworthy in itself. For example, although the azurins from *P. aeruginosa* and *P. denitrificans* have quite similar ESR parameters ($g_{\|}$, $|A_{\|}|$, $g_{\perp}$), their reduction potentials near pH 7 differ by 80 mV.[24] It, therefore, seems reasonable that conclusions regarding the structural properties of protein copper binding sites (i.e., geometry and ligands) as deduced from spectroscopic and crystallographic studies of a limited number of copper proteins may be extended at the very least to protein copper with similar ESR parameters, regardless of variations of the order of ±100 mV among the redox potentials of the proteins. These results also suggest, that while the redox potential of a metalloprotein is *indicative* of the nature of a metal's coordination environment, it is likely to be sensitive enough to influences outside the first coordination sphere so as not to be valuable as a detailed diagnostic criterion for the coordination sphere.

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Registry No. HP2A-Ph-CH_3, 14479-37-9; HP2A-Ph-$N(CH_3)_2$, 66562-68-3; Zn(P2A-Ph-CH_3)$_2$, 66562-92-3; Zn(P2A-Ph-$N(CH_3)_2$)$_2$, 66562-99-0; Ni(P2A-Ph-$N(CH_3)_2$)$_2$, 66563-00-6; Cu(P2A-Ph-CH_3)$_2$, 15490-11-6; Cu(P2A-Ph-OCH_3)$_2$, 66563-01-7; Cu(P2A-Ph-I)$_2$, 66562-93-4; Cu(P2A-Ph-Br)$_2$, 66562-94-5; Cu(P2A-Ph-Cl)$_2$, 66562-95-6; Cu(P2A-Ph-F)$_2$, 66562-96-7; Cu(P2A-Ph-NO_2)$_2$, 66562-97-8; Cu(P2A-Ph-$COCH_3$)$_2$, 66562-98-9; Cu(P2A-Ph-$N(CH_3)_2$)$_2$, 66563-03-9; Cu(P2A-Ph-CF_3)$_2$, 66563-02-8; Cu(P2A-Ph-Ph)$_2$, 66563-04-0; Cu(P2A-Ph-$COOC_2H_5$)$_2$, 66563-05-1; Cu(P2A-Ph-2,4,6-$(CH_3)_3$)$_2$, 66609-89-0; Cu(P2A-Ph-4-Br-2,6-$(CH_3)_2$)$_2$, 66563-06-2; Cu(P2A-Ph)$_2$, 15170-41-9; Cu(P2A-Ph-NO_2)$^-$, 66563-07-3; Cu(P2A-Ph-$COCH_3$)$_2^-$, 66563-08-4; Cu(P2A-Ph-$COOC_2H_5$)$_2^-$, 66563-09-5; Cu(P2A-Ph-CF_3)$_2^-$, 66563-12-0; Cu(P2A-Ph-Cl)$_2^-$, 66563-13-1; Cu(P2A-Ph-Br)$_2^-$, 66563-14-2; Cu(P2A-Ph-I)$_2^-$, 66563-15-3; Cu(P2A-Ph-F)$_2^-$, 66563-16-4; Cu(P2A-Ph-C_6H_5)$_2^-$, 66563-17-5; Cu(P2A-Ph)$_2^-$, 66563-18-6; Cu(P2A-Ph-CH_3)$_2^-$, 66563-19-7; Cu(P2A-Ph-OCH_3)$_2^-$, 66563-10-8; Cu(P2A-Ph-$N(CH_3)_2$)$_2^-$, 66563-11-9.

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(9) Abbreviations: DPPH, diphenylpicrylhydrazyl radical; TEAP, tetraethylammonium perchlorate; RDE, rotating disk electrode; RPE, rotating platinum electrode; Ph, phenyl; ESR, electron spin resonance; NMR, nuclear magnetic resonance; SCE, saturated calomel electrode; NMe_2, dimethylamino group; prn, trimethylene group.
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Rate of Inversion of Sulfur in Cobalt(III)–Thioether Complexes

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The synthesis and characterization of several isomers of cobalt(III)–tren complexes containing (*R*)-cysteine, cysteamine, and their S-methylated derivatives as ligands are described. It is shown that the rate of sulfur inversion in the S-bonded thioether–cobalt(III) complexes is slow ($k_i < 10$ s^{-1}) on the NMR time scale at 25 °C but it exceeds 0.1 s^{-1}.

Introduction

It was recently demonstrated that sulfenates (RSO^-) S-bonded to octahedral cobalt(III) do not readily invert about sulfur[1] and are analogous to free sulfoxides (RR′SO) in this respect (Figure 1). Thioethers (RR′S) like sulfenates are rendered chiral on coordination and it is known that the

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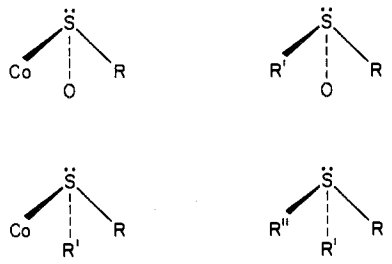

Figure 1. Analogy between alkyl- and cobalt-substituted sulfenates (top) and thioethers (bottom). (Formal charges are omitted.)

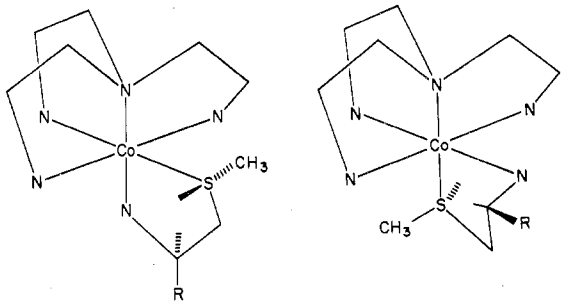

Figure 2. Left: p-*N*,*S*-Co(tren)-(*R*)-cysSCH$_3^{3+}$, R = COOH; p-Co(tren)(NH$_2$(CH$_2$)$_2$SCH$_3$)$^{3+}$, R = H. Right: t-*N*,*S*-Co(tren)-(*R*)-cysSCH$_3^{3+}$, R = COOH; t-Co(tren)(NH$_2$(CH$_2$)$_2$SCH$_3$)$^{3+}$, R = H.

cobalt–sulfur bond in these complexes is not easily broken.[2] It follows that such S-bound thioether complexes,[2-9] the simpler of which have only recently been prepared,[2-5] might show comparable optical stability to free sulfonium ions (Figure 1) which are resolvable, and this paper explores that prospect.

Results and Discussion

Synthesis and Isomer Assignments. Co(tren)(NH$_2$-(CH$_2$)$_2$S)$^{2+}$ and Co(tren)-(*R*)-(NH$_2$CH(CO$_2$H)CH$_2$S)$^{2+}$ were prepared from Co(II), tren,[26] and the disulfide of the appropriate mercaptan, and each was separated into its two (primary (p) and tertiary (t))[10] isomeric forms (~10:1 ratio) using ion-exchange chromatography. The thioether derivatives (Figure 2) were obtained from these by alkylation (CH$_3$I) in dimethyl sulfoxide (Me$_2$SO). Co(tren)(NH$_2$(CH$_2$)$_2$SCH$_3$)$^{3+}$ could also be prepared directly from the free ligand *S*-methylcysteamine and [Co(tren)(Me$_2$SO)$_2$](ClO$_4$)$_3$ in Me$_2$SO, a reaction which gives exclusively the t isomer. The corresponding reaction between Co(tren)(Me$_2$SO)$_2^{3+}$ and *S*-methyl-(*R*)-cysteine and ((*R*)-cysSCH$_3$) did not give the bound thioether but rather exclusively p-*N*,*O*-Co(tren)-(*R*)-cysSCH$_3^{2+}$. Reaction between Co(tren)(OH$_2$)OH^{2+} and *S*-methyl-(*R*)-cysteine ethyl ester afforded the other N,O form, t-Co(tren)-(*R*)-cysSCH$_3^{2+}$.

p and t forms of both the *N*,*S*- and *N*,*O*-Co(tren)-(*R*)-cysSCH$_3^+$ linkage isomers were characterized in order to pinpoint the nature of further diastereoisomerism to be considered later. It is noted that the S-bonded (*R*)-cysSCH$_3$ and *S*-methylcysteamine complexes all show the characteristic Co–S charge-transfer transitions[2] in their UV spectra which obscure the second ligand field band, otherwise expected around 340 nm. The two *N*,*O*-(*R*)-cysSCH$_3^{2+}$ isomers clearly show this latter band.

The isomers were assigned following the recognition of clear patterns underlying an accumulation of facts, now summarized. The visible spectra of p and t isomers of CoN$_5$O, CoN$_5$S, and CoN$_5$Cl chromophores in the Co(tren) systems differ significantly. For all isomeric pairs, one isomer has a first ligand field band at lower wavelength or more obviously split into its (three) components than the other. These differences are best rationalized in terms of *cis*- and *trans*-CoN$_4$*NO, -CoN$_4$*NS, or -CoN$_4$*NCl chromophores as appropriate, in which the (different) tertiary tren nitrogen (*N) exerts a weaker ligand field than the primary nitrogens (N).[13] This criterion is only useful where both isomers are known and for this reason all have been synthesized in this work.

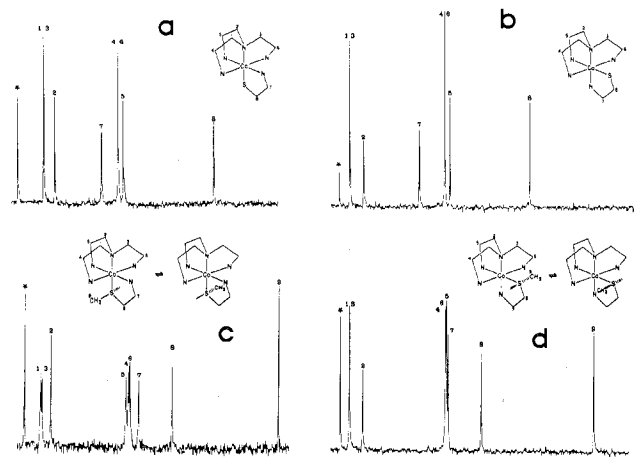

Figure 3. ^{13}C NMR of t-[Co(tren)(NH$_2$(CH$_2$)$_2$S)]Cl$_2$ (a), p-[Co(tren)NH$_2$(CH$_2$)$_2$S]Cl$_2$ (b), t-[Co(tren)(NH$_2$(CH$_2$)$_2$SCH$_3$)]Cl$_3$ (c), and p-[Co(tren)(NH$_2$(CH$_2$)$_2$SCH$_3$)]Cl$_3$ (d) in D$_2$O. Dioxane was used as the internal standard.

Assignments made on this basis alone proved consistent with those deduced independently using other criteria. For example, the more polar "cis" isomers (e.g., p-*N*,*O*-Co(tren)-(*R*)-cysSCH$_3^{2+}$) were eluted more slowly than the "trans" forms from Dowex 50W-X2 cation-exchange resin using HCl, a well-established characteristic of *cis*- and *trans*-Co(en)$_2$X$_2^{n+}$. However, elution characteristics can be so modified by the choice of eluent that the anion (e.g., HPO$_4^{2-}$, H$_2$PO$_4^-$, or SO$_4^{2-}$) can ion-pair preferentially with the more dipolar cis form thereby lowering its effective charge, even to the extent of inverting the elution order. Indeed this property has been utilized in separating p- from t-Co(tren)-(*R*)-(serinato)$^{2+}$[2] and similarly Co(tren)(glycinato)$^{2+}$.[2]

A further characteristic which distinguishes p and t isomers is the reactivity of the two sites cis and trans to the tertiary nitrogen. A detailed study of the Co(tren)(NH$_3$)Cl^{2+} system has shown[11] conclusively that, at least in base hydrolysis, the more reactive site is cis.[14] The reactivities of the p and t isomers of this work fit this pattern. Further evidence was provided by the internal consistency of the assignments. Thus corresponding isomers in the (*R*)-cysteine and cysteamine systems were readily identified by their distinctive chemistry (see Experimental Section—visible spectra, relative yields of the p- and t-thiols, reactivity toward alkylation at sulfur (thiols) and base hydrolysis (thioethers), and chromatography). Also, S-alkylation occurs without Co–S rupture and therefore the thioether derivatives prepared this way inherit the isomerism of the parent thiolato ions. The assignments of p- and t-*N*,*O*-Co(tren)-(*R*)-cysSCH$_3^{2+}$ match those of their red (t) and yellow (p) *N*,*O*-Co(tren)(NH$_2$CH$_2$OCO)$^{2+}$ analogues,[12] the crystal structures of which are both known.[13] Finally, base hydrolysis of the p thioethers was retentive (see later), a stereochemical feature of p- but not t-Co(tren)(NH$_3$)Cl^{2+}.

A detailed study of the NH proton exchange rates which might have provided definitive structural assignments[11] was not undertaken. It is emphasized that the conclusions reached herein do not hinge on these assignments.

Inversion at Chiral Sulfur. Provided five-membered ring conformational interchange is sufficiently rapid, each Co(tren)(NH$_2$(CH$_2$)$_2$S)$^{2+}$ isomer has an effective symmetry plane on an NMR time scale. The ^{13}C NMR spectra (D$_2$O, 25 °C) bear this out, the enantiotopic carbons 1,3 and 4,6 being

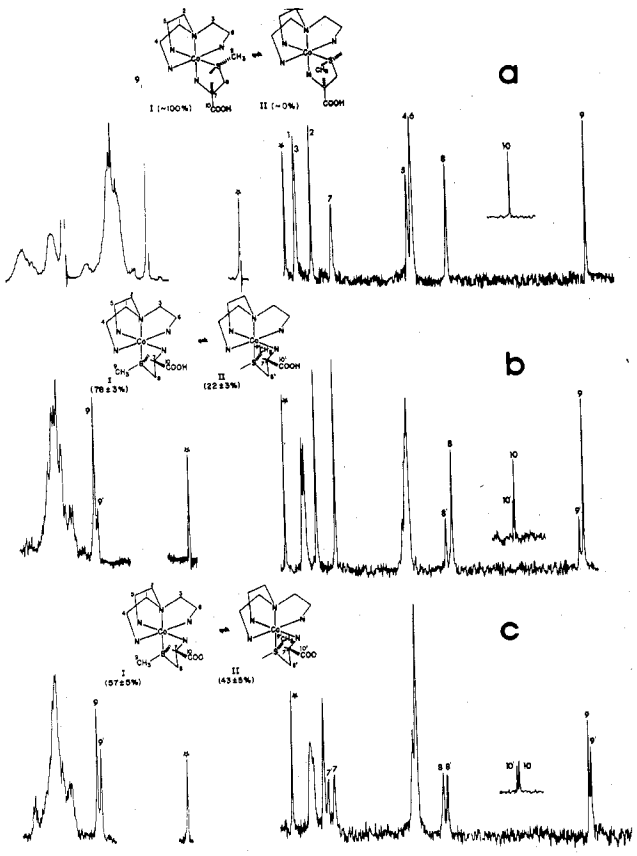

Figure 4. ^1H (left) and ^{13}C (right) NMR of p-*N*,*S*-[Co(tren)-(*R*)-cysSCH$_3$]Cl$_3$ in 10^{-2} M DCl (a), ^1H and ^{13}C NMR of t-*N*,*S*-[Co(tren)-(*R*)-cysSCH$_3$]Cl$_3$ in 10^{-2} M DCl (b), ^1H and ^{13}C NMR of t-*N*,*S*-[Co(tren)-(*R*)-cysSCH$_3$]Cl$_2$ in HPO_4^-/HPO_4^{2-} (10^{-2} M in Na^+, pH ~6) (c). Dioxane (★) and sodium trimethylsilylpropanesulfonate (☆) were used as internal references in the ^{13}C and ^1H NMR, respectively. S–CH$_3$ diastereoisomer assignments are arbitrary. The insets (^{13}C NMR) show the –COOH signals contracted twofold in ppm; these peaks actually occur downfield of dioxane.

(pairwise) anisochronous (Figure 3a, b). The introduction of chiral sulfur through alkylation (CH_3) removes both these degeneracies, provided S inversion is slow. The clearly resolved diastereotopic C signals at least in t-Co(tren)(NH_2-$(CH_2)_2SCH_3)^{3+}$ (Figure 3c), therefore clearly demonstrates the stability of Co(III)-bound thioether toward inversion, at least on an NMR time scale.

The presence of both asymmetric carbon and sulfur centers in *N*,*S*-Co(tren)-(*R*)-cysSCH$_3^{3+}$ generates two diastereoisomers for each of the p and t isomers. In dilute DCl, these two isomers of t-Co(tren)-(*R*)-cysSCH$_3^{3+}$ were clearly seen in both the ^1H and ^{13}C NMR spectra (Figure 4b), in the ratio 3.5:1, confirming slow inversion at sulfur. However p-*N*,*S*-Co(tren)-(*R*)-cysSCH$_3^{3+}$ exists as a single isomer (Figure 4a). Its NMR spectra were unchanged from 35 down to 5 °C. In the unlikely event of multiple accidental degeneracies or coalesced spectra it appears that here the *S*-methyl is stereospecifically oriented. Molecular models offer no obvious explanation for the last observation and further comment awaits a crystallographic investigation.

Attempted fractionation of t-*N*,*S*-Co(tren)-(*R*)-cysSCH$_3^{3+}$ as Cl^-, I^-, and NCS^- salts from water all yielded homogeneous crystals[15] but in dilute DCl they had identical NMR spectra (Figure 4b), i.e., that corresponding to the ~3.5:1 mixture of isomers. Also, the complex chromatographed as a single band under a variety of conditions on cation-exchange resin. These observations and our repeated inability to resolve p- and t-Co(tren)$(NH_2(CH_2)_2SCH_3)^{3+}$ and $Co(NH_3)_4(NH_2$-$(CH_2)_2SCH_3)^{3+}$ (from $[Co(NH_3)_4(Me_2SO)_2](ClO_4)_3$ and $NH_2(CH_2)_2SCH_3$ in Me_2SO) therefore suggested that S inversion was thermally rapid. Thus an unexpected but revealing observation was as follows. At a pH sufficient to deprotonate the uncoordinated CO_2H group (pH ≥3, HCO_3^- or $H_2PO_4^-$) the isomer ratio changed detectably (Figure 4c, ~1.3:1; cf. ~3.5:1, 4b), but, more significantly, the change was instantaneous (<5 s). This result and the fact that the pH changes were totally reversible exclude a trivial explanation such as decomposition and clearly show that S inversion is fast, albeit frozen on the NMR time scale at 30 °C. Potential solvent, anion, or temperature dependence of the isomer ratio was not explored other than noting that the isomer ratio in Me_2SO was similar to that in water. Decomposition at elevated temperatures precluded observation of coalescence phenomena associated with I ⇄ II in t-*N*,*S*-Co(en)-(*R*)-cysSCH$_3^{3+}$ (Figure 4b and c), and $C_1 \rightleftarrows C_3$, $C_4 \rightleftarrows C_6$ in t-Co(tren)$(NH_2(CH_2)_2SCH_3)^{3+}$ (Figure 3c), which might have quantified the S inversion rates.

p-*N*,*S*-Co(tren)-(*R*)-cysSCH$_3^{3+}$ rapidly and irreversible rearranges to give mainly p-*N*,*O*-Co(tren)-(*R*)-cysSCH$_3^{2+}$ on removing the CO_2H proton, and it should be noted that the (reversible) pH-dependent NMR spectra described for the p isomer are not explicable in terms of a similar transformation. As was the case in acid solution for the 3+ ion, only a single isomer of p-*N*,*S*-Co(tren)-(*R*)-cysSCH$_3^{2+}$ was observed prior to this rearrangement.

Thioether complexes of Pt(II), Pd(II), Rh(III), and Ir(III) have been reported to invert about sulfur on the NMR time scale.[16-21] In all cases this conclusion rests with coalescence phenomena associated with diastereotopic groups or diastereoisomers. Potential ambiguities in interpretation have been pointed out[21] and it is not always possible to positively associate the observations with sulfur inversion. This is emphasized by noting the diastereotopic methylene protons in methyl benzyl sulfoxide undergo apparent coalescence (twice!),[23] yet the molecule does not racemize under the same conditions. The conclusions derived from the present work do not suffer this problem, and moreover they unambiguously answer the question of resolvability of the thioether bound to Co(III). Some doubt is now cast on the early report[22] that $[Pt^{IV}(NH_2(CH_2)_2S(CH_2)_2NH_3)Cl_4]Cl$ can be resolved although it is not inconceivable that the metal can slow the inversion rate by the factor of $\sim 10^5$ required. This work is under reexamination.[27] Also, the apparently facile sulfur inversion observed during the interconversion of some isomeric cobalt(III) complexes of a sexadentate ligand containing two inner chiral sulfur donor atoms[6,8] now has some foundation.

Experimental Section

^1H NMR spectra were measured on a Jeol Minimar 100-MHz instrument on external lock. Fourier-transform ^{13}C NMR spectra were recorded with a Jeol FX60 machine using an internal lock (D_2O). Peak assignments were made with the aid of spectra of a range of closely related complexes. The S–CH$_3$ signals (^1H) were assigned using CD_3I and from accurate integration against the reference NaTPS; these exercises were important because some unusually high field and sharp tren CH_2 resonances are easily confused with S–CH$_3$ signals. Visible spectra were recorded on a Cary Model 118C instrument.

S-Methylcysteamine was obtained from cysteamine, sodium methoxide (1 equiv), and methyl iodide in methanol and purified by vacuum distillation. *S*-Methyl-(*R*)-cysteine was prepared from (*R*,*R*)-cystine which was reduced by Na in liquid ammonia and treated with methyl iodide. Purification was achieved via the hydrochloride salt recrystallized from methanol/ether. The ethyl ester was prepared by refluxing in ethanol saturated with dry HCl. An aqueous paste of the purified hydrochloride from methanol/ether was treated with K_2CO_3 and the free ester extracted into ether.

Khaki brown $[Co(tren)NO_2]_2O_2(ClO_4)_2$[11] was prepared and converted to blue-green [Co(tren)Br$_2$]Br by digestion in 48% HBr.

$[Co(tren)CO_3]ClO_4$ was obtained from the dibromo complex and excess Na_2CO_3 in hot water using $NaClO_4$ to crystallize the red complex. This was then treated with $HClO_4$ (3 equiv), N_2 to remove CO_2, and then NaOH (2 equiv) to pH 7 from which the mauve $[Co(tren)(OH_2)OH](ClO_4)_2$ crystallized readily as needles. $[Co(tren)(Me_2SO)Br]Br_2$ was obtained from $[Co(tren)Br_2]Br$ in hot Me_2SO from which it readily crystallized. The violet filtrate was reheated and ethanol used to crystallize more product. The product was recrystallized from water ($NaClO_4$ or $HClO_4$) as $[Co(tren)(Me_2SO)Br](ClO_4)_2$ (one pure isomer). $[Co(tren)(Me_2SO)_2](ClO_4)_3$ was prepared from $[Co(tren)Br_2]Br$ and $AgClO_4$ (3.1 equiv) in Me_2SO (60 °C, 20 min) or more cheaply from $[Co(tren)(Me_2SO)Br](ClO_4)_2$ and $AgClO_4$ (1.1 equiv). Addition of ethanol and ether produced an oil from which the red-violet complex crystallized on prolonged trituration. It was recrystallized from water/$NaClO_4$.

p- and t-*N,S*-Co(tren)-(*R*)-cysS^{2+}. $CoCl_2 \cdot 6H_2O$ (35.7 g, 0.15 mol) was dissolved in water (150 mL) and the solution flushed with nitrogen (10 min). To this was added rapidly under nitrogen a solution of tren·3HCl·1.5H_2O (42.5 g, 0.15 mol) and (*R,R*)-cystine (19.0 g, 0.08 mol) in deoxygenated water (150 mL) containing NaOH (24.0 g, 0.60 mol). The initially violet solution darkened rapidly to a deep brown. After 48 h in the absence of air, the mixture was carefully acidified with $HClO_4$ (70%) to pH 3 and then a further 50 mL of $HClO_4$ added. Ice cooling produced brown crystals which after 24 h were collected, washed with ethanol and ether, and air-dried; yield 62.2 g (79%). This material which is essentially one pure isomer was recrystallized from hot 10^{-3} M HCl by addition of $HClO_4$. It deposited as deep brown needles. This and the bulk preparation filtrates were combined, diluted, and sorbed on Dowex 50W-X2 cation-exchange resin (H^+ form, 200–400 mesh). Elution with 2 M HCl moved first the minor isomer as an ink blue band followed by and well separated from residual brown-orange isomer. The HCl was rotaevaporated and the blue-black complex crystallized twice from water as the brown-black $ZnCl_4^{2-}$ salt using excess $ZnCl_2$ in 3 M HCl; yield 6.8 g (8.5%). An additional 4.1 g of the major brown isomer was recovered from the column as the perchlorate—total 66.3 g (84%); overall *N,S*-Co(tren)-(*R*)-cysS^{2+} yield 92.5%. The minor isomer was also obtained as the dithionate ($Li_2S_2O_6$) and chloride salts from water/methanol. Visible spectra (H_2O): major isomer, λ_{max} 580 (br, sh), 485, λ_{min} 443 nm; minor isomer, λ_{max} 580 (sh), 484, λ_{min} 410 nm. Anal. Calcd for $CoC_9H_{26}N_5SCl_2O_{11}$: C, 19.9; H, 4.8; N, 12.9; S, 5.9; Cl, 13.1. Found (major): C, 19.6; H, 4.7; N, 13.0; S, 6.0; Cl, 13.1. Calcd for $CoC_{9.5}H_{27}N_5SCl_2O_3$: C, 27.1; H, 6.5; N, 16.6; S, 7.6; Cl, 16.8. Found (minor): C, 27.2; H, 6.6; N, 16.7; S, 7.6; Cl, 16.8. Calcd for $CoC_9H_{24}N_5SZnCl_4O_2$: C, 20.3; H, 4.5; N, 13.2; S, 6.0; Cl, 26.6. Found (minor): C, 20.6; H, 4.7; N, 13.0; S, 5.9; Cl, 26.2. Calcd for $CoC_9H_{26}N_5S_3O_9$: C, 21.5; H, 5.2; N, 13.9; S, 19.1. Found (minor): C, 21.4; H, 5.3; N, 13.6; S, 19.3.

p-*N,O*-Co(tren)-(*R*)-cysSCH$_3^{2+}$. *S*-Methyl-(*R*)-cysteine (2.02 g, 0.015 mol) was added to $[Co(tren)(Me_2SO)_2](ClO_4)_3$ (6.6 g, 0.01 mol) dissolved in Me_2SO (100 mL) containing Tris (1.5 g, 0.015 mol) or triethylamine (0.015 mol). The mixture was heated on a steam bath (~80 °C, 20–30 min) and slowly changed from violet to orange-brown. The cooled solution was poured into dilute HCl (1 L, 10^{-2} M) and sorbed on Dowex. Elution with 3 M HCl gave a single orange band. The eluate was reduced to dryness and methanol followed by acetone was added to the residue in water until faintly turbid. After 2 h at 20 °C the yellow crystals of p-*N,O*-[Co(tren)-(*R*)-cysSCH$_3$]Cl$_2$ were collected, washed with methanol and ether, and air-dried; yield 3.7 g (90%). Crystals were also readily obtained from water with NaI or $HClO_4$ and analyzed satisfactorily. The ^1H and ^{13}C NMR spectra on these salts and the bulk product were consistent with the presence of a single isomer only and chromatography failed to reveal the t form. Visible spectrum (H_2O): λ_{max} 470, 335 (sh), λ_{min} 396 nm (cf. 470, 340 nm, gly analogue[12]). Anal. Calcd for $CoC_{10}H_{26}N_5SO_2Cl_2$: C, 29.3; H, 6.4; N, 17.1; S, 7.8; Cl, 17.3. Found: C, 29.5; H, 6.5; N, 17.2; S, 7.6; Cl, 17.2.

t-*N,O*-Co(tren)-(*R*)-cysSCH$_3^{2+}$. $[Co(tren)(OH_2)OH](ClO_4)_2$ (6.6 g, 0.015 mol) suspended in water (100 mL) was treated with excess *S*-methyl-(*R*)-cysteine ethyl ester (4.9 g, 2 equiv, 0.03 mol) and the pH was adjusted to 7 with $HClO_4$ after complete dissolution through raising the temperature. The deep wine red solution turned orange-brown after 45 min at 80 °C and was cooled. It was diluted, sorbed, washed, and then eluted (3 M HCl) from Dowex. After 48 h, the now red-orange solution was rechromatographed from Dowex, eluting first with 2 M NaCl to remove violet $Co(tren)(OH_2)Cl^{2+}$ and burgundy $Co(tren)(OH_2)_2^{3+}$. Elution with 2 M HCl then removed the pink-orange t-*N,O*-Co(tren)-(*R*)-cysSCH$_3^{2+}$, followed closely by but separated from yellow-orange p-*N,O*-Co(tren)-(*R*)-cysSCH$_3^{2+}$. Comparable amounts of both isomers were present. The t isomer was crystallized from water as the dithionate monohydrate ($Li_2S_2O_6$ + CH_3OH) and recrystallized slowly from hot water as pink needles by simply cooling or addition of $Li_2S_2O_6$ and CH_3OH; yield 4.7 g (60%). Visible spectrum: λ_{max} 497, 338 (sh), λ_{min} 410 nm (cf. 499, 347 nm; gly analogue[12]). Anal. Calcd for $CoC_9H_{28}N_5S_3O_9$: C, 23.1; H, 5.5; N, 13.5; S, 18.6. Found: C, 23.2; H, 5.5; N, 13.6; S, 18.4.

p- and t-*N,S*-[Co(tren)(NH$_2$CHRCH$_2$SCH$_3$)]Cl$_3$ (R = H, COOH). The thioether derivatives were all prepared in quantitative yield from the thiolato ions by reaction with excess CH_3I in Me_2SO. For each system the minor thiol isomer methylated more rapidly. The procedure is described for one (typical) preparation below.

p-*N,S*-[Co(tren)-(*R*)-cysSCH$_3$]Cl$_3$. p-*N,S*-[Co(tren)-(*R*)-cysS]-$(ClO_4)_2$ (major isomer, 5.2 g, 0.01 mol) was dissolved in Me_2SO (100 mL) and CH_3I (14.2 g, 0.1 mol) added. Within minutes the deep orange-brown solution had become a light orange. After 30 min the mixture was poured into dilute HCl (0.001 M, 1 L), decanted from any excess CH_3I, and extracted with $CHCl_3$ (2 × 200 mL), and the orange aqueous phase was sorbed on Dowex. Washing and then elution with 2–3 M HCl removed the single orange band which crystallized as needles from water/methanol/acetone after removal of the HCl; yield 4.3 g, 95%. Visible spectra (10^{-3} M $HClO_4$): p-*N,S*-(*R*)-cysSCH$_3^{3+}$, λ_{max} 485, λ_{min} 407; t-*N,S*-(*R*)-cysSCH$_3^{3+}$, λ_{max} 479, λ_{min} 405; p-$(NH_2(CH_2)_2SCH_3)^{3+}$, λ_{max} 484, λ_{min} 406; t-$(NH_2(CH_2)_2SCH_3)^{3+}$, λ_{max} 478, λ_{min} 404 nm. The p- and t-cysteine derivatives crystallized as hemimethanol hemihydrate and dihydrate solvates, respectively, and the corresponding cysteamine complexes as the anhydrous and dihydrate salts. Anal. Calcd for $CoC_{10.5}H_{30}N_5SO_3Cl_3$: C, 25.7; H, 6.4; N, 14.9; S, 6.8; Cl, 22.5. Found (p): C, 26.4; H, 6.5; N, 15.1; S, 6.8; Cl, 22.8. Calcd for $CoC_{10}H_{31}N_5SO_4Cl_3$: C, 24.9; H, 6.5; N, 14.5; S, 6.6; Cl, 22.0. Found (t): C, 24.4; H, 6.8; N, 14.2; S, 6.5; Cl, 22.5. Calcd for $CoC_9H_{27}N_5SCl_3$: C, 26.8; H, 6.8; N, 17.4; S, 8.0; Cl, 26.4. Found (p): C, 26.7, H, 6.7; N, 17.2; S, 7.9; Cl, 26.7. Calcd for $CoC_9H_{32}N_5SCl_3O_2$: C, 24.6; H, 7.1; N, 16.0; S, 7.3; Cl, 24.2. Found (t): C, 24.6; H, 7.1; N, 15.9; S, 7.2; Cl, 24.1. The iodides of p- and t-Co(tren)$(NH_2(CH_2)_2SCH_3)^{3+}$ from water/NaI, t-[Co(tren)-(*R*)-cysSCH$_3$](NCS)$_3$ from water/NaNCS, and p-[Co(tren)-(*R*)-cysSCH$_3$]$(ClO_4)_3$ from water/$HClO_4$ were also characterized; the analyses were satisfactory.

t-Co(tren)$(NH_2(CH_2)_2SCH_3)^{3+}$ was also obtained from $[Co(tren)(Me_2SO)_2](ClO_4)_3$ and $NH_2(CH_2)_2SCH_3$ using the method and scale described for p-*N,O*-Co(tren)-(*R*)-cysSCH$_3^{2+}$. The ^1H and ^{13}C NMR spectra and chromatography of the bulk product showed the exclusive formation of the t isomer, isolated as the trichloride salt.

Rearrangement of *N,S*-Co(tren)-(*R*)-cysSCH$_3^{3+}$ in Base. The chloride of the p complex in water (5 g/20 mL) was treated with excess $NaHCO_3$ or Na_2HPO_4 (30–100 equiv) and a rapid[24] color change ensued from orange-red to first red-brown and then yellow-orange. After acidification to pH 2 ($HClO_4$) on completion of the color change, the mixture was chromatographed on Dowex. Elution with 3 M HCl removed first a small bright yellow band followed by the bulk yellow-orange product. This minor product was crystallized as the dithionate from water/methanol/$Li_2S_2O_6$ and also as the chloride (methanol/water). The major product crystallized as shiny plates from water/methanol/acetone and was identified as p-*N,O*-[Co(tren)-(*R*)-cysSCH$_3$]Cl$_2$, by comparison with the independently prepared material (analytical, visible, ^1H and ^{13}C NMR spectra). No t isomer was detected. The same reaction monitored in the ^1H NMR indicated ~10% of side product, identified as CH_3SH. The minor yellow product isolated above has been identified by independent synthesis as the imine p-Co(tren)$(NH{=}CH(CH_3)OCO)^{2+}$. This desulfurization reaction[25] is not relevant to the present work and will be reported in detail later.

Rearrangement of *N,S*-Co(tren)$(NH_2(CH_2)_2SCH_3)^{3+}$ in Base. The following reactions were monitored by ^1H NMR. As for the (*R*)-cysSCH$_3$ analogues, the t isomer decomposed but the p form reacted smoothly in 0.1 M NaOH to give red Co(tren)$(OH)(NH_2(CH_2)_2SCH_3)^{2+}$. The final ^1H NMR, after acidification ($HClO_4$) giving orange Co(tren)$(OH_2)(NH_2(CH_2)_2SCH_2)^{3+}$ and partial subsequent ring closure (~18 h, 80 °C) through recoordination of the thioether function, revealed only the t isomer. We infer that p-Co(tren)$(OH_2)(NH_2(CH_2)_2SCH_3)^{3+}$ is stable with respect to ring

closure and that the t product arises through ring closure in t-Co(tren)$(OH_2)(NH_2(CH_2)_2SCH_3)^{3+}$ formed by slow isomerization of the p isomer.

Registry No. p-*N*,*S*-Co(tren)-(*R*)-cysS^{2+}, 66495-52-1; t-*N*,*S*-Co(tren)-(*R*)-cysS^{2+}, 66609-59-4; t-[Co(tren)$(NH_2(CH_2)_2S)]Cl_2$, 66495-53-2; p-[Co(tren)$(NH_2(CH_2)_2S)]Cl_2$, 66537-70-0; p-*N*,*O*-[Co(tren)-(*R*)-cys$SCH_3]Cl_2$, 66574-20-7; t-*N*,*O*-[Co(tren)-(*R*)-cys$SCH_3]S_2O_6$, 66495-50-9; p-*N*,*S*-[Co(tren)$(NH_2(CH_2)_2SCH_3)]Cl_3$, 66495-51-0; t-*N*,*S*-[Co(tren)$(NH_2(CH_2)_2SCH_3)]Cl_3$, 66538-33-8; p-*N*,*S*-[Co(tren)-(*R*)-cys$SCH_3]Cl_3$, 66505-74-6; t-*N*,*S*-[Co(tren)-(*R*)-cys$SCH_3]Cl_3$, 66537-95-9; p-[Co(tren)$(NH_2(CH_2)_2SCH_3)]I_3$, 66505-75-7; t-[Co(tren)$(NH_2(CH_2)_2SCH_3)]I_3$, 66537-96-0; t-[Co(tren)-(*R*)-cys$SCH_3](NCS)_3$, 66537-98-2; p-[Co(tren)-(*R*)-cys$SCH_3](ClO_4)_3$, 66495-55-4; [Co(tren)$(OH_2)(OH)](ClO_4)_2$, 66495-57-6; [Co(tren)$(Me_2SO)_2](ClO_4)_3$, 66495-59-8; t-[Co(tren)$(NH_2(CH_2)_2SCH_3)]^{3+}$ (*S*), 66537-71-1; t-[Co(tren)$(NH_2(CH_2)_2SCH_3)]^{3+}$ (*R*), 66537-72-2; t-*N*,*S*-[Co(tren)-(*R*)-cys$SCH_3]^{3+}$ (*S*), 66537-73-3; t-*N*,*S*-[Co(tren)-(*R*)-cys$SCH_3]^{3+}$ (*R*), 66537-74-4; p-*N*,*S*-[Co(tren)-(*R*)-cys$SCH_3]^{3+}$ (*S*), 66537-75-5; p-[Co(tren)-$(NH_2(CH_2)_2SCH_3)]^{3+}$ (*R*), 66537-76-6; p-[Co(tren)$(NH_2(CH_2)_2SCH_3)]^{3+}$ (*S*), 66537-77-7; ^{13}C, 14762-74-4.

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(24) This rate is not easily reproduced and hours may be necessary at ~20 °C. This irreproducibility is a kinetic characteristic of substitution reactions of such S-bound Co(III) complexes.[2]
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(26) tren = $N(CH_2CH_2NH_2)_3$ = β,β',β''-tris(aminoethyl)amine.
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Nucleophilic Reactions of Lithium Bis(trifluoromethyl)sulfimide

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Lithium bis(trifluoromethyl)sulfimide, $LiN{=}S(CF_3)_2$, is a moderately stable precursor to several new bis(trifluoromethyl)sulfimides. With $(CH_3)_3SiCl$, $CF_3C(O)Cl$, CNCl, CF_3SO_2F, $ClSO_2F(SO_2Cl_2)$, and OPF_2Cl, $(CH_3)_3SiN{=}S(CF_3)_2$, $CF_3C(O)N{=}S(CF_3)_2$, $NCN{=}S(CF_3)_2$, $CF_3SO_2N{=}S(CF_3)_2$, $ClSO_2N{=}S(CF_3)_2$, and $OPF_2N{=}S(CF_3)_2$ are formed. The bis[bis(trifluoromethyl)sulfimides] $(CH_3)_2Si[N{=}S(CF_3)_2]_2$ and $CO[N{=}S(CF_3)_2]_2$ result with $(CH_3)_2SiCl_2$ and $COCl_2$. With the exception of the carbonyl compound which is a stable white crystalline solid, all of the sulfimides are moderately stable liquids of low volatility.

The reactive nucleophile lithium hexafluoroisopropylidenimine, $LiN{=}C(CF_3)_2$, is a valuable precursor to a large number of new compounds and interesting reactions.[1-11] Recently we reported the syntheses of bis(trifluoromethyl)-sulfimide, $(CF_3)_2S{=}NH$,[12,13] and its lithium salt.[12] Although

$$(CF_3)_2SF_2 + NH_3 \xrightarrow{RNH_2} (CF_3)_2S{=}NH \qquad 60\% \quad (1)$$

$$(CF_3)_2S{=}NH + n\text{-}C_4H_9Li \xrightarrow{\text{hexane}} (CF_3)_2S{=}NLi + C_4H_{10} \qquad 80\% \quad (2)$$

the route to this sulfimide salt is a multistep, moderate-yield process, the unusual opportunity for comparison of the reaction possibilities and properties of the products obtained with those of the carboimide, $(CF_3)_2C{=}NLi$, made further study of $(CF_3)_2S{=}NLi$ a worthwhile undertaking.

$$Cl_3CSCl + NaF \xrightarrow{TMSO} CF_3SCl \qquad 47\%$$

$$CF_3SCl + AgOC(O)CF_3 \rightarrow CF_3SOC(O)CF_3 + AgCl \qquad 90\text{–}100\%$$

$$CF_3SOC(O)CF_3 \xrightarrow[\text{Pyrex}]{h\nu} CF_3SCF_3 \qquad 90\text{–}100\%$$

$$CF_3SCF_3 + ClF \rightarrow CF_3SF_2CF_3 \qquad 75\%$$

+ reactions 1 and 2

While lithium bis(trifluoromethyl)sulfimide is less stable than its carbon analogue, it can be retained at 25 °C for brief periods without measurable decomposition. It undergoes reactions with a variety of molecules with electropositive centers but the stability of the products obtained is a function of the oxidation state of the elements at those centers. This is a difficulty inherent in sulfur(IV) systems which is not

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