ever, remarkably high, 200, for the Pb–F system. On the other hand, K_1/K_2 for the Li–F and Li–OH systems is 6 and 3, respectively. The values for the Li systems are close to what is expected from a random cationic ligand exchange situation where only direct metal–anion interactions are operative, i.e. the case of an ideal quasi-lattice ligand exchange.[38] A coordination number, *Z*, of 4 gives $(K_1/K_2)_{\text{theor}} \approx 3$ and a specific quasi-lattice interaction energy parameter for the cation exchange in steps 6a and 6b of -14 ± 2 kJ mol^{-1} for the Li–F and -17 ± 2 kJ mol^{-1} for the Li–OH system. The fact that the exchange interaction energy is largely the same in both steps 6a and 6b for either system further suggests that the same solvent cation (Na^+ or K^+) is exchanged for Li^+ in every step.

The thermodynamic parameters obtained from the temperature dependence of ΔG°_{m1} in fact confirm these results. The ΔH°_{m1} values are in close agreement with the specific interaction energy parameter for the lithium fluoride system. Consequently, the ΔS°_{m1} changes obtained are also nearly identical with the ideal configurational entropy values predicted by a quasi-lattice model approach ($Z = 4$).

It was demonstrated for the Pb(II) systems, however, that the ΔH°–ΔS° patterns for the single complexation steps, as estimated from the temperature dependence of the standard free energy changes, clearly show the second step (6b) to be favored by a negative ΔH° in spite of the strong cation–cation repulsion. The ΔS° does not contribute significantly to the stability of M_2X. A positive entropy contribution from the release of coordinated nitrate ions is thought to be balanced by a negative configurational entropy change, yielding a ΔS° close to zero, which—by coincidence—almost agrees with the quasi-lattice model prediction.

This interpretation of the thermodynamics of step 6b for the Pb–F system is based on our knowledge of the structure of Pb_2F^{3+}, which indicates that a direct Pb–Pb bond is formed in the second complexation step. In the Li_2X^+ ions (X = F or OH), there is, in contrast, no thermodynamic evidence of any stabilizing Li–Li bond.

Acknowledgment. This study has been supported by a grant from the Swedish Natural Science Research Council.

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Stereospecificity in the Synthesis of the Tris((*R*)-cysteinato-*N*,*S*)- and Tris((*R*)-cysteinesulfinato-*N*,*S*)cobaltate(III) Ions

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Tris(bidentate ligand)metal complexes can exist in Λ and Δ catoptric forms, and if the bidentate ligand is unsymmetrical, there are *fac* and *mer* isomers to consider as well. Furthermore, if the bidentate ligand is chiral, there will exist a diastereomeric form for each hand of the ligand. The case of three (*R*)-cysteine ligands coordinated to cobalt(III) is an especially interesting one because, in addition to the above possibilities for isomerism, there are the prospects for N,S-, N,O-, or S,O-chelation, leading to a total of $2 \times 2 \times 3 = 12$ possible isomers, for a given absolute configuration of the cysteine ligand. Tridentate chelation is another prospect,[1] but the question of specificity, which this note addresses, does not arise here because (*R*)-cysteine can wrap in only one way on a face of an octahedron.

The synthesis of the green tris((*R*)-cysteinato)cobaltate(III) complex $[Co((R)\text{-cysS-}N,S)_3]^{3-}$ was described long ago,[2] and it has been claimed that not only does the cysteine ligand bind N,S[3-5] but also the *fac* isomer seems to be formed exclusively over the *mer* form. Similar claims have been made in a study dealing with the related complexes of cysteine methyl ester[6] and cysteamine,[7] work substantiated by single-crystal X-ray studies of some of their derivatives.[8,9]

The $[Co((R)\text{-cysS})_3]^{3-}$ ion constitutes a tris-gauche ring system with three equatorial carboxylate substituents (rendering each ring λ), and it would be expected to favor the Δ-λλλ configuration ((*lel*)$_3$).[10,11] Gillard and Maskill[12] have claimed that the synthesis of the tris((*R*)-cysteine) complex is stereospecific and that the Δ-*RRR* form is formed exclusively over its Λ-*RRR* diastereomer. A similar claim has been made for the uncharged tris complex $[Co((R)\text{-MecysS})_3]$ of its *O*-methyl ester.[6] In our view this question has never been settled unambiguously. Conclusions have been based upon the composition of isolated materials without regard to yield or to the prospect of a second-order[13] asymmetric synthesis.

The specificity of the synthesis is an important question for a number of reasons. For example, the rationalization of the product distribution for oxidation at sulfur,[6] whereupon up to three chiral sulfenate centers arise, rests with the assumption that the starting material is itself a single diastereomer. Furthermore, the peroxidized derivative $[Co((R)\text{-cysSO}_2\text{-}N,S)_3]^{3-}$ appears[14] to be a useful resolving agent, and the success of resolutions using this ion could hinge critically on the diastereomeric purity.

Results and Discussion

The complex $K_3[Co((R)\text{-cysteinate-}N,S)_3]\cdot 6H_2O$ is synthesized from (*R*)-cysteine and a suitable Co(III) precursor such as $[Co(NH_3)_6]^{3+}$.[2-5,12,14] The complex can also be synthesized from Co(III) reactants such as $Na_3[Co(OCO_2)_3]$, $K[Co(edta)]\cdot 2H_2O$, or *trans*-$[Co(py)_4Cl_2]Cl\cdot 6H_2O$, by direct substitution using free (*R*)-cysteine.[15] Schubert[2] originally synthesized the tris complex from Co(II) reactants and free (*R*)-cysteine by aerial oxidation in the usual way, and presumably equilibrium between the various possible isomers is achieved under these conditions.

In our hands the synthesis of the tris complex by the original route using Co(II) and free (*R*)-cysteine gave a high yield of a dark olive green complex. For the potassium salt, high-resolution ^{13}C NMR spectroscopy (Figure 1; lower spectrum)[16] of a D_2O

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(16) In D_2O at 25 °C, the ^{13}C chemical shifts downfield from dioxane are as follows. $K_3[Co((R)\text{-cysS})_3]$: Δ, δ 111.75 ($CO_2$–), –0.02 (CH), –31.77 (–CH_2S–); Λ, δ 112.47 (CO_2), –3.49 (CH), –31.85 (–CH_2S–). $K_3[Co((R)\text{-cysSO}_2)_3]$: Δ, δ 107.15 ($CO_2$–), –0.46 (CH), –13.18 (–CH_2S–); Λ, δ 108.87 (CO_2–), 1.53 (CH), –15.05 (–CH_2S–).

(17) The complex is reported[4] as stable only in basic solution in the presence of excess cysteine. We find the purified complex to be stable at least in the pH range 7–13 over several hours.

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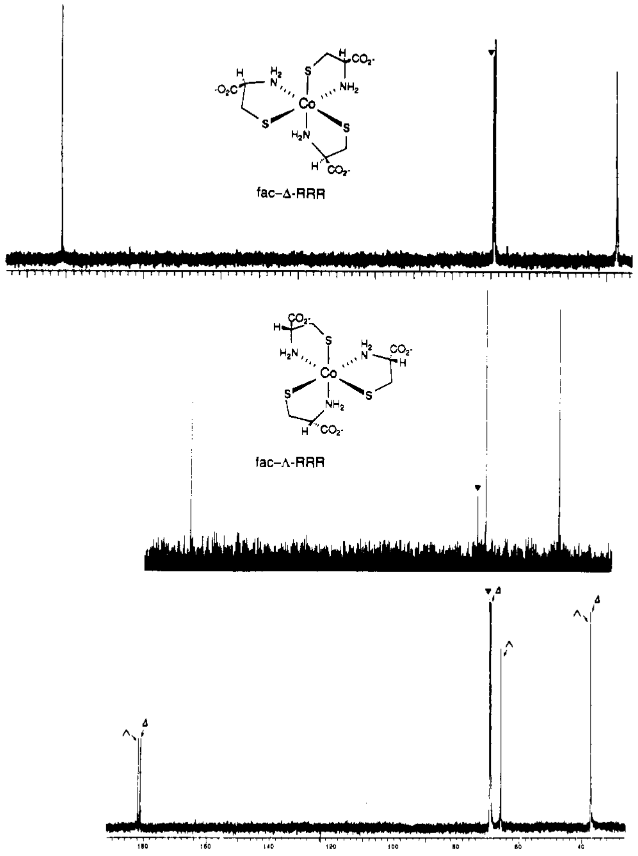
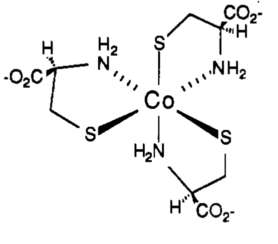
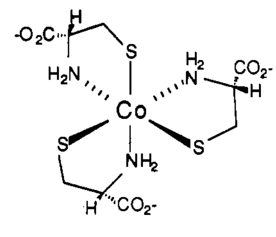


Figure 1. ^{13}C NMR spectra for Δ-[Co((*R*)-cysS-*N*,*S*)$_3$]$^{3-}$ (upper spectrum), Λ-[Co((*R*)-cysS-*N*,*S*)$_3$]$^{3-}$ (central spectrum), and the 1:1 Δ- and Λ-[Co((*R*)-cysS-*N*,*S*)$_3$]$^{3-}$ isomer mixture (lower spectrum) in D_2O (25 °C). Shifts are relative to NaTPS; ▼ denotes the dioxane reference signal.

solution (pH = 12)[17] of this material shows a spectrum clearly indicative of a 1:1 diastereomeric mixture of the two isomers:



fac-Δ-RRR



fac-Λ-RRR

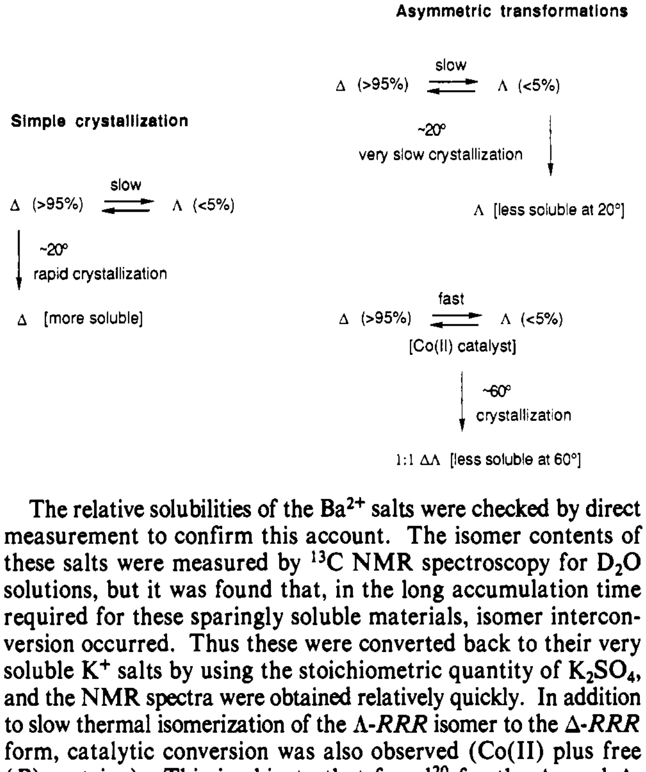
These have C_3 symmetry so that each isomer shows a single resonance for each of the carboxyl, methine, and methylene carbons; the *mer* isomers on the other hand have C_1 symmetry and would each show a nine-line ^{13}C NMR spectrum. [The ^{13}C NMR spectra for free cysteine and cystine show separate signals, as does the spectrum for the [Co((*R*)-cysS-*N*,*S*,*O*)$_2$]$^-$ isomer[18,19] of C_3 symmetry containing tridentate cysteine.] The chemical shifts for the cysteine carbons in these molecules are very similar to the corresponding ones in Λ- and Δ-[Co(en)$_2$((*R*)-cysS-*N*,*S*)]$^+$, where the bidentate N,S bonding has been confirmed by a single-crystal X-ray study.[20]

The potassium salts do not crystallize well and tend to gel, but for the less soluble and more tractable Ba^{2+} salts, we obtained a material that crystallized as nice black-olive green granules from warm water. This material was also a 1:1 mixture of the diastereomeric *fac* isomers; the isomers probably deposit in the same crystal, since the material appears to be homogeneous and the isomer ratio is unaltered on fractional crystallization.

In repeating the synthesis of the potassium salt, we more often obtained what seemed to be a single isomer (based on its ^{13}C NMR spectrum), in high yield (the Δ-*RRR* form, Figure 1, upper spectrum). Clearly, the 1:1 isomer result for our first synthesis was serendipitous. This fortuitous circumstance did however expose a problem that led us to repeat and modify the synthesis, and the following further facts shed light upon this apparent variability in the isomeric composition of the product.

An aqueous solution of the potassium salt when treated with Ba^{2+} immediately yielded a fibrous gray crystalline mass in high yield, and this was shown (vide infra) to be a single isomer, the more stable (and abundant) Δ-*RRR* form. When the suspension was warmed to about 60 °C, it transformed suddenly into a deeper colored granular crystalline mass; this material proved to be the 1:1 isomer mixture (of the Δ-*RRR* and Λ-*RRR* forms). Finally, when the mixture was allowed to cool and stir for a longer period, these transformed to fine green crystals that were a single isomer, different from the original (Figure 1, central spectrum); this is a new substance, the less abundant but much less soluble Λ-*RRR* isomer. This behavior was found to be quite reproducible.

These facts have a reasonable explanation, which could be tested. We propose that there is a second-order asymmetric transformation[13] compounded by a phase change with temperature; at low temperature the less stable Λ-*RRR* isomer is the least soluble material whereas at the higher temperature the 1:1 double salt (or "active racemate") is the less soluble material. The more soluble but more stable Δ-*RRR* isomer is obtained by allowing the system to equilibrate in solution, cooling to slow the isomer interconversion, and then crystallizing rapidly:



The relative solubilities of the Ba^{2+} salts were checked by direct measurement to confirm this account. The isomer contents of these salts were measured by ^{13}C NMR spectroscopy for D_2O solutions, but it was found that, in the long accumulation time required for these sparingly soluble materials, isomer interconversion occurred. Thus these were converted back to their very soluble K^+ salts by using the stoichiometric quantity of K_2SO_4, and the NMR spectra were obtained relatively quickly. In addition to slow thermal isomerization of the Λ-*RRR* isomer to the Δ-*RRR* form, catalytic conversion was also observed (Co(II) plus free (*R*)-cysteine). This is akin to that found[20] for the Λ- and Δ-[Co(en)$_2$((*R*)-cysS-*N*,*S*)]$^+$ isomer system and is probably an outer-sphere process involving the respective Co(II)/Co(III) complexes.

In view of the fact that rapid isomer equilibration can occur, especially under the usual synthetic conditions (Co(II) and/or heat), in the isomer analysis by NMR spectroscopy it was necessary to mix D_2O solutions of 1:1 isomer samples with D_2O solutions of supposed pure Δ-*RRR* samples to check that the "pure Δ-*RRR*" did not catalytically isomerize the Λ-*RRR* component. When the resultant spectrum was simply that expected for its components, we could be sure that the crystallized Δ-*RRR* sample

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(18) By analogy with the known (*S*)-penicillamine complexes.[19]

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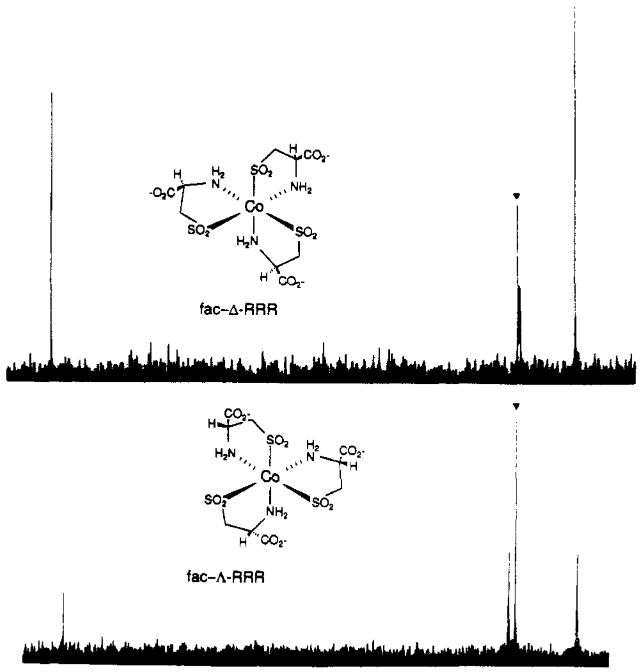

Figure 2. ^{13}C NMR spectra for Δ-$[Co((R)\text{-cysSO}_2\text{-}N,S)_3]^{3-}$ (upper spectrum) and Λ-$[Co((R)\text{-cysSO}_2\text{-}N,S)_3]^{3-}$ (lower spectrum) in D_2O (25 °C). Shifts are given in ref 16; ▼ denotes the reference signal.

was indeed pure, and not a Δ-*RRR*/Λ-*RRR* mixture that on dissolution had all isomerized to Δ-*RRR*.

It is now clear that, irrespective of which isomer or stoichiometric isomer mixture crystallizes preferentially, the Δ-*RRR* isomer is the much more abundant under equilibrium conditions—we could detect no Λ-*RRR* isomer by ^{13}C NMR spectroscopy. The Δ assignment is based on that predicted to be the more stable (the $(lel)_3$ form)[10,11] by methods shown experimentally to be reliable with, for example, the well-studied $[Co((R)\text{-pn})_3]^{3+}$ system. Perhaps ironically, it is the same isomer that Gillard and Maskill[12] isolated as the potassium salt and claimed to be that formed stereospecifically, although their conclusions were erroneously based on observations on the isomeric composition of isolated material. This does not necessarily relate to the equilibrium solution composition, as demonstrated in this work.

The related methyl ester cysteine complex $K_3[Co((R)\text{-MecysS})_3]\cdot H_2O$ has been synthesized, and it has been assumed that it resembles the cysteine analogue and is formed stereospecifically.[6] Athough its peroxide oxidation products were separated chromatographically and characterized by ^{13}C NMR and CD spectroscopic measurements, the starting material was not, and therefore there is no clear way of knowing if the various sulfenato products differ in the absolute configuration at sulfur or cobalt or both. The peroxidized tris(cysteinesulfinate) species, after hydrolysis of the ester groups, was similar in optical properties to the authentic Δ-*fac-RRR* isomer, suggesting that the starting material may have been a single isomer, but with no yield reported for the synthesis the claim to a stereospecific synthesis[6] cannot be upheld.

Finally, Dollimore and Gillard[14] have used the yellow $[Co((R)\text{-cysSO}_2\text{-}N,S)_3]^{3-}$ anion, first obtained by Schubert,[2] to optically resolve a number of cationic coordination complexes. Since this complex is made directly from the tris(cysteinate) by peroxidation, a reaction that does not affect the chirality at cobalt, one would reasonably suspect that the geometry of this complex would reflect that of its precursor. In view of our findings for the tris(cysteine) species, the Δ isomer, the Λ isomer, or a mixture might be obtained depending upon the configuration of the starting material and the conditions of crystallization. Accordingly, we have repeated Dollimore and Gillard's experiments[14] using not only the Δ form but also the Λ isomer and the stoichiometric 1:1 mixture as the substrates. We obtain the same less soluble material (Figure 2, upper spectrum) from the syntheses using Δ or the Δ/Λ mixture; it crystallizes as fibrous needles from H_2O/ethanol, and the ORD and CD spectra establish that it is the same isomer which was described by Dollimore and Gillard and which they (correctly) assigned as Δ.[12,14] (The ^{13}C NMR spectrum[16] has not been published previously, but Gillard[21] has described it as "remarkably simple".) The material obtained from the Λ starting material is quite different, and must be the corresponding Λ isomer (Figure 2, lower spectrum), a new substance. As the Ba^{2+} salts, the Δ isomer was much less soluble than the Λ isomer, accounting for their ready separation above, and there no longer seems to be a facile thermal or catalytic path to equilibrate the isomers.

The inference is that if one intends to use the Δ tris(cysteinate) trianion as a resolving agent, the material should be carefully recrystallized to remove the more soluble Λ form (as K^+ or Ba^{2+} salts), which may well have been present. Also the material should be routinely checked for the presence of the other diastereomer by a technique such as ^{13}C NMR spectroscopy.

Experimental Section

The basic starting complexes, which include $K_3[Co((R)\text{-cysS-}N,S)_3]\cdot 3H_2O$, $Na[Co(OCO)_2)_3]\cdot 3H_2O$, *trans*-$[Co(py)_4Cl_2]Cl\cdot 6H_2O$, and $K[Co(edta)]\cdot 2H_2O$, were prepared as described in the literature.[2,22-24] The several barium salts of $[Co((R)\text{-cysS-}N,S)_3]^{3-}$ were obtained as follows. By the slow addition of a strong aqueous $BaCl_2$ solution to one of the potassium salt containing a little KOH, at ambient temperature, gray fibrous needles were readily deposited (Δ isomer, $Ba_3[Co(R)\text{-cysS-}N,S)_3]_2\cdot 7H_2O$). These were collected immediately, washed with ice water, ethanol, and ether, and air-dried. In a separate preparation, these crystals transformed to darker granular crystals on prolonged gentle warming (ca. 60 °C); shortly after this phase change, the crystals were collected and washed and dried as above (1:1 Δ:Λ phase, $Ba_3[Co((R)\text{-cysS-}N,S)_3]_2\cdot 7H_2O$). In yet another separate synthesis, these crystals were allowed to stir at ambient temperature for several hours; fine dull green crystals resulted (Λ isomer, $Ba_3[Co((R)\text{-cysS-}N,S)_3]_2\cdot 7H_2O$). The H_2O_2 oxidations of the K^+ and Ba^{2+} salts were carried out as described[14] at ca. 5 °C with 30% H_2O_2. The products have the stoichiometry $K_3[Co((R)\text{-cysSO}_2\text{-}N,S)_3]\cdot 3H_2O$ and $Ba_3[Co((R)\text{-cysSO}_2\text{-}N,S)_3]_2\cdot 6H_2O$. The insoluble Ba^{2+} salts of the reactants dissolved readily as the sulfenate complexes formed but crystallized essentially quantitatively when the insoluble tris(sulfinate) species finally resulted. The recrystallization included a fine-porosity filtration step to remove a decomposition product resulting from the H_2O_2 oxidation procedure. The K^+ and Ba^{2+} salts of $[Co((R)\text{-cysS-}N,S)_3]^{3-}$ and $[Co((R)\text{-cysSO}_2\text{-}N,S)_3]^{3-}$ were fractionally crystallized from water/ethanol. Carbon-13 NMR spectra (18 °C) were obtained on a Varian XL 300 instrument using dioxane as the internal reference. Slurries of the insoluble Ba^{2+} salts in D_2O were treated with 1.5 equiv of K_2SO_4 to effect dissolution and then centrifuged or filtered prior to the NMR experiments.

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A Note on Symmetry and the Single-Crystal NMR Shift Tensor of the $CdCl_2\cdot$18-Crown-6 Complex

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Kennedy, Ellis, and Jakobsen recently determined the single-crystal NMR shift tensor for cadmium in $CdCl_2\cdot$18-crown-6,[1] whose crystal structure was determined by Paige and Richardson.[2]

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