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# The effect of counter cations on second-order asymmetric transformations in *fac*-Δ- and Λ-tris(*R*-cysteinato-*N*,*S*)cobaltate(III) complexes and the kinetics of mutarotation

**Masakazu Kita** *[a] **and Kazuaki Yamanari** [b]

[a] *Chemistry Department, Naruto University of Education, Takashima, Naruto 772-8502, Japan. E-mail: kitam@naruto-u.ac.jp*

[b] *Department of Chemistry, Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan*

***Received 19th October 1998, Accepted 18th February 1999***

A rapid reversible inversion (epimerization) between the Δ-(*R*,*R*,*R*) and Λ-(*R*,*R*,*R*) diastereomers for *fac*-Δ- and Λ-tris(*R*-cysteinato-*N*,*S*)cobaltate(III) occurs at room temperature in an aqueous solution of each salt. The half-lives for the mutarotation were measured ($k = k_\Lambda + k_\Delta$): 80 and 6 minutes at 20 and 40 °C, respectively. The equilibrium constants, $K = [\Lambda\text{-}(R,R,R)]/[\Delta\text{-}(R,R,R)]$, are 1.2 at 20 °C and 1.0 at 40 °C, which means that the cobalt inversion rate constant $k_\Lambda$ nearly equals $k_\Delta$. Eight kinds of metal salts, $M_3[Co(R\text{-cys-}N,S)_3]$ [M = $Li^+$, $Na^+$, $K^+$, $Rb^+$, $Cs^+$; $M_{1/2}$ = $Ca^{2+}$, $Sr^{2+}$, $Ba^{2+}$], were prepared. It was found that all these salts show a second-order asymmetric transformation under a solid-solution equilibrium at room temperature of the kind first demonstrated for the $Ba^{2+}$ salt by Arnold and Jackson. The phenomenon led to the Δ-(*R*,*R*,*R*) diastereomer for the salts of $Li^+$, $Na^+$, $K^+$, $Rb^+$, $Cs^+$, $Ca^{2+}$ and $Sr^{2+}$, but to the Λ-(*R*,*R*,*R*) diastereomer for $Ba^{2+}$. These results could be clearly explained by solubility measurements of each diastereomeric salt pair.

Asymmetric transformation between diastereomers causes the change of a diastereomeric ratio from unity. The equilibrium shift in homogeneous solution is known as a first-order asymmetric transformation and the subsequent selective crystallization of one of the diastereomers under conditions of relatively rapid isomer equilibration in solution is called a second-order asymmetric transformation.[1] The extent of the former phenomenon can depend on the solvent and has been reported in the neutral chromium(III) complexes such as (−)cyclo-*O*,*O*′-(1*R*, 2*R*-dimethylethylene)dithiophosphate(1−)[2] and *O*,*O*′-bis{(+)-*S*-2-methylbutyl}dithiophosphate(1−).[3] The latter one has been applied for the asymmetric synthesis of a Λ-tris(ethylenediamine)cobalt(III)(3+) complex[4] and the optical resolution of a tris(oxalato)chromate(III)(3−) complex.[5]

The synthesis of the green tris(*R*-cysteinato)cobaltate(III) complex $[Co(R\text{-cys-}N,S)_3]^{3-}$ was first reported by Schubert in 1933.[6] From many studies concerning this complex, it has been claimed that only the *fac* isomer seems to be formed and that the formation of *fac*-$[Co(R\text{-cys-}N,S)_3]^{3-}$ is stereospecific,[7] and that the Δ-(*R*,*R*,*R*) diastereomer is formed exclusively over the Λ-(*R*,*R*,*R*) diastereomer.[8] Recently, Arnold and Jackson have reported some important findings in this *fac*-$[Co(R\text{-cys-}N,S)_3]^{3-}$ system: two diastereomers, the Δ-(*R*,*R*,*R*) and Λ-(*R*, *R*,*R*) diastereomers, were confirmed to exist in solution by $^{13}C$ NMR spectroscopy and the previously unknown Λ-(*R*,*R*,*R*) diastereomer was successfully isolated as the barium salt through a novel second-order asymmetric transformation.[9] They also isolated a metastable $Ba^{2+}$ double salt containing a 1:1 ratio of the two diastereomers through crystallisation at *ca.* 60 °C where this salt is the least soluble amongst the three alternatives (Λ, Δ or ΛΔ).

Our work has been concerned with cobalt(III)-thiolato complexes containing (*R*)-cysteinato and their oxidation derivatives, which show unique behaviour, *i.e.*, stereospecificity,[10] *trans* influence,[11] linkage isomerism,[12,13] and sulfur chirality induced through metal coordination.[10–13] Therefore, we became interested in the above second-order asymmetric transformation phenomenon for *fac*-$[Co(R\text{-cys-}N,S)_3]^{3-}$ and started a preliminary investigation. We discovered new results, some of which relate to the differing views of the two groups.[14,15] Herein we report the following: eight kinds of metal salts in *fac*-Δ- and Λ-tris(*R*-cysteinato-*N*,*S*)cobaltate(III), $M_3[Co(R\text{-cys-}N,S)_3]$ [M = $Li^+$, $Na^+$, $K^+$, $Rb^+$, $Cs^+$ and $M_{1/2}$ = $Ca^{2+}$, $Sr^{2+}$, $Ba^{2+}$] were prepared and the solution kinetics of mutarotation were investigated in these salts.

## Experimental

### Δ-$Li_3[Co(R\text{-cys-}N,S)_3]$ and Δ-$M_3[Co(R\text{-cys-}N,S)_3]$ (M = $Na^+$, $K^+$, $Rb^+$ and $Cs^+$; $M_{1/2}$ = $Ca^{2+}$, $Sr^{2+}$ and $Ba^{2+}$)

An aqueous solution (20 cm³) of 1.64 g (9.5 mmol) of (*R*)-$H_2cys{\cdot}HCl{\cdot}H_2O$ and 1.20 g (28.5 mmol) of $LiOH{\cdot}H_2O$ was added to an aqueous solution (50 cm³) of 0.50 g (1.9 mmol) of $[Co(NH_3)_6]Cl_3$. The mixture was stirred for 2 h at 70 °C until no further evolution of ammonia could be detected. The resulting deep green solution showed a CD (circular dichroism) spectrum with the *ca.* 3:2 mixture of the Δ-(*R*,*R*,*R*) and Λ-(*R*,*R*,*R*) diastereomers. Addition of 20 cm³ of ethanol to the solution gave a gray-blue precipitate and then the suspension was stirred at 20 °C for 12 h to yield blue needles of the pure Δ(*R*,*R*,*R*) diastereomer. It should be noted that the immediate addition of an excess of ethanol (100 cm³) resulted in the precipitation of the *ca.* 3:1 mixture of the Δ-(*R*,*R*,*R*) and Λ-(*R*,*R*,*R*) diastereomers. Yield = 0.90 g (82%). Found: C, 18.74; H, 5.01; N, 7.40. Calc. for Δ-$Li_3[Co(R\text{-cys})_3]{\cdot}7H_2O = C_9H_{29}N_3O_{13}S_3CoLi_3$: C, 19.19; H, 5.19; N, 7.46%.

The other alkali-metal salts of the pure Δ-diastereomer were obtained by using the appropriate alkali-metal hydroxide instead of LiOH. The yields were *ca.* 80–90%. Found for the sodium salt: C, 15.55; H, 5.10; N, 6.02. Calc. for Δ-$Na_3[Co(R\text{-cys})_3]{\cdot}11H_2O = C_9H_{37}N_3O_{17}S_3CoNa_3$: C, 15.82; H, 5.46; N, 6.15%. Found for the potassium salt: C, 16.62; H, 4.45; N, 6.46. Calc. for Δ-$K_3[Co(R\text{-cys})_3]{\cdot}6.5H_2O = C_9H_{28}N_3O_{12.5}S_3CoK_3$: C, 16.61; H, 4.34; N, 6.46%. Found for the rubidium salt: C, 12.88; H, 3.62; N, 5.00. Calc. for Δ-$Rb_3[Co(R\text{-cys})_3]\cdot 9H_2O = C_9H_{33}N_3O_{15}S_3CoRb_3$: C, 12.95; H, 3.98; N, 5.03%. Found for the caesium salt: C, 11.19; H, 2.92; N, 4.37. Calc. for Δ-$Cs_3[Co(R\text{-cys})_3]\cdot 8H_2O = C_9H_{31}N_3O_{14}S_3CoCs_3$: C, 11.27; H, 3.26; N, 4.38%.

The $Ca^{2+}$ and $Sr^{2+}$ salts of the pure Δ-(*R*,*R*,*R*) diastereomer were obtained by a similar asymmetric transformation, but the experiments were carried out under Ar to prevent the formation of insoluble $MCO_3$. The pure Δ-(*R*,*R*,*R*) diastereomer of the lithium salt could be converted to $Ca^{2+}$, $Sr^{2+}$ or $Ba^{2+}$ salt by rapid addition of concentrated aqueous $CaCl_2$, $SrCl_2$ or $BaCl_2$. Found for the calcium salt: C, 16.77; H, 4.71; N, 6.45. Calc. for Δ-$Ca_{1.5}[Co(R\text{-cys})_3]\cdot 9H_2O = C_9H_{33}N_3O_{15}S_3CoCa_{1.5}$: C, 16.93; H, 5.21; N, 6.58%. Found for the strontium salt: C, 15.24; H, 3.47; N, 5.63. Calc. for Δ-$Sr_{1.5}[Co(R\text{-cys})_3]\cdot 9H_2O = C_9H_{33}N_3O_{15}S_3CoSr_{1.5}$: C, 15.23; H, 4.69; N, 5.92%. Found for the barium salt: C, 13.76; H, 3.38; N, 5.15. Calc. for Δ-$Ba_{1.5}[Co(R\text{-cys})_3]\cdot 9H_2O = C_9H_{33}N_3O_{15}S_3CoBa_{1.5}$: C, 13.78; H, 4.24; N, 5.36%.

### Λ-$Ba_{1.5}[Co(R\text{-cys-}N,S)_3]$ and Λ-$M_3[Co(R\text{-cys-}N,S)_3]$ ($M = Na^+, K^+, Rb^+$, and $Cs^+$; $M_{1/2} = Ca^{2+}$ and $Sr^{2+}$)

All experiments were performed under an Ar atmosphere. An aqueous solution (20 $cm^3$) of 1.64 g (9.5 mmol) of (*R*)-$H_2cys\cdot HCl\cdot H_2O$ and 4.45 g (14.3 mmol) of $Ba(OH)_2\cdot 8H_2O$ was added to a hot aqueous solution (50 $cm^3$) of 0.50 g (1.9 mmol) of $[Co(NH_3)_6]Cl_3$. A green precipitate began to deposit before long and the mixture was stirred for 2 h at 70°C. This crystalline precipitate was composed of the pure Λ-(*R*,*R*,*R*) salt. Yield = 2.30 g (96%). Found: C, 15.09; H, 3.29; N, 5.82. Calc. for Λ-$Ba_{1.5}[Co(R\text{-cys})_3]\cdot 5H_2O = C_9H_{25}N_3O_{11}S_3CoBa_{1.5}$: C, 15.17; H, 3.54; N, 5.90%.

The pure Λ-(*R*,*R*,*R*) barium salt could be converted to the $Li^+$, $Na^+$, $K^+$, $Rb^+$ or $Cs^+$ salt by adding a stoichiometric amount of an aqueous $Li_2SO_4$, $Na_2SO_4$, $K_2SO_4$, $Rb_2SO_4$ or $Cs_2SO_4$ solution. Then the resultant precipitate of $BaSO_4$ was rapidly removed by filtration and the addition of an excess of ethanol to the filtrate gave the desired salt: all yields were *ca.* 50%. The lithium salt could be further converted into the $Ca^{2+}$ and $Sr^{2+}$ salts by adding stoichiometric amounts of aqueous $CaCl_2$ and $SrCl_2$ solutions, respectively, and a small amount of methanol. Each yield was *ca.* 30%. Found for the lithium salt: C, 19.64; H, 5.19; N, 7.52. Calc. for Λ-$Li_3[Co(R\text{-cys})_3]\cdot 6.5H_2O = C_9H_{28}N_3O_{12.5}S_3CoLi_3$: C, 19.50; H, 5.09; N, 7.58%. Found for the sodium salt: C, 17.64; H, 4.51; N, 6.47. Calc. for Λ-$Na_3[Co(R\text{-cys})_3]\cdot 7H_2O = C_9H_{29}N_3O_{13}S_3CoNa_3$: C, 17.68; H, 4.78; N, 6.87%. Found for the potassium salt: C, 16.58; H, 4.40; N, 6.36. Calc. for Λ-$K_3[Co(R\text{-cys})_3]\cdot 7H_2O = C_9H_{29}N_3O_{13}S_3CoK_3$: C, 16.38; H, 4.43; N, 6.37%. Found for the rubidium salt: C, 13.19; H, 3.65; N, 5.01. Calc. for Λ-$Rb_3[Co(R\text{-cys})_3]\cdot 8H_2O = C_9H_{31}N_3O_{14}S_3CoRb_3$: C, 13.23; H, 3.83; N, 5.14%. Found for the caesium salt: C, 11.34; H, 2.99; N 4.41. Calc. for Λ-$Cs_3[Co(R\text{-cys})_3]\cdot 7H_2O = C_9H_{29}N_3O_{13}S_3CoCs_3$: C, 11.49; H, 3.11; N, 4.46%. Found for the calcium salt: C, 14.37; H, 4.37; N, 5.51. Calc. for Λ-$Ca_{1.5}[Co(R\text{-cys})_3]\cdot 7.5H_2O = C_9H_{30}N_3O_{13.5}S_3CoCa_{1.5}$: C, 17.67; H, 4.85; N, 6.64%. Found for the strontium salt: C, 17.67; H, 4.94; N, 6.87. Calc. for Λ-$Sr_{1.5}[Co(R\text{-cys})_3]\cdot 10H_2O = C_9H_{35}N_3O_{16}S_3CoSr_{1.5}$: C, 14.85; H, 4.85; N, 5.77%.

The purity of each diastereomer was checked by $^1H$ NMR measurements as shown in Figs. 1 and 2.

### Determination of kinetic data

The exact values of $\Delta\varepsilon$ and $\varepsilon$ for the Δ-(*R*,*R*,*R*) and Λ-(*R*,*R*,*R*) diastereomers could be determined by extrapolating to time zero: $\varepsilon = 376 \pm 1$ $dm^3\ mol^{-1}\ cm^{-1}$ at 582 ± 1 nm and $\Delta\varepsilon = -9.90 \pm 0.05$ $dm^3\ mol^{-1}\ cm^{-1}$ at 598 ± 1 nm for the Δ-(*R*,*R*,*R*) diastereomer and 355 ± 1 $dm^3\ mol^{-1}\ cm^{-1}$ at 595 ± 1 nm and $\Delta\varepsilon = +10.00 \pm 0.05$ $dm^3\ mol^{-1}\ cm^{-1}$ at 585 ± 1 nm for the Λ-(*R*,*R*,*R*) diastereomer. In the absence of an excess of (*R*)-cysteinate, the mononuclear complex *fac*-$[Co(R\text{-cys})_3]^{3-}$ is known to be readily converted to the trinuclear complex

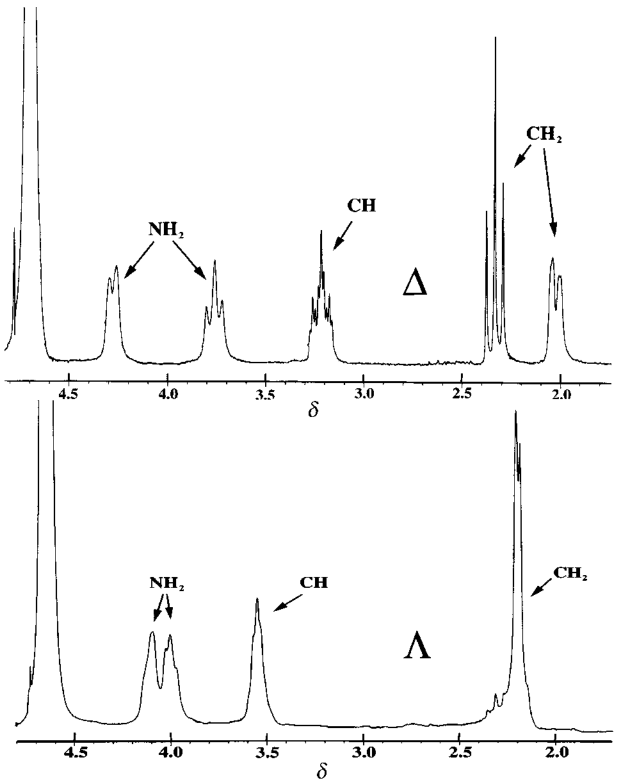

**Fig. 1** $^1H$ NMR spectra of *fac*-Δ- and *fac*-Λ-$Li_3[Co(R\text{-cys-}N,S)_3]$ in $D_2O$ measured within 5 minutes after dissolving at 30 °C.

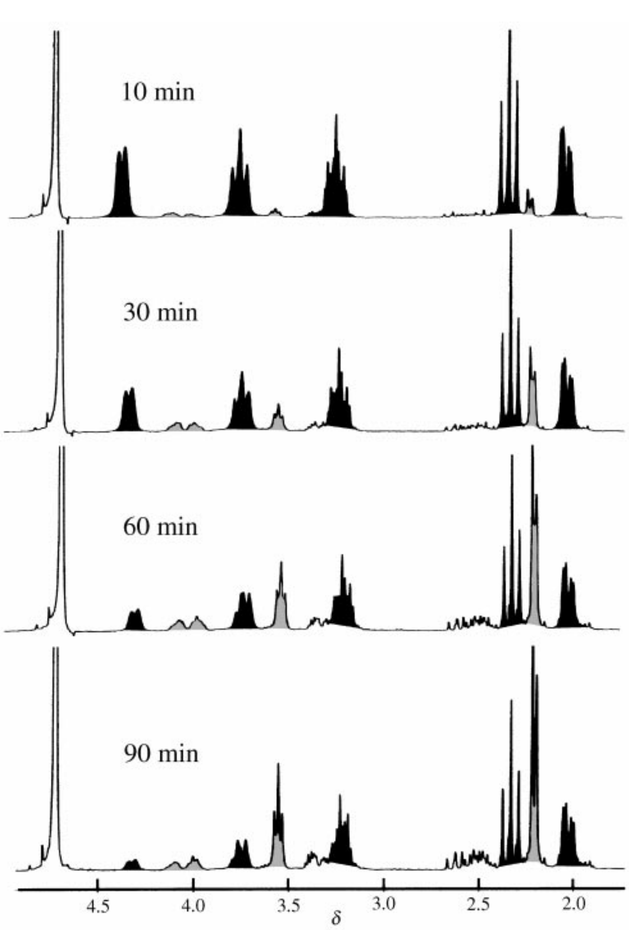

**Fig. 2** $^1H$ NMR spectral change with time at 30 °C: *fac*-Δ-$Li_3[Co(R\text{-cys-}N,S)_3]$ in $D_2O$ as a starting complex.

**Table 1** Equilibrium constants and thermodynamic parameters of *fac*-$Li_3[Co(R\text{-cys})_3]$ in 0.1 M $Li_2(R\text{-cys})$ aqueous solutions[a]

| $T$/°C | 20 | 30 | 40 |
|---|---|---|---|
| $\Delta\varepsilon_{eq}$/dm$^3$ mol$^{-1}$ cm$^{-1}$ | +0.85 | +0.35 | +0.14 |
| $K = [\Lambda\text{-}(R,R,R)]/[\Delta\text{-}(R,R,R)]$ | 1.17 | 1.08 | 1.01 |
| $\Delta H°$/kJ mol$^{-1}$ | −5.6 ± 0.2 | | |
| $\Delta G°$/kJ mol$^{-1}$ | −0.35 ± 0.1 | | |
| $\Delta S°$/J mol$^{-1}$ K$^{-1}$ | −17.6 ± 0.5 | | |

[a] The solutions were prepared with complex concentrations of 2 mmol dm$^{-3}$.

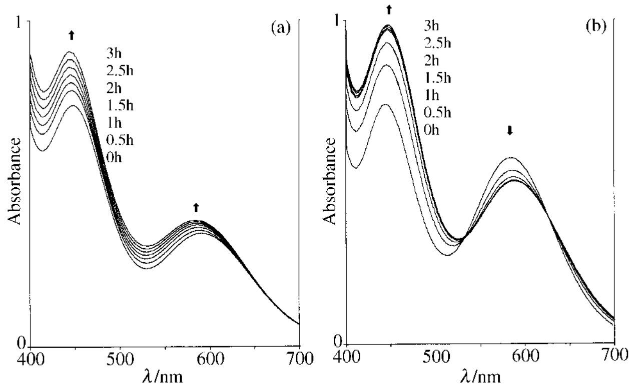

**Fig. 3** Absorption spectral changes with time at 20 °C: (a) the Δ-(*R*,*R*,*R*) diastereomer in water and (b) the Δ-(*R*,*R*,*R*) one in a 0.1 M $Li_2(R)$-cysteinate solution.

$[Co\{Co(R\text{-cys})_3\}_2]^{3-}$ in aqueous solution.[16,17] In fact, the absorption spectral change in aqueous solution had no isosbestic points as shown in Fig. 3(a). Therefore, the equilibrium state for the $\Delta\text{-}(R,R,R) \rightleftharpoons \Lambda\text{-}(R,R,R)$ inversion could not be realised under such conditions.

In order to prevent the polymerization reaction we treated $[Co(R\text{-cys})_3]^{3-}$ in a 0.1 M $M_2\{(R)\text{-cysteinate}\}$ aqueous solution. After this treatment the absorption spectral change with time exhibited isosbestic points as shown in Fig. 3(b). The concentration of the free (*R*)-cysteinate may affect the inversion rates. Within 3 h, however, the CD change rate of the lithium salt of the Λ-(*R*,*R*,*R*) (or Δ-(*R*,*R*,*R*)) diastereomer in aqueous solution is similar to that in a 0.1 M $Li_2(R\text{-cys})$ aqueous solution, where the isodichroic point at 503 nm in the aqueous solution is coincident with that in a 0.1 M $Li_2\{(R)\text{-cysteinate}\}$ aqueous solution. Thus, the CD contribution due to the trinuclear complex formation is negligible small. The equilibrium constants and inversion rate constants (Tables 1 and 2) were obtained at different temperatures: 20, 30 and 40 °C, with a complex concentration of *ca.* 2 mmol dm$^{-3}$. The manner of typical exponential CD change and the equilibrium state (23 h after dissolution) of the Λ complex agreed with those of the Δ one as shown in Fig. 4. The kinetic measurements by CD spectra were recorded at a fixed wavelength (598 nm). The data treatment was carried out according to the scheme of general reversible unimolecular reactions.[18] The plots of $\ln(\Delta\varepsilon_{eq} - \Delta\varepsilon_t)_\Delta$ against time are shown in Fig. 5, where the subscript "t" or "eq" means at time *t* or at equilibrium, respectively, and the subscript Δ means an initial complex configuration. $\Delta\varepsilon_t$ is expressed as $\Delta\varepsilon_\Lambda(1 - x_t) + \Delta\varepsilon_\Delta x_t$ where the character "*x*" represents the mole fraction $(x = [\Delta\text{-}(R,R,R)]/\{[\Delta\text{-}(R,R,R)] + [\Lambda\text{-}(R,R,R)]\}$. The slopes of linear regressions, $-(k_\Delta + k_\Lambda)$, of $\ln(\Delta\varepsilon_{eq} - \Delta\varepsilon_t)_\Delta$ *versus* time in Fig. 5 were in fair agreement of the mean values for the Δ and Λ complexes as starting materials, and hence they were used for evaluating the individual rate constants.

### Solubility measurement

Solubilities of the diastereomeric salts were measured at 20 °C in water for the $Ca^{2+}$, $Sr^{2+}$ and $Ba^{2+}$ salts and in water–ethanol (1 : 3) for the $Li^+$, $Na^+$, $K^+$, $Rb^+$ and $Cs^+$ salts with use of the molar absorption coefficients at 582 nm for Δ-(*R*,*R*,*R*) ($\varepsilon = 376$ dm$^3$ mol$^{-1}$ cm$^{-1}$) and at 595 nm for Λ-(*R*,*R*,*R*) ($\varepsilon = 355$ dm$^3$ mol$^{-1}$ cm$^{-1}$). Since both the diastereomers rapidly epimerize as shown in Fig. 2, we measured the solubility of the solution within ten minutes after mixing a sample with the solvent. These solubility data are listed in Table 3 and the solubility ratios were used in the discussion.

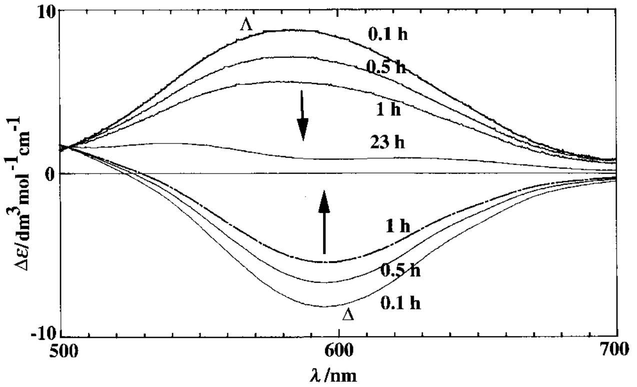

**Fig. 4** CD spectra of the Δ- and Λ-diastereomers in a 0.1 M $Li_2$-(*R*)-cysteinate solution and at an equilibrium state at 20 °C.

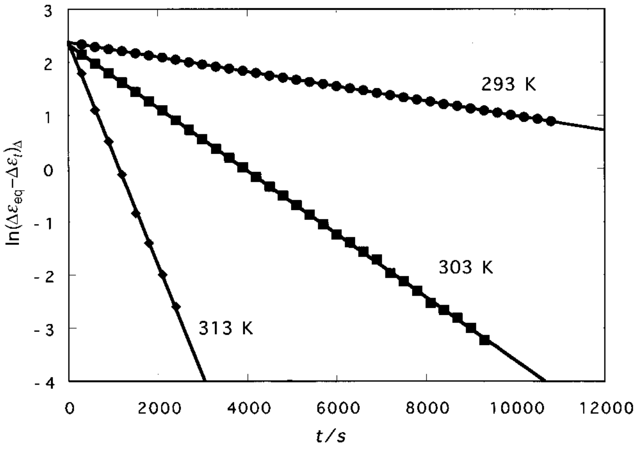

**Fig. 5** The relationship between time and $\ln(\Delta\varepsilon_{eq} - \Delta\varepsilon_t)_\Delta$. The subscript Δ denotes the configuration of the starting complex.

### Measurements

UV/Visible absorption spectra were recorded on a Hitachi U-3400 spectrophotometer, $^1H$ NMR spectra on a Bruker ARX300 spectrometer, and CD spectra on a JASCO J-600 spectropolarimeter.

## Results and discussion

### Kinetics of mutarotation

The $^1H$ NMR spectra of *fac*-(*S*)-Δ- and Λ-$[Co(R\text{-cys-}N,S)_3]^{3-}$ in $D_2O$ are shown in Fig. 1; they were recorded within 5 minutes after dissolution. The diastereomeric purity could be checked based on these $^1H$ NMR spectra. Fig. 2 shows the spectral changes of the Δ-(*R*,*R*,*R*) diastereomer during the first 90 minutes after dissolution and clearly indicates rapid inversion around a cobalt center. The signals of the amino protons in the coordinated *R*-cysteinate gradually disappeared with time because of H–D exchange. The two amino protons at 4.3(doublet) and 3.75(triplet) ppm can be assigned to the axial sites (which are noted at $H_\perp$ in Fig. 6) and to the perpendicular sites (which are noted as $H_\parallel$) to the $C_3$ molecular axis, respectively. This assignment was confirmed by the following NMR

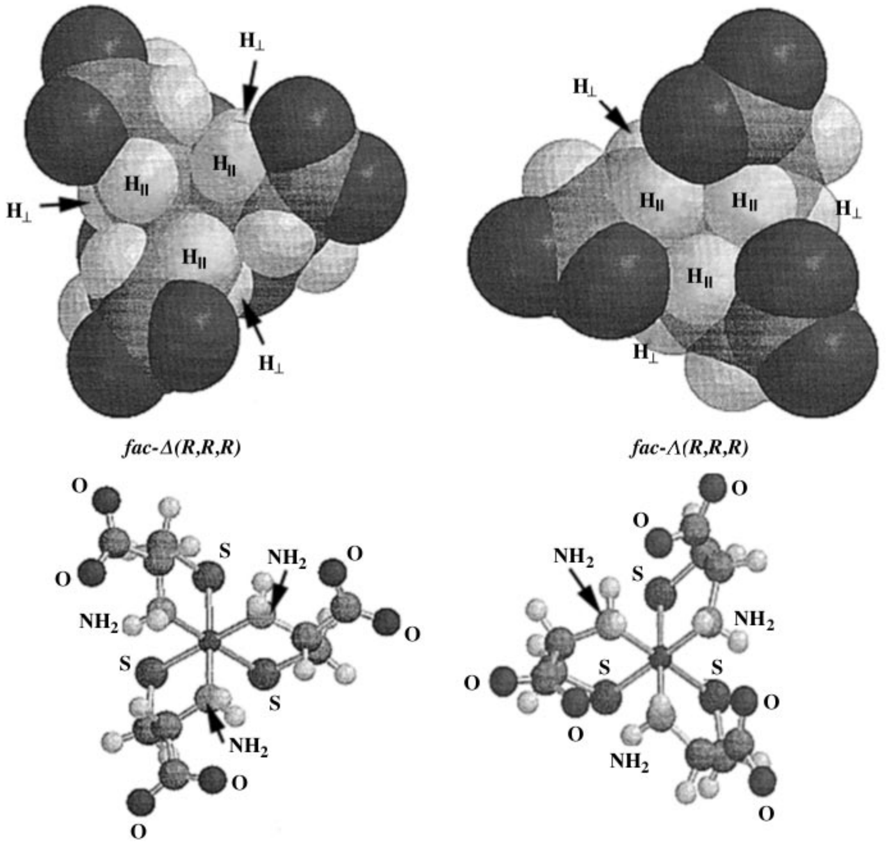

**Fig. 6** SPARTAN molecular models of the Λ-(*R*,*R*,*R*) (right) and Δ-(*R*,*R*,*R*) (left) diastereomers. The axial sites are noted as $H_\perp$ and the perpendicular sites are noted as $H_\parallel$ to the $C_3$ molecular axis.

**Table 2** Rate constants and activation parameters for mutarotation of *fac*-Δ $\rightleftharpoons$ Λ-$Li_3[Co(R\text{-cys})_3]$ in 0.1 M $Li_2(R\text{-cys})$ aqueous solutions[a]

| $T$/°C | 20 | 30 | 40 |
|---|---|---|---|
| $k = k_\Delta + k_\Lambda/s^{-1}$ | $(1.45 \pm 0.08) \times 10^{-4}$ | $(5.77 \pm 0.17) \times 10^{-4}$ | $(2.00 \pm 0.09) \times 10^{-3}$ |
| $k_\Delta/s^{-1}$ | $(7.8 \pm 0.08) \times 10^{-5}$ | $(3.00 \pm 0.17) \times 10^{-4}$ | $(1.00 \pm 0.09) \times 10^{-3}$ |
| $k_\Lambda/s^{-1}$ | $(6.7 \pm 0.08) \times 10^{-5}$ | $(2.77 \pm 0.17) \times 10^{-4}$ | $(1.00 \pm 0.09) \times 10^{-4}$ |
| | $\Delta(R,R,R) \longrightarrow \Lambda(R,R,R)$ | $\Lambda(R,R,R) \longrightarrow \Delta(R,R,R)$ | |
| $E_a$/kJ mol$^{-1}$ | 101 ± 2 | 107 ± 2 | |
| ln $A$ | 32 ± 2 | 32 ± 2 | |
| $\Delta H^{\neq}$/kJ mol$^{-1}$ | 98.5 ± 0.6 | 104.5 ± 0.6 | |
| $\Delta G^{\neq}$/kJ mol$^{-1}$ | 94 ± 7 | 94 ± 6 | |
| $\Delta S^{\neq}$/J mol$^{-1}$ K$^{-1}$ | 16 ± 20 | 35 ± 19 | |

[a] The solutions were prepared with complex concentrations of 2 mmol dm$^{-3}$.

**Table 3** Solubilities ($10^{-3}$ mol dm$^{-3}$) of *fac*-Λ- and Δ-$M_3[Co(R\text{-cys})_3]$ in $H_2O$–EtOH (1 : 3) or in $H_2O$ at 20 °C and their solubility ratios

| M | $S_\Lambda$ | $S_\Delta$ | $S_\Lambda/S_\Delta$ |
|---|---|---|---|
| *fac*-Λ- and Δ-$M_3[Co(R\text{-cys})_3]$ in $H_2O$–EtOH (1 : 3) | | | |
| Li | 4.8 | 2.7 | 1.8 |
| Na | 3.1 | 0.14 | 22 |
| K | 7.7 | 0.18 | 43 |
| Rb | 3.5 | 1.3 | 2.7 |
| Cs | 1.6 | 0.74 | 2.2 |
| *fac*-Λ- and Δ-$M_{1.5}[Co(R\text{-cys})_3]$ in $H_2O$ | | | |
| Ca | >100 | 0.23 | *ca.* 430 |
| Sr | >70 | 5.2 | *ca.* 13 |
| Ba | 1.1 | 9.7 | 0.11 |

experiment. Addition of $Li_2SO_4$ to the sample solution caused a lower-field shift from 4.3 to 5.0 ppm, whereas no change was observed for the signal at 3.75 ppm. It is well known that the axial amino protons along the $C_3$ axis preferentially interact with sulfate anion and form intermolecular hydrogen bonds,[19] which leads to the lower field shift of the axial site protons. Furthermore, the signal at 4.3 ppm is more quickly reduced by the H–D exchange than that at 3.75 ppm as shown in Fig. 2. The result can be interpreted in terms of the site differences: the $H_\parallel$ amino protons at 4.3 ppm are located at uncovered sites but the $H_\perp$ protons at 3.75 ppm are blocked by the carboxyl groups as shown in Fig. 6. On the other hand, a similar NMR experiment of $Li_2SO_4$ addition to Λ-$Li_3[Co(R\text{-cys})_3]$ solution did not change the chemical shifts of the amino protons. The multiplets at 2.5 and 3.4 ppm gradually appeared with time. These signals are due to the trinuclear complex formation, $[Co\{Co(R\text{-cys})_3\}_2]^{3-}$. Upon addition of an excess of the (*R*)-cysteinate salts, however, the appearance of the signals at 2.5 and 3.4 ppm is clearly suppressed. Therefore, the same conditions were applied for the kinetic experiments.

Fig. 3(b) shows absorption spectral changes of the Δ-(*R*,*R*,*R*) diastereomer with time in a 0.1 M $Li_2\{(R)\text{-cysteinate}\}$ aqueous solution. The first d–d absorption band at 582 nm decreases with time, which corresponds to the increase of the Λ-(*R*,*R*,*R*) diastereomer. Two isosbestic points were observed at 625 and 531 nm. The CD spectra changes in Fig. 4 also indicate that the interconversion of two components occurs in 0.1 M (*R*)-cysteinate aqueous solution. The relationships between time and $\ln(\Delta\varepsilon_t - \Delta\varepsilon_{eq})_\Lambda$ [or $\ln(\Delta\varepsilon_{eq} - \Delta\varepsilon_t)_\Delta$] at three different temperatures are shown in Fig. 5. The good linear relationships confirm that the present system can be treated as a reversible first order reaction in a 0.1 M (*R*)-cysteinate solution. This reaction corresponds to the configuration inversion of the cobalt centre as shown in the following scheme:

$$fac\text{-}\Delta\text{-}(R,R,R) \underset{k_\Delta}{\overset{k_\Lambda}{\rightleftharpoons}} fac\text{-}\Lambda\text{-}(R,R,R)$$

The equilibrium constants at 20, 30 and 40 °C are listed in Table 1. The $\Delta\varepsilon_{eq}$ values gave the mole fractions of the two diastereomers in solution. The equilibrium constant $K = [\Lambda\text{-}(R,R,R)]/[\Delta\text{-}(R,R,R)]$ gradually approaches unity with an increase in temperature, which indicates that the Δ-(*R*,*R*,*R*) diastereomer is more favourable at higher temperatures. The calculated standard free energy and entropy at 25 °C are also listed in Table 1. The negative enthalpy change ($\Delta H^\circ = -5.6 \pm 0.2$ kJ mol$^{-1}$) indicates the higher stability of the Λ-(*R*,*R*,*R*) ion over the Δ-(*R*,*R*,*R*) ion. The negative entropy change ($\Delta S^\circ = -17.6 \pm 0.5$ J K$^{-1}$ mol$^{-1}$) suggests that the Λ-(*R*,*R*,*R*) complex has less degrees of freedom (less flexibility) or occupies less space in solution than the Δ-(*R*,*R*,*R*) one. This fact is supported by SPARTAN calculations[20] for the present complexes as shown in Fig. 6. The Δ-(*R*,*R*,*R*) diastereomer adopts the $(lel)_3$ conformation and has the carboxyl groups at equatorial positions. On the other hand, the Λ-(*R*,*R*,*R*) diastereomer can also take the $(lel)_3$ conformation if the carboxyl groups are directed axially along the $C_3$ axis. The electrostatic interactions between the anionic carboxyl groups and the partially positive amino protons may relate to the unexpected stability of this Λ-(*R*,*R*,*R*) diastereomer. Thus, there is almost no energy difference between these two diastereomers in the $[Co(R\text{-cys-}N,S)_3]^{3-}$ system. The present system provides a striking contrast to $[Co(R\text{-pn})_3]^{3+}$. In the $[Co(R\text{-pn})_3]^{3+}$ system, there is a large energy difference between two diastereomers and the $\Delta\text{-}[Co(R\text{-pn})_3]^{3+}$ diastereomer is more stable than $\Lambda\text{-}[Co(R\text{-pn})_3]^{3+}$.[21]

The inversion rate constants and activation parameters are listed in Table 2. The half-lives for epimerisation were calculated from the observed rate constants ($k = k_\Lambda + k_\Delta$): 80 and 6 minutes at 20 and 40 °C respectively. This means that higher temperatures can readily accelerate the inversion rate and the equilibrium state is rapidly reached. Activation parameters for inversion of Λ-[Co{(−)-*N*-(α-phenylethyl)dithiocarbamato)}$_3$] in $CH_2Cl_2$ are $\Delta H^{\neq} = 80.3$ kJ mol$^{-1}$ and $\Delta S^{\neq} = -39$ J mol$^{-1}$ K$^{-1}$. The inversion in these dithiocarbamato[22] or acetylacetonato[23] Co(III) complexes is usually thought to occur by a trigonal twist mechanism, though the inversion of the tris(diphenyldithiocarbamato)cobalt(III) complex is considered to occur *via* a bond rupture mechanism from an NMR study on $\Delta V^{\neq}$.[24] On the other hand, the activation parameters for inversion of Λ-tris{(−)cyclo-*O*,*O*′-(1*R*,2*R*-dimethylethylene)dithiophosphato}chromium(III)[2] in $CHCl_3$ are $\Delta H^{\neq} = 101$ kJ mol$^{-1}$ and $\Delta S^{\neq} = 38$ J mol$^{-1}$ K$^{-1}$: a one-ended dissociative mechanism through a five-coordinated intermediate has been proposed in this system.[2] In our system, the higher $\Delta H^{\neq}$ (*ca.* 100 kJ mol$^{-1}$) and the positive $\Delta S^{\neq}$ values (*ca.* 25 J mol$^{-1}$ K$^{-1}$) in Table 2 are indicative of the one-ended dissociation mechanism rather than the trigonal twist one.

The inversion rate around a cobalt centre has been suggested to be catalysed by $Co^{2+}$/(*R*)-cysteinate ions[9] but this is unlikely. We examined whether the presence of 1, 5 or 10 ppm of $Co^{2+}$ in 0.1 M $Li^2(R)$-cysteinate can affect the inversion rate of 2 mmol dm$^{-3}$ of $\Delta\text{-}[Co(R\text{-cys})_3]^{3-}$ solution: the inversion rates are unchanged within $k = (1.4 \pm 0.1) \times 10^{-4}$ s$^{-1}$. On the other hand, the presence of $Co^{2+}$ alone caused the formation of a trinuclear complex, $[Co\{Co(R\text{-cys})_3\}_2]^{3-}$.[16,17] In fact, addition of a few ppm of $Co^{2+}$ to a 1 mmol dm$^{-3}$ aqueous solution of $\Delta\text{-}[Co(R\text{-cys})_3]^{3-}$ without free (*R*)-cysteinate showed instantaneously the characteristic absorption and CD spectra of the (Λ,Λ)-trinuclear complex. This results agrees well with the trinuclear complex study.[16]

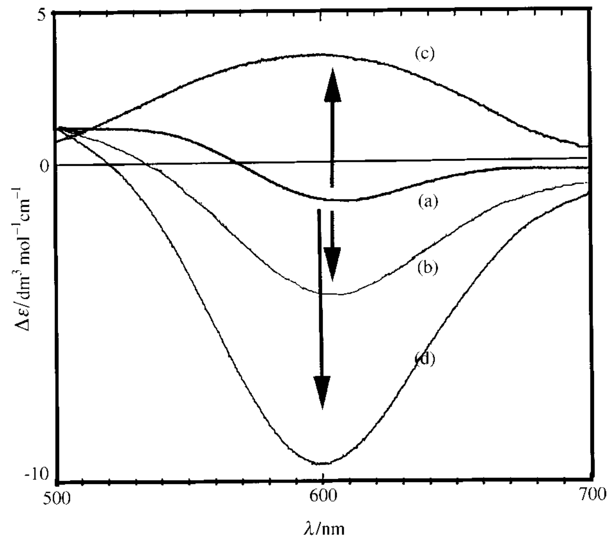

**Fig. 7** CD spectra due to (a) preparative reaction solution ($[Co(NH_3)_6]Cl_3$ and $5K_2(R)$-cysteinate) at 70 °C for 2 h; (b) precipitate obtained by adding an equal volume of ethanol to (a); (c) its filtrate; (d) the precipitate after the suspension of (b) and (c) was stirred at 20 °C for 12 h.

All of the Δ- or Λ-*fac*-tris(*R*-cysteinato-*N*,*S*)cobaltate(III) complexes with alkali and alkaline earth metal cations gave the same $^1$H NMR, absorption and CD spectra in dilute aqueous solution. Furthermore, the inversion rates and equilibrium states of $\Lambda\text{-}Ba_{1.5}[Co(R\text{-cys-}N,S)_3]$ in 0.1 M Ba(*R*-cys) and Δ- and $\Lambda\text{-}Na_3[Co(R\text{-cys-}N,S)_3]$ in 0.1 M $Na_2(R\text{-cys})$ are in fair agreement with those of the corresponding lithium complexes in 0.1 M $Li_2(R\text{-cys})$. Thus, the type of counter cation does not affect the mutarotation in such a dilute aqueous solution, which is in contrast to the following second-order asymmetric transformation.

## Second-order asymmetric transformations in the present salts

When $[Co(NH_3)_6]^{3+}$ (*ca.* 2 mmol dm$^{-3}$) and an excess of $M_2(R)$-cysteinate (9.5 mmol) in 50 cm$^3$ of water were stirred at 70 °C for 2 h, all solution compositions of $Li^+$, $Na^+$, $K^+$, $Rb^+$ and $Cs^+$ salts became Δ-(*R*,*R*,*R*): Λ=(*R*,*R*,*R*) = *ca.* 57:43 as shown in Fig. 7(a). On addition of an equal volume of ethanol, the obtained green precipitate (0.8 g, yield 71%) was composed of Δ-(*R*,*R*,*R*): Λ-(*R*,*R*,*R*) = *ca.* 71:29 (Fig. 7(b)) and its filtrate was of Δ-(*R*,*R*,*R*): Λ-(*R*,*R*,*R*) = *ca.* 33:67 (Fig. 7(c)). Furthermore, the subsequent stirring of the resultant suspension of (b) and (c) at 20 °C for 12 h led to the almost optically pure Δ-(*R*,*R*,*R*) diastereomer as a solid in these systems. Fig. 7(d) exhibits the CD spectrum of the Δ-(*R*,*R*,*R*) diastereomer finally obtained, whose diastereomeric ratio was Δ-(*R*,*R*,*R*): Λ-(*R*,*R*,*R*) = *ca.* 98:2. Such a change should be due to a second-order asymmetric transformation.

On the other hand, the reaction mixtures containing $Ca^{2+}$, $Sr^{2+}$ and $Ba^{2+}$ salts under an Ar atmosphere immediately resulted in less-soluble precipitates. The precipitates were not optically pure. However, stirring the suspension at 70 °C for 2 h gave the pure Δ-(*R*,*R*,*R*) diastereomer for $Ca^{2+}$ and $Sr^{2+}$ and the Λ-(*R*,*R*,*R*) diastereomer for $Ba^{2+}$ as a solid.

Arnold and Jackson have reported the second-order asymmetric transformation of the barium salt and obtained the Λ-(*R*,*R*,*R*) diastereomer as the final solid in the systems starting from $Na_3[Co(CO_3)_3]\cdot 3H_2O$, *trans*-$[CoCl_2(py)_4]Cl\cdot 6H_2O$ or $K[Co(edta)]\cdot 2H_2O$.[9] In the present systems, we found that the second-order asymmetric transformation exists in all salts and the opposite Δ-(*R*,*R*,*R*) diastereomer is obtainable as the final solid in all salts except for the barium salt. It is quite interesting that the absolute configurations of the final product dramatically change depending upon the counter cations.

Solubilities were determined for each salt of the diastereomeric pair (in Table 3). Though the fairly rapid mutarotation in each system prevents the accurate determination of solubility, the solubility ratio becomes a useful index. The diastereomeric solubility ratio ($S_\Lambda/S_\Delta$) is larger than unit in the salts of $Li^+$, $Na^+$, $K^+$, $Rb^+$, $Cs^+$, $Ca^{2+}$ and $Sr^{2+}$, whereas the ratio ($S_\Lambda/S_\Delta$) is smaller than unity in the $Ba^{2+}$ salt. The potassium salt shows the largest solubility ratio. In alkaline earth metal salts, the solubility ratios decrease with increasing atomic number (or ionic radii) of the cation. The solubility ratio becomes less than unity only in the barium salt. It seems quite reasonable to consider that these solubility relationships determine which diastereomer would be obtained as the final solid.

When a 0.1 M $Li_2$(*R*)-cysteinate aqueous solution of $[Co(R\text{-cys})_3]^{3-}$ (*ca.* 1 mmol $dm^{-3}$) was kept standing for 1 day, the resultant equilibrium ratio became *ca.* 1:1 of the Δ-(*R*,*R*,*R*) and Λ-(*R*,*R*,*R*) diastereomers. When $[Co(NH_3)_6]^{3+}$ (*ca.* 30 mmol $dm^{-3}$) and an excess of $M_2$(*R*)-cysteinate were reacted at 70 °C for 2 h, the obtained solution composition was fairly Δ-rich, Δ-(*R*,*R*,*R*) : Λ-(*R*,*R*,*R*) = *ca.* 3:2. The difference of these diastereomeric ratios may be ascribed to the different solution concentrations. The solution concentration in the former system is very dilute for both species but the concentration of the latter is very high. In fact, the dilution of the concentrated solution with water led to a diastereomeric ratio of *ca.* 1:1 in several hours. In addition, since the preparative solution is highly viscous, it may contain some microcrystals and the second-order asymmetric transformation to the Δ-(*R*,*R*,*R*) diastereomer may be induced by the microcrystals. This speculation is supported by the observation that the diastereomeric ratio of the concentrated solution increased to Δ-(*R*,*R*,*R*) : Λ-(*R*,*R*,*R*) = *ca.* 2:1 by standing overnight in a refrigerator.

After Arnold and Jackson's work, there were some disputes between Gillard[14] and Arnold and Jackson.[15] The main point raised was a concern with the optical purity of potassium *fac*-Δ-tris(*R*-cysteinato-*N*,*S*)cobaltate(III).[25] Arnold and Jackson were correct in noting that if crystallisation of $M_3[Co(R\text{-cys})_3]$ is carried out too rapidly, a Δ/Λ mixture results, as confirmed in this work. However, as clearly shown by the present work, optically pure *fac*-Δ-$K_3[Co(R\text{-cys})_3]$ can be obtained if the experimental conditions are carefully chosen to induce a second-order asymmetric transformation even though there is a reversible inversion between the Δ-(*R*,*R*,*R*) and Λ-(*R*,*R*,*R*) diastereomers in solution.

## Acknowledgements

We are grateful for a Grant-in-Aid for Scientific Research No. 09640669 (for M. K.) from the Ministry of Education, Science, Sports and Culture.

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*Paper 8/08097F*