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# Separation of optical isomers of *fac*-triscobalt(III) chelates of several L-$\alpha$-amino acids and dissolution behavior of their isomers in water

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## Abstract

*fac*-Triscobalt(III) chelates of L-$\alpha$-amino acids such as L-alanine (L-ala), L-2-aminobutanoic acid (L-ambt), L-valine (L-val), and L-leucine (L-leu) were synthesized and the separation of the optical isomers of these chelates was attempted. For the chelates of L-ala and L-leu, (+)- and (−)-isomers were obtained separately, while for the chelates of L-ambt and L-val only the (+)-isomer was isolated. The solubilities of the chelates thus obtained in water were determined over the temperature range of 5 to 55 °C. The thermodynamic parameters of solution were estimated from the temperature dependence of the solubilities and the dissolution behavior was considered in terms of the thermodynamic parameters. A contribution of hydrophobic effect of these chelates to their solubilities was found to be cancelled out by a compensation relation between the enthalpy and the entropy changes accompanied by the hydrophobic hydration. As a first approximation it is concluded that the relatively low solubilities of these chelates are attributed to highly negative entropy of solution and that the chelates with relatively smaller enthalpy of solution are more soluble.

## Introduction

Water is highly associated through hydrogen bonding and hydrophobic solutes affect this hydrogen-bonded network structure of water, resulting in a significant decrease in both enthalpy and entropy of the system [1–8]. This phenomenon is termed 'hydrophobic hydration'. The hydrophobic hydration and the related hydrophobic interaction [1, 9] among apolar sites of the hydrophobic solutes are also of great significance in the biochemical field [10].

The majority of metal ions in biological materials seem to form complexes with biopolymers such as proteins. These metal complexes of biopolymers have large hydrophobic parts and may be expected to reveal appreciable hydrophobic effect. But an investigation of the hydrophobic effect of these complexes is rather difficult because of their complicated structures.

The author has investigated the dissolution behavior of tris(2,4-pentanedionato)cobalt(III) ($Co(acac)_3$) in water or aqueous mixtures of some organic solvents and reported that $Co(acac)_3$ is subject to hydrophobic hydration [11–14]. These studies have suggested that temperature dependence of the solubility may present thermodynamic information about hydrophobic hydration [11, 12] and that the hydrophobic hydration of *fac*-tris(glycinato)cobalt(III)* ($Co(gly)_3$) is negligible [14].

One of the procedures for interpreting the properties of complicated biopolymers such as proteins is the comparative analysis of model compounds including substances of low molecular weight which contain the atomic groups specific for the biopolymers. Similarly, metal complexes of amino acids may be expected to give fundamental information for interpreting the properties of metal–protein complexes such as metalloenzymes.

Thus, in this work triscobalt(III) chelates of various L-amino acids which are constituents of natural proteins are selected as model compounds. From temperature dependence of solubility the dissolution behavior of these chelates in water is investigated and their hydrophobic effect is estimated by using the procedure previously reported [11, 12].

Moreover, since these tris-chelates have both geometric and optical isomers, a difference in the solubilities of these isomers is also of interest from the standpoint

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*As an amino acid binds to a metal ion through both oxygen and nitrogen atoms, the resulting octahedral tris-complex has the following geometric isomers: in the *facial* (*fac*) isomer, three oxygen (or nitrogen) atoms form one face of the octahedron; in the *meridional* (*mer*) isomer, three oxygen (or nitrogen) atoms align on one meridian of the octahedron.

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of coordination chemistry. In the present study, first the solubilities for two optical isomers, that is, the (+)- and (−)-isomers of the geometric *fac* isomer are discussed.

## Experimental

### *Synthesis of cobalt(III) chelates and separation of their optical isomers*

The following amino acids (reagent grade, Wako Chemical Industries Ltd.) were used without purification: L-alanine (L-ala), L-2-amino-butanoic acid (L-ambt), L-valine (L-val), L-leucine (L-leu), DL-2-aminobutanoic acid (DL-ambt), DL-norvaline (DL-nval) and DL-norleucine (DL-nleu). Their cobalt(III) chelates were synthesized by refluxing the aqueous mixture (adjusted to pH 10 with 6 M (M is mol dm$^{-3}$) potassium hydroxide) of hexaamminecobalt(III)chloride and the desired amino acid (mole ratio = 1:3) [15]. This procedure gave the *fac* isomer as the main product.

The resulting chelate was dissolved in 60% sulfuric acid. This solution was slowly diluted with water until a crystalline precipitate started to separate, then it was left to stand overnight. The precipitate was filtered under vacuum, washed with water, and air-dried at room temperature. The chelates of the L-amino acids thus obtained were (+)-isomers, while those of the DL-amino acids were optically inactive.

The above filtrate was further diluted with water and after standing for a few days this solution was filtered again. The resulting filtrate was neutralized with 3 M sodium hydroxide and then concentrated at about 40 °C. (−)-Isomers of the chelates of L-ala and L-leu could be isolated by this procedure, but the crystalline precipitates of the (−)-isomers of the chelates of L-val and L-ambt could not be obtained.

The CD spectrum of the solution of each chelate in 60% sulfuric acid was measured for the identification of the optical isomer.

### *Determination of solubility*

The solubility was measured by the apparatus and procedure similar to those previously used [11–14]. In the procedure, an aliquot of solution saturated with each chelate was placed into a 5 or 10 cm$^3$ volumetric flask by weight, 0.5 or 1 cm$^3$ of 60% sulfuric acid was added in connection with the preparation of the calibration curve (see below), and water was added to the mark. The concentration (in mol dm$^{-3}$) of the chelate in this solution was analyzed spectrophotometrically and the solubility in mol kg$^{-1}$ ($S_m$) was obtained by calculating the mole numbers of the chelate in the aliquot of the saturated solution from the above concentration. In the spectrophotometric determination, the absorbance was measured at the wavelengths of 219 nm for *fac*-Co(ala)$_3$ and 221 nm for the others.

The preparation of calibration curves was carried out for *fac*-$(-)_{589}$Co(L-ala)$_3$, *fac*-$(+)_{589}$Co(L-ambt)$_3$ and fac-$(+)_{589}$Co(L-val)$_3$ in the following manner. The stock solutions of the chelates were prepared by dissolving weighed crystals in 60% sulfuric acid (concentration was about $2 \times 10^{-3}$ M); the working solutions ranging in concentration from $4 \times 10^{-6}$ to $3 \times 10^{-5}$ M were made up by diluting aliquots of the above stock solutions with water; the influence of sulfuric acid on the absorbance was normalized by adding 0.5 cm$^3$ of 60% sulfuric acid per 5 cm$^3$ of the working solutions; the resulting calibration curves were straight in the concentration regions tested and the Beer's law equations were obtained by the least-squares method.

In the solubility measurement of *fac*-Co(DL-nval)$_3$, *fac*-Co(DL-nleu)$_3$ and *fac*-Co(L-leu)$_3$, the calibration curve for *fac*-$(+)_{589}$Co(L-val)$_3$ was used without correction because of the extremely low solubilities of these chelates.

## Results and discussion

### *Solubilities of cobalt(III) chelates*

The CD spectra for both (+)-and (−)-isomers of *fac*-Co(L-ala)$_3$ are shown in Fig. 1 as a typical example. These spectra essentially agreed with those reported in the literature [16]. The CD spectra for the (+)-

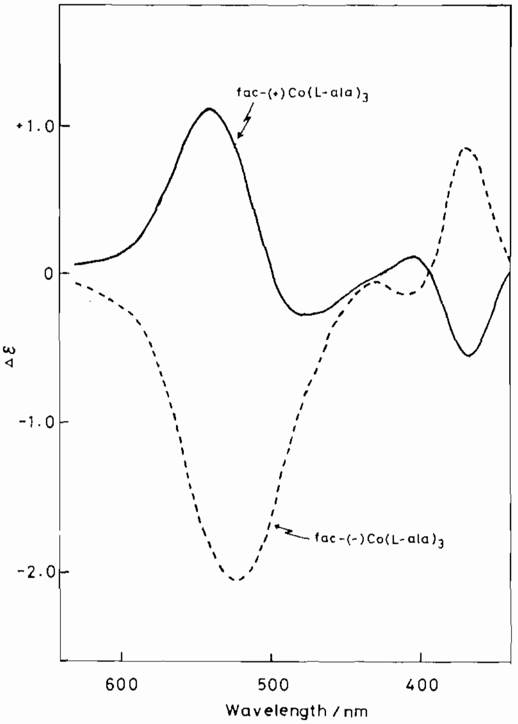

Fig. 1. CD spectra of the optical isomers of *fac*-Co(L-ala)$_3$. ——, *fac*-$(+)_{589}$Co(L-ala)$_3$, – – –, *fac*-$(-)_{589}$Co(L-ala)$_3$.

TABLE 1. Solubilities in mol kg$^{-1}$ ($S_m$) of *fac*-(+)Co(L-ala)$_3$, *fac*-(−)Co(L-ala)$_3$, *fac*-(+)Co(L-ambt)$_3$, *fac*-Co(DL-ambt)$_3$ and *fac*-(+)Co(L-val)$_3$ in water[a]

| Temperature (°C) | *fac*-(+)Co(L-ala)$_3$ $S_m \times 10^5$ | *fac*-(−)Co(L-ala)$_3$ $S_m \times 10^3$ | *fac*-(+)Co(L-ambt)$_3$ $S_m \times 10^4$ | *fac*-Co(DL-ambt)$_3$ $S_m \times 10^4$ | *fac*-(+)Co(L-val)$_3$ $S_m \times 10^4$ |
|---|---|---|---|---|---|
| 5 | 1.01±0.02 | 0.999±0.006 | 1.89±0.02 | 2.93±0.01 | 1.26±0.01 |
| 10 | 1.00±0.03 | 1.00±0.02 | 1.88±0.03 | 2.98±0.02 | 1.38±0.01 |
| 15 | 0.996±0.030 | 0.968±0.013 | 1.94±0.03 | 3.03±0.01 | 1.58±0.02 |
| 20 | 0.976±0.020 | 0.993±0.027 | 1.96±0.02 | 3.08±0.04 | 1.77±0.01 |
| 25 | 1.03±0.02 | 0.987±0.014 | 2.00±0.02 | 3.17±0.01 | 2.04±0.02 |
| 30 | 1.03±0.02 | 1.03±0.01 | 2.05±0.02 | 3.28±0.01 | 2.44±0.02 |
| 35 | 1.01±0.02 | 1.04±0.02 | 2.11±0.03 | 3.44±0.01 | 2.89±0.03 |
| 40 | 1.07±0.02 | 1.06±0.01 | 2.18±0.02 | 3.59±0.05 | 3.37±0.02 |
| 45 | 1.13±0.02 | 1.09±0.01 | 2.28±0.03 | 3.83±0.01 | |
| 50 | 1.21±0.01 | 1.10±0.01 | 2.38±0.05 | 4.09±0.06 | |
| 55 | 1.31±0.03 | | 2.50±0.03 | 4.49±0.02 | |

[a]Errors denote 95% confidence levels.

TABLE 2. Solubilities in mol kg$^{-1}$ ($S_m$) of *fac*−Co(DL-nval)$_3$, *fac*-(+)Co(L-leu)$_3$, *fac*-(−)Co(L-leu)$_3$ and *fac*-Co(DL-nleu)$_3$ in water[a]

| Temperature (°C) | *fac*-Co(DL-nval)$_3$ $S_m \times 10^5$ | *fac*-(+)Co(L-leu)$_3$ $S_m \times 10^6$ | *fac*-(−)Co(L-leu)$_3$ $S_m \times 10^5$ | *fac*-Co(DL-nleu)$_3$ $S_m \times 10^6$ |
|---|---|---|---|---|
| 5 | 2.21±0.04 | 1.85±0.14 | 1.35±0.03 | 3.96±0.11 |
| 10 | 2.22±0.05 | 1.71±0.07 | 1.29±0.02 | 3.77±0.13 |
| 15 | 2.25±0.01 | 2.16±0.11 | 1.25±0.02 | 3.80±0.09 |
| 20 | 2.27±0.05 | 2.32±0.10 | 1.23±0.02 | 4.21±0.14 |
| 25 | 2.41±0.06 | 2.40±0.18 | 1.16±0.02 | 4.22±0.10 |
| 30 | 2.62±0.06 | 2.31±0.19 | 1.16±0.04 | 4.43±0.13 |
| 35 | 3.05±0.08 | 2.42±0.10 | 1.10±0.03 | 4.40±0.18 |
| 40 | 3.35±0.07 | 2.70±0.10 | 1.18±0.01 | 4.49±0.19 |
| 45 | 3.63±0.10 | 3.43±0.18 | 1.27±0.02 | 4.93±0.06 |
| 50 | 3.83±0.07 | 4.03±0.16 | 1.38±0.02 | 5.68±0.07 |
| 55 | 4.35±0.07 | 5.07±0.23 | 1.48±0.03 | 6.43±0.06 |

[a]Errors denote 95% confidence levels.

isomers of the other chelates and for *fac*-(−)$_{589}$Co(L-leu)$_3$ were identical with the CD spectra for the corresponding optical isomers given in Fig. 1. These results indicate that the optical isomers are separated satisfactorily by the present procedure.

The values for $S_m$ in water are listed in Table 1 for *fac*-Co(L-ala)$_3$, *fac*-(+)$_{589}$Co(L-ambt)$_3$, *fac*-Co(DL-ambt)$_3$ and *fac*-(+)$_{589}$Co(L-val)$_3$ and in Table 2 for *fac*-Co(DL-nval)$_3$, *fac*-Co(DL-nleu)$_3$ and *fac*-Co(L-leu)$_3$. The solubility measurement was repeated at least four times at each temperature. The $S_m$ values in these tables are the mean of the respective found values. The errors denote deviations at a 95% confidence level and are less than 3%, except for *fac*-(+)$_{589}$Co(L-leu)$_3$ and *fac*-Co(DL-nleu)$_3$ whose solubilities are extremely low.

An incomplete separation of the optical isomers produced the result that the found values for the solubility became progressively greater beyond the above experimental errors. In such a case, the constant values for the solubility could be obtained by repeating the procedure for the separation.

When the solubility measurement was carried out at temperatures higher than 60 °C, the values found for the solubility became progressively greater probably because of optical isomerization. In a few cases, it was found that when the solutions at the end experiment at 50 °C were allowed to attain equilibrium at 25 °C, the solubility data at 25 °C were reproducible within the experimental errors. This result shows that the optical isomerization may be neglected at temperatures lower than 50 °C. In the previous work [14], it has been demonstrated that geometrical isomerization of *fac*-Co(gly)$_3$ can be ruled out even at 60 °C.

The $S_m$ values were converted to solubility in mole fraction ($X_s$) and ln $X_s$ was plotted against $1/T$. These solubility curves are shown in Fig. 2 for *fac*-(−)$_{589}$Co(L-ala)$_3$, *fac*-(+)$_{589}$Co(L-val)$_3$, *fac*-(+)$_{589}$Co(L-ambt)$_3$ and *fac*-Co(DL-ambt)$_3$ and in Fig. 3 for *fac*-Co(DL-nval)$_3$, *fac*-(+)$_{589}$Co(L-ala)$_3$, *fac*-(−)$_{589}$Co(L-leu)$_3$, *fac*-(+)$_{589}$Co(L-leu)$_3$ and *fac*-Co(DL-nleu)$_3$. For comparison the solubility curve of *fac*-Co(gly)$_3$ is also included in Fig. 2.

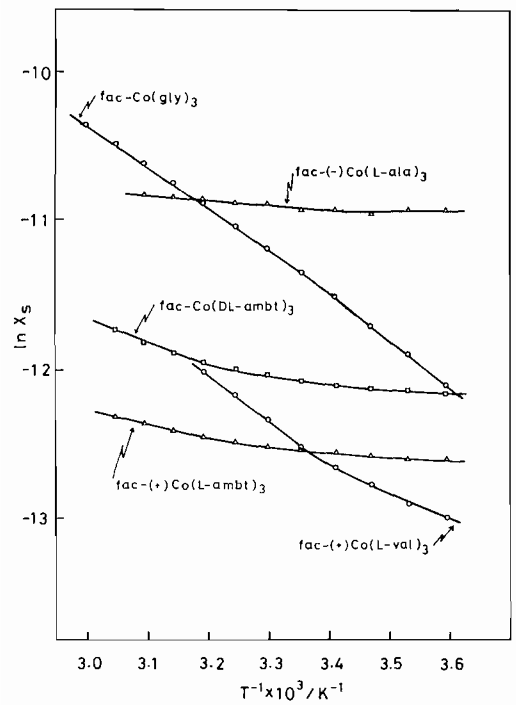

Fig. 2. Solubility curves of *fac*-$(-)_{589}$Co(L-ala)$_3$, *fac*-$(+)_{589}$Co(L-val)$_3$, *fac*-$(+)_{589}$Co(L-ambt)$_3$ and *fac*-Co(DL-ambt)$_3$ in water depicted by plotting ln $X_s$ against $1/T$. For comparison the solubility curve of *fac*-Co(gly)$_3$ reported in ref. 14 is also included.

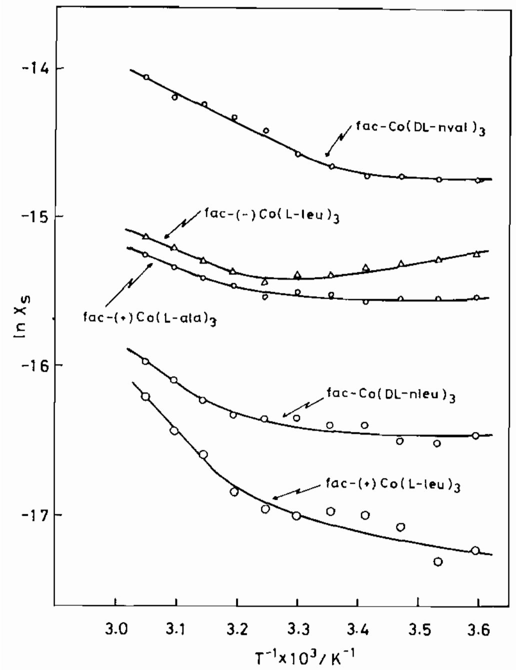

Fig. 3. Solubility curves of *fac*-$(+)_{589}$Co(L-ala)$_3$, *fac*-$(-)_{589}$Co(L-leu)$_3$, *fac*-$(+)_{589}$Co(L-leu)$_3$, *fac*-Co(DL-nval)$_3$ and *fac*-Co(DL-nleu)$_3$ in water depicted by plotting ln $X_s$ against $1/T$.

*Thermodynamic parameters of dissolution process*

Since the solubilities of all the chelates studied in this work are relatively low, these saturated solutions may be regarded as ideal dilute solutions which are the standard states for the solutes [14].

The free energy ($\Delta G_s^\circ$), enthalpy ($\Delta H_s^\circ$), entropy ($\Delta S_s^\circ$), and heat capacity of solution ($\Delta C_{p,s}^\circ$) at 25 °C were estimated by using the Clarke and Glew procedure [17, 18]. Details of the estimation have been reported elsewhere [13]. These thermodynamic parameters thus estimated are listed in the first column of Table 3, where the values for *fac*-Co(gly)$_3$ are also included for comparison.

As an attempt to examine the dissolution behavior in terms of the thermodynamic parameters, both $\Delta H_s^\circ$ and $T\Delta S_s^\circ$ were plotted against $\Delta G_s^\circ$ separately (not shown in Figure) and the following rough features were found: (i) the chelates which have relatively high solubilities, that is, small $\Delta G_s^\circ$ (*fac*-Co(gly)$_3$, *fac*-$(-)_{589}$Co(L-ala)$_3$, *fac*-$(+)_{589}$Co(L-ambt)$_3$, *fac*-Co(DL-ambt)$_3$ and *fac*-$(+)_{589}$Co(L-val)$_3$) are divided into two groups, that is, one group (*fac*-Co(gly)$_3$ and *fac*-$(+)_{589}$Co(L-val)$_3$) has unfavorable $\Delta H_s^\circ$ and favorable $\Delta S_s^\circ$, while the other chelates have favorable $\Delta H_s^\circ$ and unfavorable $\Delta S_s^\circ$; (ii) the chelates with low solubilities have favorable $\Delta H_s^\circ$ and more unfavorable $\Delta S_s^\circ$. But it was very difficult to draw a clear-cut regularity to explain the dissolution behavior from these plots.

The entropy and heat capacity seem to be sensitive to the hydrophobic effect on the network structure of water [19]. Grunwald has found that there is a linear trend between $\Delta S_s^\circ$ and $\Delta C_{p,s}^\circ$ for the dissolution of gaseous aliphatic alcohols in water and pointed out that this trend may be explained by the two-state sitewise equilibrium model which takes into account the effect on the network of water [20]. In Fig. 4, the $\Delta S_s^\circ$ values are plotted against $\Delta C_{p,s}^\circ$ for the dissolution process of the present chelates. A rough linear trend is found and the slope of the correlation line is negative in agreement with Grunwald's prediction [20]. This result suggests that the thermodynamic parameters of solution given in the first column of Table 3 include a contribution of the hydrophobic effect.

*Thermodynamic parameters of hydrophobic hydration*

In order to derive the thermodynamic parameters of the hydrophobic hydration, the thermodynamic parameters of the hypothetical dissolution process that a hydrophobic solute dissolves in water without any effect on the network structure of water must be estimated [19, 21, 22].

The solubility curves given in Figs. 2 and 3 may present a useful suggestion for the above hypothetical dissolution process. The solubility curve of *fac*-Co(gly)$_3$ is practically straight over the temperature range of 5 to 60 °C, while the solubility curves of the other chelates are curved. The curvature becomes sharper with an increase in the alkyl chain length of the amino acids.

TABLE 3. Thermodynamic parameters at 25 °C accompanied by real dissolution process, hypothetical dissolution process without hydrophobic hydration, and hydrophobic hydration for *fac*-triscobalt(III) chelates of α-amino acids[a]

| | Chelate | Real dissolution | | | | Hypothetical dissolution | | | Hydrophobic hydration | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $\Delta G_s^\circ$ | $\Delta H_s^\circ$ | $\Delta S_s^\circ$ | $\Delta C_{p,s}^\circ$ | $\Delta G_{s,hp}^\circ$ | $\Delta H_{s,hp}^\circ$ | $\Delta S_{s,hp}^\circ$ | $\Delta G_{hh}$ | $\Delta H_{hh}$ | $\Delta S_{hh}$ |
| 1 | *fac*-Co(gly)$_3$[b] | 28.1 | 24.2 | −13.2 | −127 | 28.1 | 23.3 | −16.1 | 0 | 0.9 | 2.9 |
| 2 | *fac*-(+)Co(L-ala)$_3$ | 38.5 | 2.3 | −121.3 | 332 | 38.9 | 11.5 | −91.8 | −0.4 | −9.2 | −29.5 |
| 3 | *fac*-(−)Co(L-ala)$_3$ | 27.1 | 1.7 | −85.1 | 139 | 27.1 | 2.9 | −80.9 | 0 | −1.2 | −4.2 |
| 4 | *fac*-(+)Co(L-ambt)$_3$ | 31.1 | 3.6 | −92.1 | 167 | 31.2 | 7.7 | −79.0 | −0.1 | −4.1 | −13.1 |
| 5 | *fac*-Co(DL-ambt)$_3$ | 29.9 | 4.4 | −85.6 | 230 | 30.2 | 12.5 | −59.4 | −0.3 | −8.1 | −26.2 |
| 6 | *fac*-(+)Co(L-val)$_3$ | 31.0 | 22.3 | −29.1 | 517 | 31.0 | 25.0 | −19.9 | 0 | −2.7 | −9.2 |
| 7 | *fac*-Co(DL-nval)$_3$ | 36.3 | 11.6 | −82.6 | 578 | 36.3 | 15.6 | −69.2 | 0 | −4.0 | −13.4 |
| 8 | *fac*-(+)Co(L-leu)$_3$ | 42.2 | 5.9 | −121.7 | 270 | 43.4 | 35.0 | −28.1 | −1.2 | −29.1 | −93.6 |
| 9 | *fac*-(−)Co(L-leu)$_3$ | 38.1 | −3.4 | −139.2 | 379 | 38.7 | 12.4 | −88.0 | −0.6 | −15.8 | −51.2 |
| 10 | *fac*-Co(DL-nleu)$_3$ | 40.7 | 5.3 | −118.7 | 405 | 41.5 | 20.9 | −69.2 | −0.8 | −15.6 | −49.5 |

[a] The units for $\Delta G$ and $\Delta H$ are kJ mol$^{-1}$, and for $\Delta S$ and $\Delta C_p$ are J K$^{-1}$ mol$^{-1}$. [b] Calculated from the data given in ref. 14.

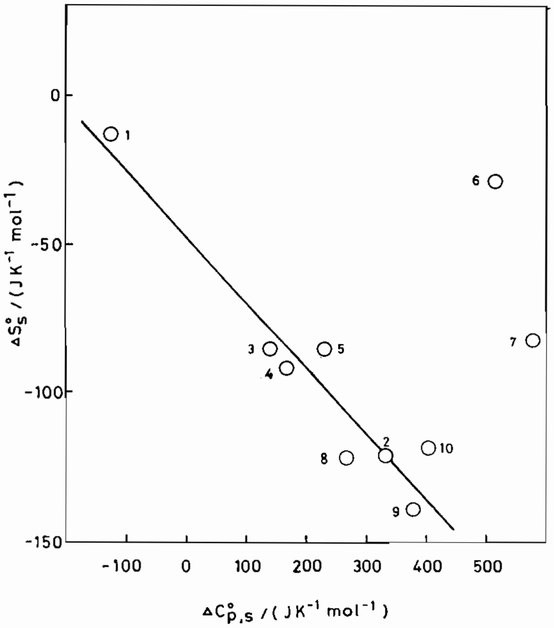

Fig. 4. Plot of $\Delta S_s^\circ$ against $\Delta C_{p,s}^\circ$ for the dissolution process in water of the series of the *fac*-triscobalt(III) chelates of α-amino acids. Numbers indicated beside the circles correspond to those listed for the chelates in Table 3.

It has been reported that the hydrophobic property of glycine is the weakest among a series of aliphatic α-amino acids [23, 24]. A similar result has been presented for formic acid in a series of alkyl carboxylic acids [25, 26]. This information suggests that *fac*-Co(gly)$_3$ scarcely brings about the hydrophobic effect on the network structure of water. If this suggestion is true, it may be concluded that the straightening of the solubility curve implies a negligibly small effect of the hydrophobic hydration.

The solubility curves of the chelates other than *fac*-Co(gly)$_3$ also become straight in high temperature regions as shown in Figs. 2 and 3. Since the order of the water structure decreases with an increase in temperature [27], the hydrophobic effect may be expected to become negligible at high temperatures. This argument proposes that the thermodynamic parameters of the hypothetical dissolution process without the hydrophobic hydration ($\Delta G_{s,\,hp}^\circ$, $\Delta H_{s,\,hp}^\circ$ and $\Delta S_{s,\,hp}^\circ$)* at 25 °C may be estimated by extrapolating the straight lines drawn in the high temperature regions to 25 °C. The values thus obtained are tabulated in the second column of Table 3.

The thermodynamic parameters of the hydrophobic hydration ($\Delta G_{hh}$, $\Delta H_{hh}$, $\Delta S_{hh}$) at 25 °C are derived by

$$\Delta Y_{hh} = \Delta Y_s^\circ - \Delta Y_{s,\,hp}^\circ \qquad (1)$$

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*The subscript hp is used to designate the hypothetical dissolution process without the hydrophobic hydration.

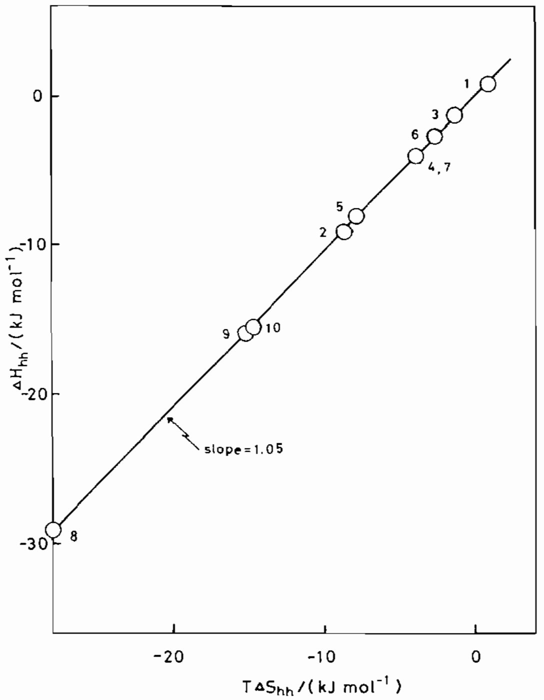

Fig. 5. Compensation relationship between $\Delta H_{hh}$ and $T\Delta S_{hh}$ accompanied by the hydrophobic hydration of the *fac*-triscobalt(III) chelates of $\alpha$-amino acids. See legend to Fig. 4 for numbering.

where $\Delta Y$ denotes $\Delta G$, $\Delta H$ and $\Delta S$. The values thus obtained are listed in the last column of Table 3. Figure 5 represents the plot of $\Delta H_{hh}$ against $T\Delta S_{hh}$. This plot shows a good compensation relation between $\Delta H_{hh}$ and $T\Delta S_{hh}$ with the slope of nearly 1. In addition, the hydrophobic hydration is not always stronger for the chelates with large alkyl groups. For example, the effect of *fac*-$(+)_{589}$Co(L-ala)$_3$ is stronger than that of *fac*-$(+)_{589}$Co(L-ambt)$_3$ and *fac*-$(+)_{589}$Co(L-val)$_3$*.

### *Interpretation of dissolution behavior*

Figure 5 indicates that $\Delta G_{hh}$ is nearly 0 and a contribution of the hydrophobic hydration to $\Delta G_s^\circ$ is negligible, that is, $\Delta G_s^\circ \approx \Delta G_{s,\,hp}^\circ$. In other words, the solubilities of the present chelates are fixed by $\Delta H_{s,\,hp}^\circ$ and $\Delta S_{s,\,hp}^\circ$. Thus, both $\Delta H_{s,\,hp}^\circ$ and $\Delta S_{s,\,hp}^\circ$ are separately plotted against $\Delta G_s^\circ$. Although these plots show some scatter, with a few exceptions the following trends are recognized: $\Delta G_s^\circ$ increases with an increase in $\Delta H_{s,\,hp}^\circ$; $\Delta S_{s,\,hp}^\circ$ is roughly similar in magnitude. In other words, a change of the solubility in the series of the present chelates predominantly depends on $\Delta H_{s,\,hp}^\circ$ and the chelate with the smaller $\Delta H_{s,\,hp}^\circ$ is more soluble. Furthermore, as a first approximation the relatively small solubilities of these chelates may be attributed to the considerably negative $\Delta S_{s,\,hp}^\circ$.

Exceptionally, in the cases of *fac*-Co(gly)$_3$ and *fac*-$(+)_{589}$Co(L-val)$_3$, slightly negative $\Delta S_{s,\,hp}^\circ$ contributes to their considerably high solubilities. The scatter of *fac*-$(+)_{589}$Co(L-leu)$_3$ is presumably attributed to the large experimental errors in the solubility measurement.

It is noteworthy that the chelates of amino acids dissolve in water with considerably negative $\Delta S_{s,\,hp}^\circ$ because $\Delta S_{s,\,hp}^\circ$ includes no contribution of the hydrophobic effect as mentioned above. It is interesting to examine whether these chelates dissolve in various solvents with negative entropy changes. Unfortunately, since these chelates are insoluble in most solvents other than water, it is impossible to examine the above negative $\Delta S_{s,\,hp}^\circ$ in terms of a comparative investigation in other solvents.

For *fac*-Co(L-ala)$_3$ and *fac*-Co(L-leu)$_3$, it was found that the $(-)$-isomer is more soluble than the $(+)$-isomer. Perhaps, this result is also valid for the chelates of the other L-amino acids for which only the $(+)$-

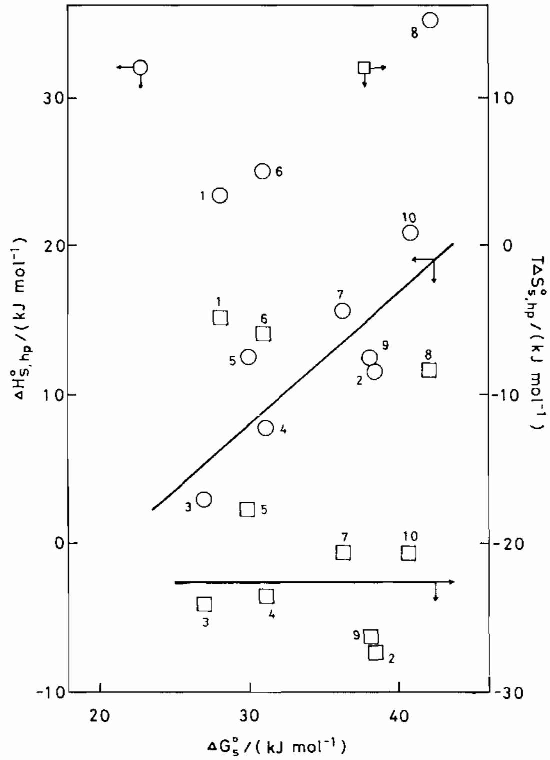

Fig. 6. Contribution of $\Delta H_{s,\,hp}^\circ$ and $T\Delta S_{s,\,hp}^\circ$ for hypothetical dissolution process without the hydrophobic hydration to observed $\Delta G_s^\circ$ for the *fac*-triscobalt(III) chelates of $\alpha$-amino acids. ○, $\Delta H_{s,\,hp}^\circ$ vs. $\Delta G_s^\circ$; □, $T\Delta S_{s,\,hp}^\circ$ vs. $\Delta G_s^\circ$. See legend to Fig. 4 for numbering.

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*Since a large number of investigators have reported that the hydrophobic effect of aliphatic compounds increases with an increase in the carbon number, this finding may be surprising. But the hydrophobic effect of *fac*-Co(L-leu)$_3$ is stronger than that of the others in accord with the expectation based on the carbon number. The possibility that the effect of the hydrophobic parts in *fac*-Co(L-ambt)$_3$ and *fac*-Co(L-val)$_3$ is hindered by a steric factor resulting from the octahedral structure may be pointed out.

isomer could be isolated. The (+)-isomer has more negative $\Delta H_{hh}$ and $\Delta S_{hh}$ than the (−)-isomer (see Fig. 5). This result suggests that the (+)-isomer is more hydrophobic than the (−)-isomer, which would result in the higher $\Delta H^{\circ}_{s,\,hp}$ for the (+)-isomer as shown in Fig. 6. The higher $\Delta H^{\circ}_{s,\,hp}$ of the (+)-isomer causes its lower solubility (see Fig. 6). In conclusion, the lower solubility of the (+)-isomer may be attributed to its larger hydrophobic property. But no clear-cut explanation for the difference in the hydrophobic property between the (+)- and (−)-isomers can be offered at the present time.

The finding that the solubilities of the (+)- and (−)-isomers of *fac*-Co(L-ala)$_3$ differ from one another implies that the antipode of *fac*-$(+)_{589}$Co(L-ala)$_3$ is not *fac*-$(-)_{589}$Co(L-ala)$_3$ but *fac*-$(-)_{589}$Co(D-ala)$_3$. The result that the chelates of DL-amino acids such as *fac*-Co(DL-ambt)$_3$ exhibit no optical activity seems to suggest that these chelates are racemates, that is, for example a mixture of *fac*-$(+)_{589}$Co(L-ambt)$_3$ and *fac*-$(-)_{589}$Co(D-ambt)$_3$. The solubility measurement for *fac*-chelates of D-amino acids may be expected to provide evidence for the above suggestion.

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