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Solubility Differences among Geometric and Optical Isomers of Tris(amino acidato)cobalt(Ⅲ)

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The solubilities of soluble *mer*-(−)-isomers of various tris(amino acidato)cobalt(Ⅲ) ([Co(aa)$_3$]) in water were determined over the temperature range 5 to 50 °C. From these data the standard free energy ($\Delta_{dis}G°$), enthalpy ($\Delta_{dis}H°$), and entropy of dissolution ($\Delta_{dis}S°$) at 25 °C were estimated and compared with the values reported for *mer*-(+)-, *fac*-(−)-, and *fac*-(+)-isomers of [Co(aa)$_3$]. The solubilities of these isomers increase in the order *fac*-(+)- < *fac*-(−)- < *mer*-(+)- < *mer*-(−)-isomers for [Co(aa)$_3$] synthesized from amino acids with longer side chains than 2-aminobutyric acid. On the other hand, the increasing sequence of the solubilities for tris(L-alaninato)cobalt(Ⅲ) ([Co(L-ala)$_3$]) and tris(L-serinato)cobalt(Ⅲ) ([Co(L-ser)$_3$]) is *fac*-(+)- < *mer*-(+)- < *fac*-(−)- < *mer*-(−)-isomers. The solubility differences between the *mer*- and *fac*-isomers and between the (−)- and (+)-isomers are discussed based on the differences of $\Delta_{dis}H°$ and $T\Delta_{dis}S°$ among these isomers. Furthermore, the influence of introducing hydroxyl and methyl groups into the side chains of the amino acids on the dissolution behavior of [Co(aa)$_3$] is discussed.

Amino acids form octahedral chelates with a cobalt(Ⅲ) ion, tris(amino acidato)cobalt(Ⅲ) ([Co(aa)$_3$]). These chelates can be separated into two geometric isomers (*mer*- and *fac*-isomers) and each geometric isomer has two optical isomers (Λ- and Δ-isomers).[1,2] The Λ- and Δ-isomers for the chelates of the L-amino acids which have asymmetric carbon atoms are not antipodes, but diastereoisomers. From X-ray diffraction studies, the absolute configurations of *mer*-(+)-tris(L-alaninato)cobalt(Ⅲ) (*mer*-(+)-[Co(L-ala)$_3$])[3] and *mer*-(−)-[Co(L-ala)$_3$][4] have been assigned to the Λ- and Δ-isomers, respectively. In this paper, the Λ- and Δ-isomers are expressed as the (+)- and (−)-isomers, respectively. The symbols (+) and (−) represent dextrorotatory and levorotatory at 589 nm, respectively.

A difference in the solubilities of these isomers has become of interest. In general, the *mer*-isomers are more soluble than the *fac*-isomers and the (−)-isomers of tris(L-amino acidato)cobalt(Ⅲ) ([Co(L-aa)$_3$]) are more soluble than the corresponding (+)-isomers. Denning and Piper[2] tried to explain the difference in the solubilities of the (+)- and (−)-isomers of [Co(L-ala)$_3$] based on a distinction in the position of the side-chain methyl groups of alanine. However, Heark et al.[4] have pointed out that the solubility differences of various isomers of [Co(L-ala)$_3$] are not closely related to the positions of the methyl groups. The extreme low solubility of *fac*-(+)-[Co(L-ala)$_3$] has been attributed to molecular association through intermolecular hydrogen bonding in its solid state.[1,5] However, *fac*-(+)-tris(L-threoninato)cobalt(Ⅲ) (*fac*-(+)-[Co(L-thr)$_3$]) has been reported to be considerably soluble.[5] Thus, the solubility differences due to the configurations seem to reflect the difference in the solute–solvent interaction.

In a series of investigations, I have reported on the dissolution behavior of *fac*-(+)-[Co(L-aa)$_3$] in water,[6,7] the effect of various salts on the solubilities of *fac*-(+)- and *mer*-(+)-isomers of [Co(L-aa)$_3$],[8–10] and the hydrophobic interaction of *mer*-(+)-[Co(L-aa)$_3$] with tetrabutylammonium ion.[11] These investigations suggest that various [Co(aa)$_3$] may provide useful information about the interactions of the side chains of amino acids with their surroundings.

In this study, the solubilities for the extremely soluble *mer*-(−)-[Co(L-aa)$_3$] and *fac*-(−)-[Co(L-aa)$_3$], prepared from various amino acids, were determined over the temperature range 5 to 50 °C. Also, the standard free energy ($\Delta_{dis}G°$), enthalpy ($\Delta_{dis}H°$), and entropy of dissolution ($\Delta_{dis}S°$) in water at 25 °C for these chelates were calculated from these solubility data. In addition to these data for *fac*-(−)-[Co(L-aa)$_3$] and *mer*-(−)-[Co(L-aa)$_3$], by employing the data so far reported for *fac*-(+)-[Co(L-aa)$_3$] and *mer*-(+)-[Co(L-aa)$_3$] the solubility differences among the above-mentioned four isomers of [Co(L-aa)$_3$] were systematically considered.

Experimental

Both [Co(L-thr)$_3$] and tris(β-alaninato)cobalt(Ⅲ) ([Co(β-ala)$_3$]) were freshly synthesized in this study. The four isomers of [Co(L-thr)$_3$] were synthesized by the reaction of Co(OH)$_3$ with L-threonine. A large quantity of the *fac*-(+)-isomer and a small amount of the *mer*-(+)-isomer precipitated from the reaction mixture. After the crude products collected by filtration were dissolved into an 80% sulfuric acid solution, pure *fac*-(+)-[Co(L-thr)$_3$] was recrystallized by dilution with water. After crude materials of the *mer*-(+)-isomer obtained by concentrating the first filtrate were filtered, the second filtrate was chromatographed on a Florisil column (100 cm high and 3.5 cm in diameter) and then eluted with water. The separation between the first purple band and the second red band was incomplete. At first, these two bands were roughly fractionated into three fractions. When the middle fractions (mixtures of the purple and red bands) from a number of preparations were collected and concentrated, crude materials of the *mer*-(+)-isomer were precipitated. These crude materials of

the *mer*-(+)-isomer were dissolved in an 80% H_2SO_4 solution and pure *mer*-(+)-[Co(L-thr)$_3$] was recrystallized by dilution with water. The leading and tailing fractions from a number of preparations were separately collected, concentrated, and then rechromatographed once again. The respective pure fractions were carefully collected by monitoring the absorption spectra of the eluents. Both *mer*-(−)- and *fac*-(−)-[Co(L-thr)$_3$] were carefully crystallized by slow evaporation of these collections.

The spectroscopic properties (λ_{max}/nm, ε_{max}/(10 dm^2 mol^{-1})) and analytical data of the thus-obtained chelates are as follows: for *fac*-(+)-[Co(L-thr)$_3$]: (530, 92); (373, 133). Calcd for $Co(C_4H_8NO_3)_3\cdot 5H_2O$: C, 28.6; H, 6.8; N, 8.4%. Found: C, 28.5; H, 5.9; N, 8.3%. For *fac*-(−)-[Co(L-thr)$_3$]: (520, 171); (375, 156). Calcd for $Co(C_4H_8NO_3)_3\cdot 2H_2O$: C, 32.1; H, 6.3; N, 9.4%. Found: C, 31.9; H, 6.5; N, 9.4%. For *mer*-(+)-[Co(L-thr)$_3$]: (531, 96); (371, 142). Calcd for $Co(C_4H_8NO_3)_3\cdot 2H_2O$: C, 32.1; H, 6.3; N, 9.4%. Found: C, 32.2; H, 6.1; N, 9.5%. For *mer*-(−)-[Co(L-thr)$_3$]: (530, 106); (374, 163). Calcd for $Co(C_4H_8NO_3)_3\cdot 3H_2O$: C, 30.8; H, 6.5; N, 9.0%. Found: C, 31.3; H, 6.5; N, 9.2%.

The *fac*- and *mer*-isomers of [Co(β-ala)$_3$] were synthesized by the reaction of hexaamminecobalt(III) chloride with β-alanine and separated by column chromatograph on alumina. The separation between the first violet band (*mer*-isomer) and the second red band (*fac*-isomer) was sufficient. The crude *mer*-isomer obtained by concentrating the leading eluent was recrystallized from water. The pure *fac*-[Co(β-ala)$_3$] was obtained in the same manner as *fac*-(−)-[Co(L-thr)$_3$]. The spectroscopic properties (λ_{max}/nm, ε_{max}/(10 dm^2 mol^{-1})) are as follows: for *mer*-[Co(β-ala)$_3$]: (574, 101); (373, 71). For *fac*-[Co(β-ala)$_3$]: (530, 68); (370, 27). The values for ε_{max} of *fac*-[Co(β-ala)$_3$] are fairly smaller than the values reported in the literature.[12] The ε_{max} values were not affected by repeated vacuum drying of *fac*-[Co(β-ala)$_3$].

The preparations of the other soluble *mer*- and *fac*-isomers, whose solubilities were determined in this study, *mer*-(−)-[Co(L-ala)$_3$], *mer*-(−)-tris(L-serinato)cobalt(III) (*mer*-(−)-[Co(L-ser)$_3$]), *mer*-(+−)-tris(DL-2-aminobutyrato)cobalt(III) (*mer*-(+−)-[Co-(DL-aba)$_3$]), *mer*-(+−)-tris(DL-norvalinato)cobalt(III) (*mer*-(+−)-[Co(DL-nval)$_3$]), *mer*-(−)-tris(L-valinato)cobalt(III) (*mer*-(−)-[Co-(L-val)$_3$]), *mer*-(−)-tris(L-leucinato)cobalt(III) (*mer*-(−)-[Co(L-leu)$_3$]), *mer*-(−)-tris(L-prolinato)cobalt(III) (*mer*-(−)-[Co(L-pro)$_3$]), *fac*-(+−)-[Co(DL-aba)$_3$], and *fac*-(−)-[Co(L-val)$_3$], were reported previously.[7,11] The spectroscopic properties (λ_{max}/nm, ε_{max}/(10 dm^2 mol^{-1})) and analytical data of these chelates are as follows: for *mer*-(−)-[Co(L-ala)$_3$]: (542, 101); (372, 148). For *mer*-(−)-[Co(L-ser)$_3$]: (538, 100); (373, 150). Calcd for $Co(C_3H_6NO_3)_3\cdot H_2O$: C, 27.8; H, 5.2; N, 10.8%. Found: C, 28.3; H, 5.0; N, 11.1%. For *mer*-(+−)-[Co(DL-aba)$_3$]: (542, 103); (373, 160). Calcd for $Co(C_4H_8NO_2)_3\cdot 2H_2O$: C, 35.9; H, 7.1; N, 10.5%. Found: C, 35.1; H, 7.1; N, 10.4%. For *mer*-(+−)-[Co(DL-nval)$_3$]: (536, 102); (373, 160). Calcd for $Co(C_5H_{10}NO_2)_3\cdot 2H_2O$: C, 40.6; H, 7.8; N, 9.5%. Found: C, 40.4; H, 7.7; N, 9.4%. For *mer*-(−)-[Co(L-val)$_3$]: (535, 111); (374, 160). For *mer*-(−)-[Co(L-leu)$_3$]: (533, 107); (373, 177). For *mer*-(−)-[Co(L-pro)$_3$]: (542, 95); (381, 151). For *fac*-(+−)-[Co(DL-aba)$_3$]: (519, 203); (377, 169). Calcd for $Co(C_4H_8NO_2)_3\cdot H_2O$: C,37.6; H, 6.8; N, 11.0%. Found: C, 36.9; H, 6.8; N, 10.9%. For *fac*-(−)-[Co(L-val)$_3$]: (525, 212); (380, 188). Elemental analyses were principally employed for chelates synthesized by procedures different from that reported. The symbol (+−)-[Co(DL-aa)$_3$] stands for a racemic mixture of (+)-[Co(D-aa)$_3$] and (−)-[Co(L-aa)$_3$].

Table 1. Solubilities (m^0) of *mer*-(−)-[Co(L-ala)$_3$], *mer*-(−)-[Co(L-ser)$_3$], *mer*-(+−)-[Co(DL-aba)$_3$], *mer*-(+−)-[Co(DL-nval)$_3$], *mer*-(−)-[Co(L-val)$_3$], *mer*-(−)-[Co(L-leu)$_3$], *mer*-(−)-[Co(L-pro)$_3$], *mer*-[Co(β-ala)$_3$], *fac*-(+−)-[Co(DL-aba)$_3$], and *fac*-(−)-[Co(L-val)$_3$] in Water[a)]

θ/°C	*mer*-(−)-[Co(L-ala)$_3$]	*mer*-(−)-[Co(L-ser)$_3$]	*mer*-(+−)-[Co(DL-aba)$_3$]	*mer*-(+−)-[Co(DL-nval)$_3$]	*mer*-(−)-[Co(L-val)$_3$]
	m^0/10^{-1} mol kg^{-1}	m^0/10^{-1} mol kg^{-1}	m^0/10^{-1} mol kg^{-1}	m^0/10^{-2} mol kg^{-1}	m^0/10^{-1} mol kg^{-1}
5	6.95(0.07)	1.72(0.01)	1.43(0.01)	2.11(0.01)	3.35(0.03)
10	6.95(0.05)	1.74(0.01)	1.43(0.01)	2.09(0.01)	3.21(0.01)
15	6.84(0.06)	1.78(0.01)	1.44(0.01)	2.09(0.01)	3.10(0.01)
20	6.80(0.07)	1.79(0.02)	1.47(0.01)	2.10(0.01)	3.03(0.03)
25	6.81(0.04)	1.81(0.02)	1.54(0.01)	2.09(0.01)	3.01(0.02)
30	6.78(0.05)	1.88(0.03)	1.59(0.02)	2.12(0.03)	3.05(0.03)
35	7.03(0.09)	1.97(0.03)	1.72(0.01)	2.18(0.01)	3.16(0.04)
40	7.21(0.10)	2.05(0.03)	1.92(0.03)	2.18(0.03)	3.21(0.08)
45		2.16(0.03)	1.99(0.02)	2.16(0.02)	
50		2.37(0.07)	2.09(0.04)		

θ/°C	*mer*-(−)-[Co(L-leu)$_3$]	*mer*-(−)-[Co(L-pro)$_3$]	*mer*-[Co(β-ala)$_3$]	*fac*-(+−)-[Co(DL-aba)$_3$]	*fac*-(−)-[Co(L-val)$_3$]
	m^0/10^{-3} mol kg^{-1}	m^0/ mol kg^{-1}	m^0/10^{-1} mol kg^{-1}	m^0/10^{-3} mol kg^{-1}	m^0/10^{-3} mol kg^{-1}
5	4.50(0.03)	0.297(0.002)	1.52(0.01)	4.52(0.03)	6.21(0.02)
10	4.36(0.08)	0.379(0.005)	1.72(0.01)	4.45(0.05)	6.15(0.07)
15	4.34(0.01)	0.526(0.005)	1.97(0.02)	4.36(0.03)	5.86(0.03)
20	4.33(0.02)	0.968(0.014)	2.25(0.03)	4.36(0.01)	5.61(0.06)
25	4.33(0.04)	1.26(0.01)	2.58(0.04)	4.37(0.03)	5.42(0.04)
30	4.32(0.07)	1.42(0.02)	3.02(0.03)	4.39(0.03)	5.27(0.04)
35	4.29(0.04)		3.49(0.03)	4.43(0.02)	5.25(0.03)
40	4.25(0.07)		4.06(0.04)	4.48(0.03)	5.25(0.05)
45	4.16(0.04)		4.71(0.08)		
50	4.08(0.05)		5.27(0.15)		

a) Errors defined as 95% confidence levels are given in parentheses.

Table 2. Solubilities (m^0) of *fac*-(+)-, *mer*-(+)-, and *mer*-(−)-[Co(L-thr)$_3$] in Water[a)]

θ/°C	*fac*-(+)-[Co(L-thr)$_3$]	*mer*-(+)-[Co(L-thr)$_3$]	*mer*-(−)-[Co(L-thr)$_3$]
	$m^0/10^{-3}$ mol kg^{-1}	$m^0/10^{-3}$ mol kg^{-1}	$m^0/10^{-2}$ mol kg^{-1}
5	3.22(0.02)		3.57(0.01)
10	3.37(0.06)	0.955(0.009)	3.88(0.02)
15	3.52(0.05)	1.08(0.02)	4.26(0.02)
20	3.75(0.03)	1.20(0.03)	4.71(0.02)
25	4.10(0.03)	1.38(0.03)	5.23(0.03)
30	4.62(0.02)	1.68(0.03)	5.89(0.04)
35	5.26(0.04)	2.12(0.03)	6.63(0.04)
40		2.63(0.06)	7.50(0.05)
45			8.56(0.03)

a) Errors defined as 95% confidence levels are given in parentheses.

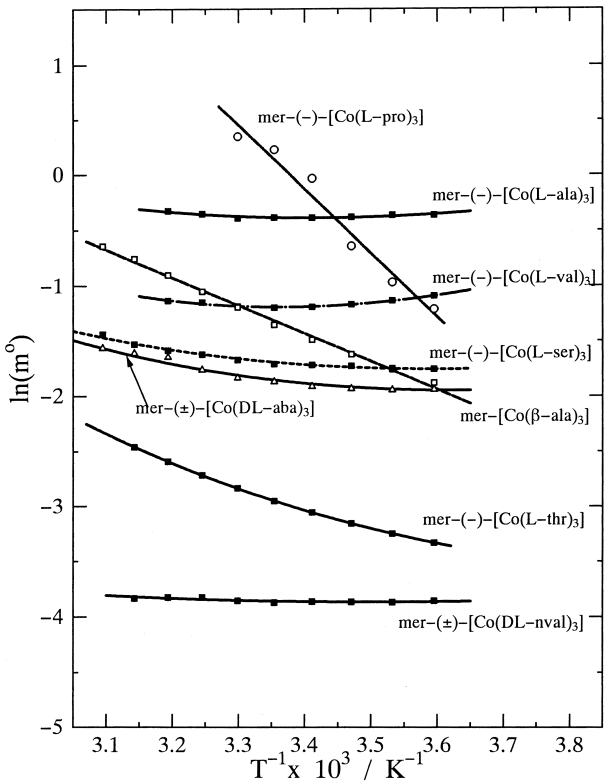

Fig. 1. Solubility curves of various soluble *mer*-[Co(aa)$_3$] in water depicted by plotting ln m^0 against 1/T. The curves are drawn by using the least-squares analysis.

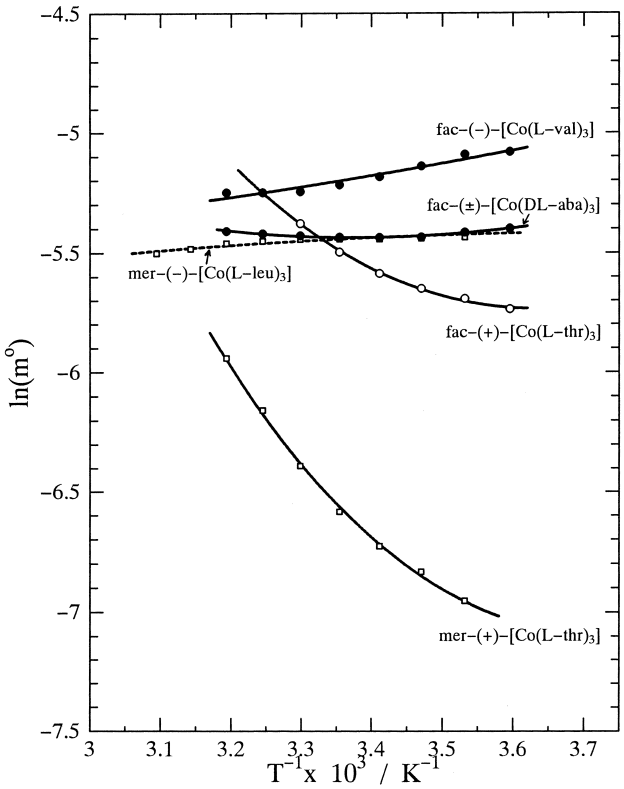

Fig. 2. Solubility curves of *mer*-(−)-[Co(L-leu)$_3$], *fac*-(−)-[Co(L-val)$_3$], *fac*-(+−)-[Co(DL-aba)$_3$], *fac*-(+)-[Co(L-thr)$_3$], and *mer*-(+)-[Co(L-thr)$_3$] in water depicted by plotting ln m^0 against 1/T. The curves are drawn by using the least-squares analysis.

The solubility in water (in mol kg^{-1}, m^0) was measured in the same manner as in previous studies.[6–11] The measurement was repeated at least four times at each temperature, and the errors defined as the deviations at the 95% confidence levels, were less than 2% of the mean values of these individual experimental values in most cases.

Results

The m^0 values for *mer*-(−)-[Co(L-ala)$_3$], *mer*-(−)-[Co(L-ser)$_3$], *mer*-(+−)-[Co(DL-aba)$_3$], *mer*-(+−)-[Co(DL-nval)$_3$], *mer*-(−)-[Co(L-val)$_3$], *mer*-(−)-[Co(L-leu)$_3$], *mer*-(−)-[Co(L-pro)$_3$], *mer*-[Co(β-ala)$_3$], *fac* -(+−)-[Co(DL-aba)$_3$], and *fac* -(−)-[Co(L-val)$_3$] are listed in Table 1. In Table 2, m^0 for the *fac*-(+)-, *mer*-(+)-, and *mer*-(−)-isomers of [Co(L-thr)$_3$] are tabulated. The solubilities of *fac*-(−)-[Co(L-thr)$_3$] and *fac*-[Co(β-ala)$_3$] are extremely large (for example, m^0 for *fac*-(−)-[Co(L-thr)$_3$] is more than 0.6 mol kg^{-1} at 5 °C.) and could not be determined because of their limited yields.

The temperature dependences of the solubilities are shown in Figs. 1 (for the *mer*-isomers) and 2 (mainly for the *fac*-isomers) with ln m^0 plotted against 1/T. The standard free energy ($\Delta_{dis}G°$), enthalpy ($\Delta_{dis}H°$), and entropy of dissolution ($\Delta_{dis}S°$) in water at 25 °C for these chelates were estimated by applying a least-squares analysis to the data illustrated in Figs. 1 and 2, as previously reported.[13] The standard state for the chelate in the solution is 1 mol kg^{-1}. As shown in Table 1, many of the

Table 3. Standard Free Energy ($\Delta_{dis}G°$), Enthalpy ($\Delta_{dis}H°$), and Entropy of Dissolution ($\Delta_{dis}S°$) in Water at 25 °C for the Four Isomers of Various [Co(aa)$_3$][a)]

Chelates	*fac*-Isomer			*mer*-Isomer		
	$\Delta_{dis}G°$	$\Delta_{dis}H°$[b)]	$T\Delta_{dis}S°$	$\Delta_{dis}G°$	$\Delta_{dis}H°$[b)]	$T\Delta_{dis}S°$
[Co(gly)$_3$]	18.2[c)]	24.2[c)]	6.0[c)]	8.6[g)]	29.8[g)]	21.2[g)]
(+)-[Co(L-ala)$_3$]	28.5[d)]	2.3[d)]	−26.2[d)]	13.7[f)]	9.1[f)]	−4.6[f)]
(−)-[Co(L-ala)$_3$]	7.5[e)]	0.2[e)]	−7.3[e)]	0.9	1.1	0.2
(+)-[Co(L-ser)$_3$]	23.4[e)]	27.7[e)]	4.3[e)]	11.1[g)]	26.1[g)]	15.0[g)]
(−)-[Co(L-ser)$_3$]	7.2[e)]	21.0[e)]	13.8[e)]	4.2	3.4	−0.8
[Co(aiba)$_3$]	16.5[h)]	−15.1[h)]	−31.6[h)]	13.5[h)]	−2.3[h)]	−15.8[h)]
(−+)-[Co(DL-aba)$_3$]	20.0[d)]	4.4[d)]	−15.6[d)]	10.4[g)]	22.1[g)]	11.7[g)]
(+−)-[Co(DL-aba)$_3$]	13.4	0.3	−13.1	4.7	6.4	1.7
(+)-[Co(L-thr)$_3$]	13.6	15.0	1.4	16.3	25.3	9.0
(−)-[Co(L-thr)$_3$]				7.3	16.4	9.1
(+)-[Co(L-val)$_3$]	21.0[d)]	22.3[d)]	1.3[d)]	5.8[g)]	−13.7[g)]	−19.5[g)]
(−)-[Co(L-val)$_3$]	12.9	−5.0	−17.9	2.9	0.4	−2.5
(−+)-[Co(DL-nval)$_3$]	26.3[d)]	11.6[d)]	−14.7[d)]	10.1[g)]	−5.2[g)]	−15.3[g)]
(+−)-[Co(DL-nval)$_3$]				9.6	1.6	−8.0
(+)-[Co(L-leu)$_3$]	32.2[d)]	5.9[d)]	−26.3[d)]	19.7[g)]	−2.6[g)]	−22.3[g)]
(−)-[Co(L-leu)$_3$]	28.1[d)]	−3.4[d)]	−31.5[d)]	13.5	−0.1	−13.6
(+)-[Co(L-pro)$_3$]	24.4[e)]	14.6[e)]	−9.8[e)]			
(−)-[Co(L-pro)$_3$]	12.9[e)]	5.7[e)]	−7.2[e)]	−0.3	48.2	48.5
[Co(pic)$_3$]	18.5[h)]	30.5[h)]	12.1[h)]			
[Co(β-ala)$_3$]				3.3	20.8	17.5

a) Units of $\Delta_{dis}G°$, $\Delta_{dis}H°$, and $T\Delta_{dis}S°$ are kJ mol^{-1}. b) Errors estimated from the standard deviations of least-squares analysis were within 0.5 kJ mol^{-1} except for *mer*-(−)-[Co(L-pro)$_3$]. c) Calculated from the data reported in Ref. 14. d) Calculated from the data reported in Ref. 6. e) Calculated from the data reported in Ref. 7. f) Calculated from the data reported in Ref. 9. g) Taken from Ref. 11. h) Taken from Ref. 10.

present *mer*-isomers have considerably large solubilities, and an activity correction may be required to estimate the standard thermodynamic quantities from the temperature dependences of the solubilities. However, these saturated solutions are tentatively regarded as being ideal dilute solutions because of the lack of the data requirement for an activity correction.

The thus-obtained values for $\Delta_{dis}G°$, $\Delta_{dis}H°$, and $T\Delta_{dis}S°$ at 25 °C are tabulated in Table 3, where the corresponding values estimated from the solubility data for the *fac*-(+)- and *mer*-(+)-isomers reported previously[6,7,10,11] are also listed. The errors of $\Delta_{dis}H°$, estimated from the standard deviations of the least-squares analysis, were less than 0.5 kJ mol^{-1}, except for *mer*-(−)-[Co(L-pro)$_3$]. The error for *mer*-(−)-[Co(L-pro)$_3$] became large (5.0 kJ mol^{-1}) because of large scatters of the solubility data from the least-squares curve.

Discussion

Solubility Differences between the *fac*- and *mer*-Isomers or between the (+)-and (−)-Isomers of Particular [Co(aa)$_3$]. The variation in the solubilities among the four isomers of the respective [Co(aa)$_3$] is illustrated in Fig. 3 as the variation of $\Delta_{dis}G°$. In addition to *fac*-(−)-[Co(L-thr)$_3$], the $\Delta_{dis}G°$ data for *fac*-(+−)-[Co(DL-nval)$_3$] and *mer*-(+)-[Co(L-pro)$_3$] were not available because these chelates could not be synthesized satisfactorily by the procedure used in the present study. The solubilities of the four isomers increase in the order *fac*-(+)- (or *fac*-(−+)-) < *fac*-(−)- (or *fac*-(+−)-) < *mer*-(+)- (or *mer*-(−+)-) < *mer*-(−)- isomers (or *mer*-(+−)-isomers) for [Co(L-aa)$_3$] (or [Co(DL-aa)$_3$]) synthesized from the amino acids with longer side chains than 2-aminobutyric acid (abaH). On the other hand, for [Co(L-ala)$_3$] and [Co(L-ser)$_3$] the solubilities increase in the order *fac*-(+)- < *mer*-(+)- < *fac*-(−)- < *mer*-(−)-isomers. Especially, for [Co(L-thr)$_3$] the increasing sequence becomes *mer*-(+)- < *fac*-(+)- < *mer*-(−)- < *fac*-(−)-isomers, that is, the *fac*-isomer is more soluble than the *mer*-isomer for the (+)- or (−)-isomer. The same result is obtained for [Co(β-ala)$_3$], that is, the solubility of *fac*-[Co(β-ala)$_3$] is larger than *mer*-[Co(β-ala)$_3$].

Attempts to synthesize [Co(aa)$_3$] from L-phenylalanine and L-tryptophan were unsuccessful. While the *fac*-(−)-, *mer*-(+)-, and *mer*-(−)-isomers of tris(L-lysinato)cobalt(III) ([Co(L-lys)$_3$]) could be successfully synthesized, no attempt was made to determine the solubilities of these chelates because of the extremely large solubilities. Thus, an extension of the above findings to the chelates of amino acids with aromatic side chains and of acidic or basic amino acids is uncertain.

In order to consider the solubility differences among the four isomers of a particular chelate, the differences of $\Delta_{dis}H°$ and $T\Delta_{dis}S°$ between more soluble isomers and less soluble isomers were calculated by

$$\delta\Delta_{dis}Y° = \Delta_{dis}Y° \text{ (more soluble isomer)} - \Delta_{dis}Y° \text{ (less soluble isomer)}, \quad (1)$$

where $\Delta_{dis}Y°$ implies $\Delta_{dis}G°$, $\Delta_{dis}H°$, or $\Delta_{dis}S°$.

In Fig. 4, the $\delta\Delta_{dis}H°$ values are plotted against $T\delta\Delta_{dis}S°$ in connection with the solubility differences between the *mer*- and *fac*-isomers. The combinations of the diastereoisomers of

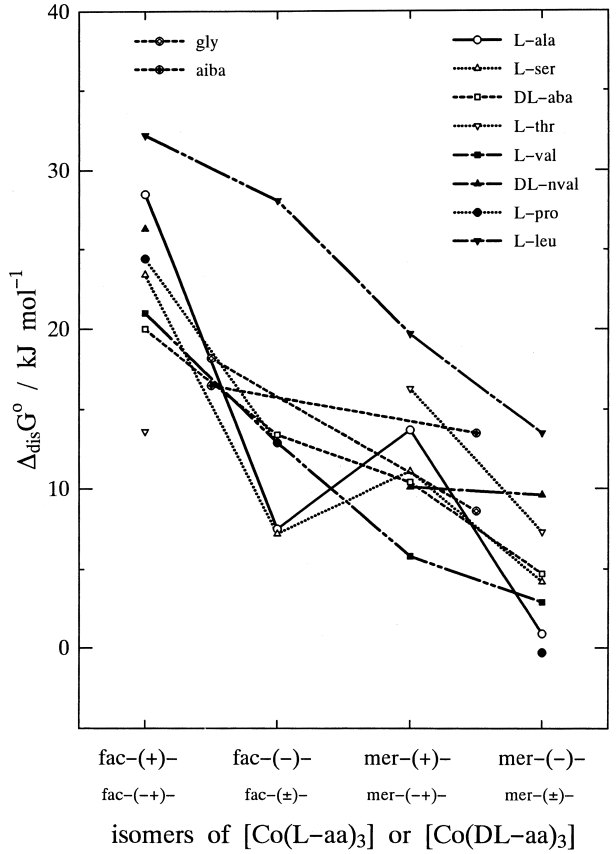

Fig. 3. Variation of $\Delta_{dis}G^\circ$ for the geometric and optical isomers of various [Co(aa)$_3$]. As both the *fac*- and *mer*-isomers of [Co(gly)$_3$] and [Co(aiba)$_3$] are racemates, these isomers are placed between the (+)- and (−)-isomers. For [Co(DL-aa)$_3$], the symbols of (−+) and (+−) stand for the racemic mixtures of (−)-[Co(D-aa)$_3$] and (+)-[Co(L-aa)$_3$], and of (+)-[Co(D-aa)$_3$] and (−)-[Co(L-aa)$_3$], respectively. The data for *fac*-(−)-[Co(L-thr)$_3$], *fac*-(+−)-[Co(DL-nval)$_3$], and *mer*-(+)-[Co(L-pro)$_3$] are unavailable (see text).

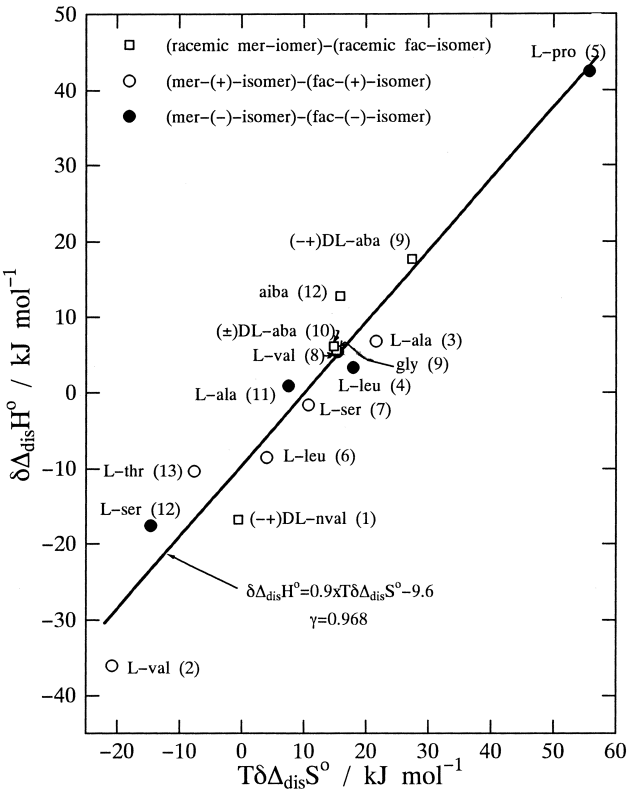

Fig. 4. Contribution of $\delta\Delta_{dis}H^\circ$ and $T\delta\Delta_{dis}S^\circ$ to the solubility differences between the *mer*- and *fac*-isomers of [Co(aa)$_3$]. The values for $\delta\Delta_{dis}H^\circ$ and $T\delta\Delta_{dis}S^\circ$ were calculated by subtracting $\Delta_{dis}H^\circ$ and $T\Delta_{dis}S^\circ$ of less soluble *fac*-[Co(aa)$_3$] from those of more soluble *mer*-[Co(aa)$_3$], respectively. The symbols of (+−) and (−+) for the racemic chelates indicate the differences between *mer*-(+−)-[Co(DL-aa)$_3$] and *fac*-(+−)-[Co(DL-aa)$_3$], and between *mer*-(−+)-[Co(DL-aa)$_3$] and *fac*-(−+)-[Co(DL-aa)$_3$], respectively. In the case of [Co(L-thr)$_3$], the $\Delta_{dis}H^\circ$ and $T\Delta_{dis}S^\circ$ values of less soluble *mer*-(+)-[Co(L-thr)$_3$] were subtracted from those of more soluble *fac*-(+)-[Co(L-thr)$_3$]. The numbers in parentheses indicate the decreasing order of the absolute values of $\delta\Delta_{dis}G^\circ$, that is, the decreasing order of the solubility differences.

[Co(L-aa)$_3$] or [Co(DL-aa)$_3$] are as follows: *mer*-(+)- and *fac*-(+)-[Co(L-aa)$_3$]; *mer*-(−)- and *fac*-(−)-[Co(L-aa)$_3$]; *mer*-(−+)- and *fac*-(−+)-[Co(DL-aa)$_3$]; *mer*-(+−)- and *fac*-(+−)-[Co(DL-aa)$_3$]. Irrespective of the combinations, all data can be represented by

$$\delta\Delta_{dis}H^\circ = 0.9\times T\delta\Delta_{dis}S^\circ - 9.6 \quad (\gamma = 0.968), \tag{2}$$

which indicates that $T\delta\Delta_{dis}S^\circ$ is larger than $\delta\Delta_{dis}H^\circ$. The larger solubilities of the *mer*-isomers compared with the *fac*-isomers, that is, more negative $\delta\Delta_{dis}G^\circ$ values are brought about by two sources: one source is a more positive $T\delta\Delta_{dis}S^\circ$ than $\delta\Delta_{dis}H^\circ$ and the other is a more negative $\delta\Delta_{dis}H^\circ$ than $T\delta\Delta_{dis}S^\circ$.

The extremely small solubility of *fac*-(+)-[Co(L-ala)$_3$] has been attributed to intermolecular hydrogen bonding in its solid state.[1,5] However, Fig. 4 shows that the larger solubility of *mer*-(+)-[Co(L-ala)$_3$] compared with that of *fac*-(+)-[Co(L-ala)$_3$] results from the above-mentioned former source. In other words, the small solubility of *fac*-(+)-[Co(L-ala)$_3$] is caused by its large negative $\Delta_{dis}S^\circ$ and its $\Delta_{dis}H^\circ$ is smaller than *mer*-(+)-[Co(L-ala)$_3$]. These results seem not to be consistent with the above-mentioned explanation for the small solubility of *fac*-(+)-[Co(L-ala)$_3$]. The *fac*-isomers can be expected to be more polar than the *mer*-isomers based on the fact that the *fac*-isomers are more strongly adsorbed on the alumina column. This expectation may explain the smaller $\Delta_{dis}H^\circ$ for the *fac*-isomers from the standpoint of an interaction with water molecules.

The contributions of the $\delta\Delta_{dis}H^\circ$ and $T\delta\Delta_{dis}S^\circ$ terms to the solubility differences between the (−)- and (+)-isomers of *mer*-[Co(L-aa)$_3$] or *fac*-[Co(L-aa)$_3$] are depicted in Fig. 5. The correlations between $\delta\Delta_{dis}H^\circ$ and $T\delta\Delta_{dis}S^\circ$ for the *mer*- and *fac*-isomers are given by

$$\delta\Delta_{dis}H^\circ = 1.1\times T\delta\Delta_{dis}S^\circ - 6.4 \quad (\gamma = 0.955) \tag{3}$$

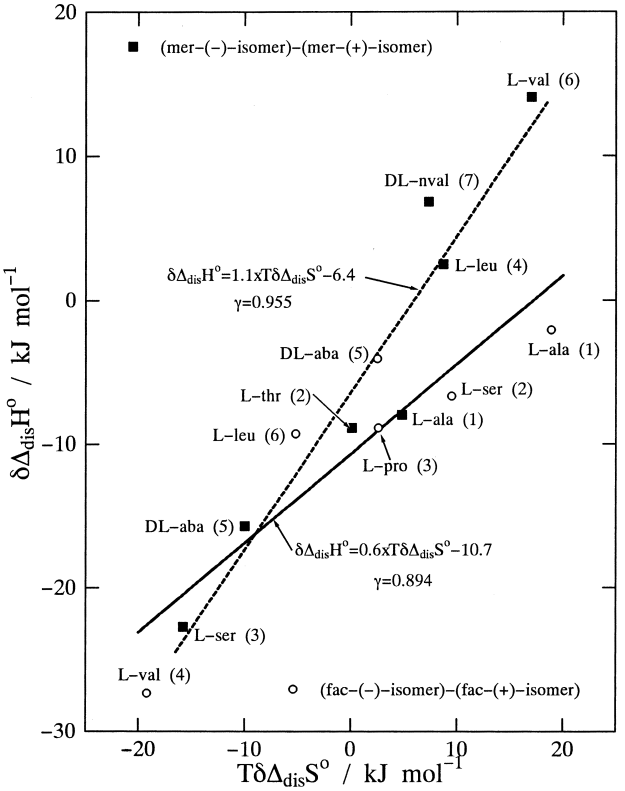

Fig. 5. Contribution of $\delta\Delta_{dis}H°$ and $T\delta\Delta_{dis}S°$ to the solubility differences between the (−)- and (+)-isomers of each geometric isomer of [Co(aa)$_3$]. The values for $\delta\Delta_{dis}H°$ and $T\delta\Delta_{dis}S°$ were calculated by subtracting $\Delta_{dis}H°$ and $T\Delta_{dis}S°$ of the (+)-isomer from those of the (−)-isomer, respectively. For the symbol of DL-aa, the differences between (+−)-[Co(DL-aa)$_3$] and (−+)-[Co(DL-aa)$_3$] were calculated for each geometric isomer. The numbers in parentheses indicate the decreasing order of the absolute values of $\delta\Delta_{dis}G°$, that is, the decreasing order of the solubility differences.

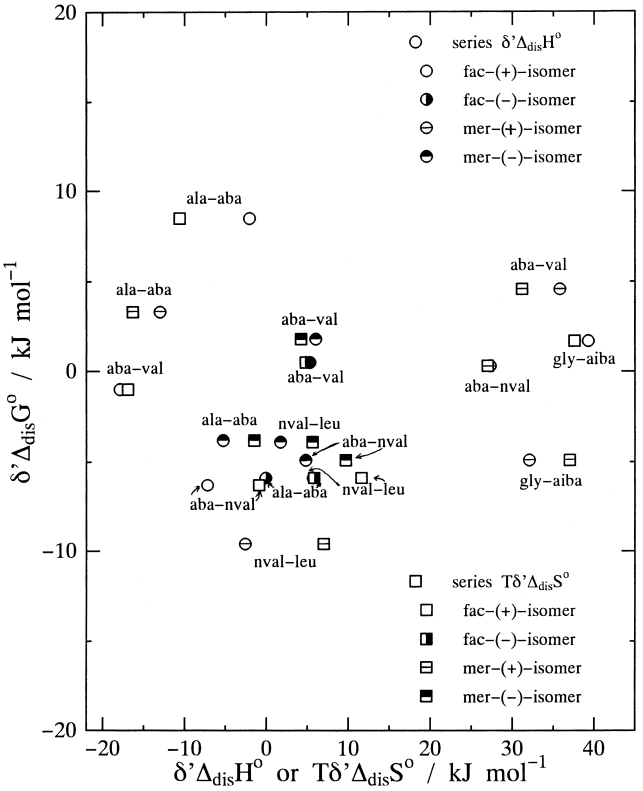

Fig. 6. Influences of the introduction of methyl group into various parent [Co(aa)$_3$]. The values for $\delta'\Delta_{dis}G°$, $\delta'\Delta_{dis}H°$, and $T\delta'\Delta_{dis}S°$ were calculated by subtracting $\Delta_{dis}G°$, $\Delta_{dis}H°$, and $T\Delta_{dis}S°$ of inductive [Co(aa)$_3$] from those of parent [Co(aa)$_3$], respectively. The combinations of the parent and inductive [Co(aa)$_3$] are as follows: [Co(L-ala)$_3$] and [Co(DL-aba)$_3$]; [Co(DL-aba)$_3$] and [Co(L-val)$_3$]; [Co(DL-aba)$_3$] and [Co(DL-nval)$_3$]; [Co(DL-nval)$_3$] and [Co(L-leu)$_3$]; [Co(gly)$_3$] and [Co(aiba)$_3$].

and

$$\delta\Delta_{dis}H° = 0.6\times T\delta\Delta_{dis}S° - 10.7 \quad (\gamma = 0.894), \tag{4}$$

respectively.

For all *fac*-[Co(aa)$_3$], $\delta\Delta_{dis}H°$ is negative, that is, $\Delta_{dis}H°$ of the *fac*-(−)-isomers is smaller than that of the *fac*-(+)-isomers. In addition, for *fac*-[Co(L-ala)$_3$] a large positive $T\delta\Delta_{dis}S°$ also contributes to the large solubility difference between *fac*-(−)-and *fac*-(+)-[Co(L-ala)$_3$].

On the other hand, the origin of the solubility differences between the *mer*-(−)-and *mer*-(+)-isomers may be classified into two categories. For the chelates of amino acids with shorter side chains than abaH, both $\Delta_{dis}H°$ and $T\Delta_{dis}S°$ are mostly positive (see Table 3), and a smaller $\Delta_{dis}H°$ of the *mer*-(−)-isomers is the main origin of larger solubility than that of the *mer*-(+)-isomers. In the cases of [Co(L-val)$_3$], [Co(DL-nval)$_3$], and [Co(L-leu)$_3$], both $\delta\Delta_{dis}H°$ and $T\delta\Delta_{dis}S°$ are positive. Despite $\Delta_{dis}H°$ of the *mer*-(−)-isomers being larger than that of the *mer*-(+)-isomers, the larger $T\Delta_{dis}S°$ for the *mer*-(−)-isomers produces larger solubilities than the *mer*-(+)-isomers. It is interesting that *mer*-[Co(L-val)$_3$], *mer*-[Co(DL-nval)$_3$], and *mer*-[Co(L-leu)$_3$] have negative $\Delta_{dis}H°$ and $T\Delta_{dis}S°$ (see Table 3). These results may indicate a large hydrophobic hydration of these chelates (see below).

Influences of the Introduction of Methyl and Hydroxyl Groups into the Side Chains of Amino Acids on the Dissolution Behavior of [Co(aa)$_3$]. In order to examine the effect of introducing methyl and hydroxyl groups into the side chains of the amino acids, the differences in the thermodynamic quantities of dissolution ($\delta'\Delta_{dis}Y°$) between the parent and inductive chelates were calculated by

$$\delta'\Delta_{dis}Y° = \Delta_{dis}Y° \text{ (parent chelate)} - \Delta_{dis}Y° \text{(inductive chelate)}. \tag{5}$$

The combinations of the parent and inductive chelates are as follows: for introducing the methyl group: [Co(L-ala)$_3$] and [Co(DL-aba)$_3$]; [Co(DL-aba)$_3$] and [Co(L-val)$_3$]; [Co(DL-aba)$_3$] and [Co(DL-nval)$_3$]; [Co(DL-nval)$_3$] and [Co(L-leu)$_3$]; tris(glycinato)cobalt(III) ([Co(gly)$_3$]) and tris(2-aminoisobutyrato)cobalt(III) ([Co(aiba)$_3$]). For introducing the hydroxyl group: [Co(L-ala)$_3$] and [Co(L-ser)$_3$]; [Co(DL-aba)$_3$] and [Co(L-thr)$_3$].

In Fig. 6, $\delta'\Delta_{dis}G°$ is plotted against $\delta'\Delta_{dis}H°$ or $T\delta'\Delta_{dis}S°$ in

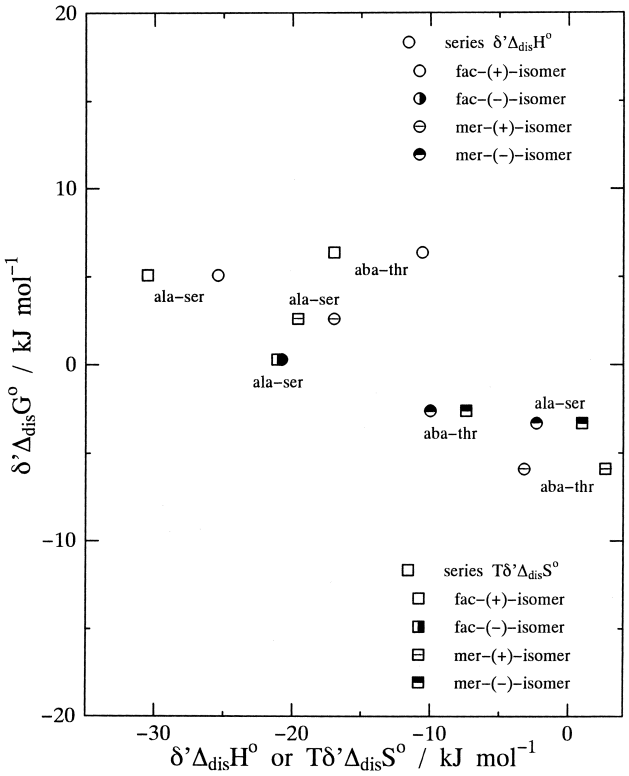

Fig. 7. Influences of the introduction of hydroxyl group into some parent $[Co(aa)_3]$. The values for $\delta'\Delta_{dis}G°$, $\delta'\Delta_{dis}H°$, and $T\delta'\Delta_{dis}S°$ were calculated by subtracting $\Delta_{dis}G°$, $\Delta_{dis}H°$, and $T\Delta_{dis}S°$ of inductive $[Co(aa)_3]$ from those of parent $[Co(aa)_3]$, respectively. The combinations of the parent and inductive $[Co(aa)_3]$ are as follows: $[Co(\text{L-ala})_3]$ and $[Co(\text{L-ser})_3]$; $[Co(\text{DL-aba})_3]$ and $[Co(\text{L-thr})_3]$.

order to display the effect of introducing the methyl group. A positive $\delta'\Delta_{dis}G°$ indicates that introducing the methyl group into the parent chelate results in an increase in the solubility, and positive $\delta'\Delta_{dis}H°$ and $T\delta'\Delta_{dis}S°$ indicate that the methyl group introduction brings about decreases in $\Delta_{dis}H°$ and $T\Delta_{dis}S°$. Introducing methyl groups into $[Co(gly)_3]$ gives large positive $\delta'\Delta_{dis}H°$ and $T\delta'\Delta_{dis}S°$. These results can be explained by the decrease in $\Delta_{dis}H°$ and $T\Delta_{dis}S°$ of $[Co(aiba)_3]$ due to hydrophobic hydration. As shown in Fig. 6, in many cases, introducing a methyl group causes decreases in $\Delta_{dis}H°$ and $T\Delta_{dis}S°$ in accord with the expectation based on the hydrophobic hydration. However, introducing a methyl group into $[Co(\text{L-ala})_3]$ results in increases in $\Delta_{dis}H°$ and $T\Delta_{dis}S°$ of $[Co(\text{DL-aba})_3]$.

In Fig. 7, the effect of introducing a hydroxyl group is illustrated by plotting $\delta'\Delta_{dis}G°$ against $\delta'\Delta_{dis}H°$ or $T\delta'\Delta_{dis}S°$. This figure shows that irrespective of the combinations of the geometric and optical isomers, introducing a hydroxyl group mostly brings about increases in $\Delta_{dis}H°$ and $T\Delta_{dis}S°$. These results may suggest that hydroxyl group introduction disturbs the hydrophobic hydration of $[Co(\text{L-ala})_3]$ and $[Co(\text{DL-aba})_3]$.

When $\delta'\Delta_{dis}H°$ becomes larger than $T\delta'\Delta_{dis}S°$ through the introduction of a methyl or hydroxyl group, this introduction brings about an increase in the solubility. On the contrary, the introduction accompanying larger $T\delta'\Delta_{dis}S°$ results in a decrease in the solubility (see Figs. 6 and 7). Thus, the solubility differences among various $[Co(aa)_3]$ are governed by the balance between $\delta'\Delta_{dis}H°$ and $T\delta'\Delta_{dis}S°$.

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