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The Role of Activated α-Carbon Atom Hydrogen in Salting-in Effect on Tris(α-amino acidato)cobalt(III)

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In order to examine the role of activated α-carbon atom hydrogen of α-amino acid in the salt effect on tris(α-amino acidato)cobalt(III) ([Co(aa)$_3$]), the solubilities of *mer*- and *fac*-tris(2-aminoisobutyrato)cobalt(III) (*mer*- and *fac*-[Co(aiba)$_3$]) in water and in aqueous NaBr and tetrabutylammonium bromide (Bu$_4$NBr) solutions were determined over the temperature range 5 to 40 °C. From these solubility data, the standard enthalpy ($\Delta_{tr}H^0$) and entropy of transfer ($\Delta_{tr}S^0$) at 25 °C for *mer*- and *fac*-[Co(aiba)$_3$] from water to the aqueous NaBr and Bu$_4$NBr solutions were estimated. A comparison with the $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ data for *mer*-[Co(aa)$_3$] of L-leucine (leuH), L-alanine (alaH), and glycine (glyH) shows that both $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ for the transfer of *mer*-[Co(aa)$_3$] to the NaBr solutions are negative; the large negative $\Delta_{tr}H^0$ increases the solubility of *mer*-[Co(aa)$_3$] (salting-in effect). Both $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ decrease in the order of *mer*-[Co(aiba)$_3$] > *mer*-(+)-[Co(L-leu)$_3$] > *mer*-(+)-[Co(L-ala)$_3$] > *mer*-[Co(gly)$_3$]. This sequence is explained by the assumption that activated α-carbon atom hydrogen enhances interactions of *mer*-[Co(aa)$_3$] with the surroundings. The effect of Bu$_4$NBr can be accounted for by hydrophobic interaction of [Co(aiba)$_3$] with Bu$_4$N$^+$ ion and the hydrophobic interaction of *fac*-[Co(aiba)$_3$] is larger than the interaction of *mer*-[Co(aiba)$_3$].

The addition of inorganic salts such as NaCl and Na$_2$SO$_4$ brings about a decrease in the solubilities of various nonpolar nonelectrolytes in water (salting-out effect)[1,2] and the salting-out effect has been explained by an increase in internal pressure due to the addition of salts.[1] The salting-out effect of ammonium sulfate ((NH$_4$)$_2$SO$_4$) is utilized to facilitate crystallization of proteins from aqueous solutions. The activity coefficients of glycine (glyH), alanine (alaH), and serine (serH) in their aqueous solutions reduce by the addition of NaCl and KCl[3] but the activity coefficient of valine (valH) increases by KCl.[4] Amino acids exist mainly as zwitterions in aqueous solutions over the wide pH range of about 2 to 9. As an interaction between the ionic parts of the amino acid zwitterions and their surroundings is expected to be greatly affected by the addition of salts, amino acids themselves are not necessarily adequate model compounds for amino acid residues of proteins.

From this standpoint, I have proposed to use tris(amino acidato)cobalt(III) ([Co(aa)$_3$]), in which the amino acid binds to the cobalt ion through both the amino nitrogen atom and the oxygen atom of the carboxylato group and loses its amphotericity, as a more suitable model compound for amino acid residues of protein.[5] In this approach, contrary to the prediction on the basis of the internal pressure, it has been found that the solubilities in water of both *fac*-[6] and *mer*-isomers[7] of [Co(aa)$_3$] (salting-in effect) increase by the addition of NaCl and NaBr. It has been reported that a strong interaction between the polar part of a nonelectrolyte and a salt component such as hydrogen bond formation brings about a large salting-in effect.[8] But the addition of NaF, CH$_3$COONH$_4$, and NaH$_2$PO$_4$, which is expected to form the hydrogen bond with [Co(aa)$_3$], decreases the solubility of *mer*-[Co(aa)$_3$].[7] This fact implies that the hydrogen bond formation between [Co(aa)$_3$] and salt components is not the origin of the salting-in effect.

The α-carbon atom hydrogen in α-amino acid is activated upon chelation with metal ion.[9] The possibility that the activated α-carbon atom hydrogen plays a part in the salting-in phenomenon may be pointed out because of the fact that amino acid itself such as phenylalanine is subject to the salting-out effect of NaCl.[6] In order to examine the possibility, tris(2-aminoisobutyrato)cobalt(III) ([Co(aiba)$_3$]) and tris(α-picolinato)cobalt(III) ([Co(pic)$_3$]) are synthesized and their solubilities in both water and some aqueous salt solutions are determined over the temperature range 5 to 40 °C. Evidently, these chelates lack the α-carbon atom hydrogens. The enthalpy ($\Delta_{tr}H^0$) and entropy of transfer ($\Delta_{tr}S^0$) at 25 °C from water to the aqueous salt solutions for these chelates are calculated from the above-mentioned solubility data and the origin of the salting-in effect is discussed on the basis of $\Delta_{tr}H^0$ and $\Delta_{tr}S^0$.

Experimental

Both [Co(aiba)$_3$] and [Co(pic)$_3$] were synthesized by the reaction of Co(OH)$_3$ with 2-aminoisobutyric acid (aibaH) and α-picolinic acid (picH). The separation of the *fac*- and *mer*-isomers of [Co(aiba)$_3$] (*fac*-[Co(aiba)$_3$] and *mer*-[Co(aiba)$_3$]) was done by column chromatography on Florisil. As complete separation between the first (*mer*-isomer) and the second bands (*fac*-isomer) was achieved, each eluent was evaporated to dryness by using evaporator. The residues were dissolved in 70% sulfuric acid and recrystallized by dilution with water. The crude product of [Co(pic)$_3$] precipitated from the reaction mixture by concentration was treated with ethanol to remove the *mer*-isomer which is soluble in ethanol.[10] The residue was dissolved in 60% sulfuric acid and recrystallized by dilution with water.

The spectroscopic properties and analytical data of the purified chelates are as follows: for *mer*-[Co(aiba)$_3$]: (λ_{max}/nm, ε_{max}/(10 dm^2 mol^{-1})): (537, 121); (375, 179). Calcd. for Co(C$_4$H$_8$NO$_2$)$_3$·2H$_2$O: C, 35.9; H, 7.1; N, 10.5%. Found: C, 36.0; H, 6.2; N, 10.7%. For *fac*-[Co(aiba)$_3$]: (λ_{max}/nm, ε_{max}/(10 dm^2 mol^{-1})): (522, 200); (378, 163). Calcd. for Co(C$_4$H$_8$NO$_2$)$_3$: C, 39.5; H, 6.6; N, 11.5%. Found: C, 38.7; H, 6.4; N, 11.4%. For *fac*-[Co(pic)$_3$]: (λ_{max}/nm, ε_{max}/(10 dm^2 mol^{-1})): (524, 98); (376, 213). Calcd. for Co(C$_6$H$_4$NO$_2$)·1/2H$_2$0: C, 49.8; H, 3.0; N, 9.5%. Found: C, 49.5; H, 3.0; N, 9.7%.

The solubility in mol kg^{-1} (m), which was defined as the moles of chelate molecules in 1 kg of water or an aqueous salt mixture, and the solubility in mol dm^{-3} (c) at 25 °C were measured as previously reported.[5—7] The values for m were used for estimation of enthalpy and entropy values from the temperature dependence of the solubility. The values for c were employed for comparison of the magnitude of the effect of various salts at 25 °C. The solubility measurement was repeated at least four times at each temperature and the errors defined as the deviations at 95% confidence levels were less than 2% of the mean values of these individual experimental values in most cases.

The other chemicals used were reagent grade. The working solution of each salt for the solubility measurement was prepared at 25 °C and the salt concentration was calculated in both mol kg^{-1} and mol dm^{-3} (m_s and c_s, respectively). Redistilled water was used.

Results and Discussion

Solubility, Standard Enthalpy, and Entropy of Dissolution of *mer*-[Co(aiba)$_3$], *fac*-[Co(aiba)$_3$], and *fac*-[Co(pic)$_3$] in Water. The solubility values in water (m^0 and c^0) of *mer*-[Co(aiba)$_3$], *fac*-[Co(aiba)$_3$], and *fac*-[Co(pic)$_3$] are listed in Table 1. Since the solubilities of these chelates are small, these saturated solutions are regarded as being ideal dilute solutions with respect to the chelates. Thus, without an activity correction the standard enthalpy ($\Delta_{dis}H^0$) and entropy of dissolution ($\Delta_{dis}S^0$) in water at 25 °C were estimated from the temperature dependence of ln (m^0) illustrated in Fig. 1 by using nonlinear least-squares analysis, as previously reported.[11] The standard state for the chelate in the solution is 1 mol kg^{-1}. The values for $\Delta_{dis}H^0$ and $T\Delta_{dis}S^0$ are tabulated in Table 2.

Table 1. Solubilities (m^0 and c^0) of *mer*-[Co(aiba)$_3$], *fac*-[Co(aiba)$_3$], and *fac*-[Co(pic)$_3$] in Water[a)]

θ/°C	*mer*-[Co(aiba)$_3$]	*fac*-[Co(aiba)$_3$]	*fac*-[Co(pic)$_3$]
	m^0/10^{-3} mol kg^{-1}	m^0/10^{-3} mol kg^{-1}	m^0/10^{-4} mol kg^{-1}
5	5.05(0.05)	2.26(0.01)	
10	4.81(0.04)	1.94(0.01)	3.12(0.06)
15	4.58(0.04)	1.67(0.02)	3.83(0.05)
20	4.43(0.02)	1.43(0.01)	4.84(0.05)
25	4.32(0.02)	1.30(0.01)	5.81(0.03)
30	4.29(0.01)	1.18(0.01)	7.19(0.06)
35	4.31(0.03)	1.11(0.02)	8.84(0.05)
40	4.36(0.02)	1.05(0.01)	10.7(0.1)
45	4.43(0.03)	0.978(0.011)	13.2(0.2)
50	4.59(0.04)	0.940(0.004)	16.1(0.2)
	c^0/10^{-3} mol dm^{-3}	c^0/10^{-3} mol dm^{-3}	c^0/10^{-4} mol dm^{-3}
25	4.41(0.02)	1.31(0.01)	5.88(0.01)

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

The solubilities in water at 25 °C for tris(glycinato)cobalt(III) ([Co(gly)$_3$]), tris(L-alaninato)cobalt(III) ([Co(L-ala)$_3$]), tris-(DL-2-amino-butyrato)cobalt(III) ([Co(DL-aba)$_3$]), and [Co(aiba)$_3$] so far investigated increase in the following order: *fac*-(+)-[Co(L-ala)$_3$] < *fac*-(−+)-[Co(DL-aba)$_3$] < *fac*-[Co(gly)$_3$] < *fac*-[Co(aiba)$_3$] for the *fac*-isomers; *mer*-(+)-[Co(L-ala)$_3$] < *mer*-[Co(aiba)$_3$] < *mer*-(−+)-[Co(DL-aba)$_3$] < *mer*-[Co(gly)$_3$] for the *mer*-isomers. In this paper, (+) and (−) represent dextrorotatory and levorotatory at 589 nm, respectively, and (−+)-[Co(DL-aba)$_3$] indicates the racemate of (−)-[Co(D-aba)$_3$] and (+)-[Co(L-

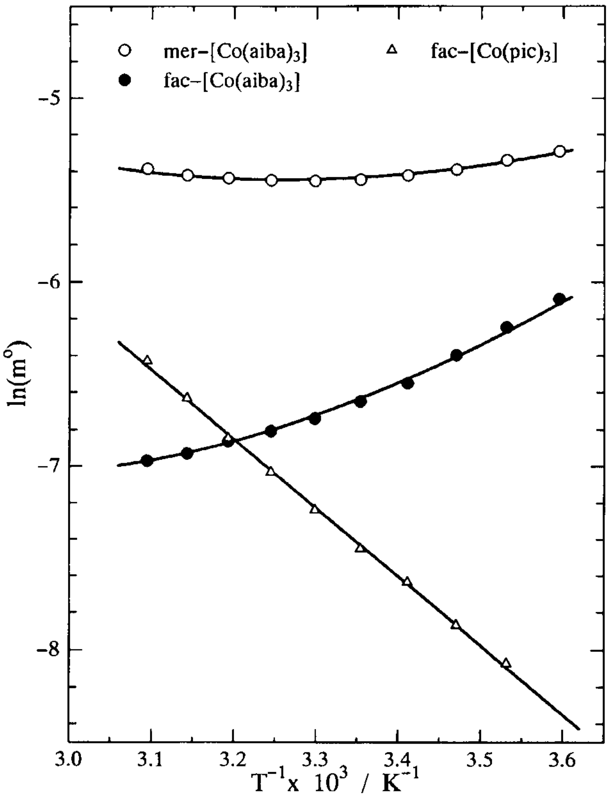

Fig. 1. Solubility curves of *mer*-[Co(aiba)$_3$], *fac*-[Co(aiba)$_3$], and *fac*-[Co(pic)$_3$] in water illustrated by plotting ln m^0 against $1/T$.

Table 2. Standard Enthalpy ($\Delta_{dis}H^0$) and Entropy of Dissolution ($\Delta_{dis}S^0$) in Water at 25 °C for *mer*-[Co(aiba)$_3$], *fac*-[Co(aiba)$_3$], and *fac*-[Co(pic)$_3$]

Compound	$\Delta_{dis}H^0$/kJ mol^{-1} [a)]	$T\Delta_{dis}S^0$/kJ mol^{-1}
mer-[Co(aiba)$_3$]	−2.3	−15.8
fac-[Co(aiba)$_3$]	−15.1	−31.6
fac-[Co(pic)$_3$]	30.5	12.1

a) Maximal error at 95% confidence level estimated from standard deviation of fit is 0.5 kJ mol^{-1}.

aba)$_3$]. It is noteworthy that the relative solubility sequence for *fac*-[Co(aiba)$_3$] differs greatly from the sequence for *mer*-[Co(aiba)$_3$]. A more detailed examination of the dissolution behavior of these chelates in water on the basis of $\Delta_{\mathrm{dis}}H^0$ and $\Delta_{\mathrm{dis}}S^0$ data will be reported elsewhere.

Salt Effect on the Solubility of *mer*-[Co(aa)$_3$]. The values for m and c of *mer*-[Co(aiba)$_3$] in aqueous NaBr, NaCl, $(NH_4)_2SO_4$, and tetrabutylammonium bromide (Bu_4NBr) solutions are tabulated in Table 3, and the m and c values of *mer*-[Co(gly)$_3$], *mer*-(+)-tris(L-leucinato)cobalt(III) (*mer*-(+)-[Co(L-leu)$_3$]), and *mer*-(+)-tris(L-serinato)cobalt(III) (*mer*-(+)-[Co(L-ser)$_3$]) in aqueous NaBr solutions are listed in Table 4. To demonstrate any change in the solubility caused by the addition of the salts, the value for $\log(c^0/c)$ is plotted against c_s in Fig. 2, where the solid lines are tentatively drawn by fitting the $\log(c^0/c)$ values to a power series of c_s. In Fig. 2 the data for the effect of NaBr on *mer*-(+)-[Co(L-ala)$_3$][7] are also displayed. The chelates of the amino acids having α-carbon atom hydrogens, that is, *mer*-[Co(gly)$_3$], *mer*-(+)-[Co(L-ala)$_3$], *mer*-(+)-[Co(L-ser)$_3$], and *mer*-(+)-[Co(L-leu)$_3$] are subject to the salting-in effect of NaBr, while the utilized salts substantially result in the salting-out effect on *mer*-[Co(aiba)$_3$].

McDevit and Long have predicted that a nonpolar nonelectrolyte without specific interaction with its surroundings is subject to the salting-out effect due to an increase in the internal pressure resulting from the addition of inorganic salts such as NaBr, NaCl, and Na_2SO_4.[1] In accord with this prediction, I have found the salting-out effect of these salts on some metal chelates of β-diketones such as 2,4-pentanedione (acacH)[6] and 1-phenyl-1,3-butanedione.[12] These findings imply that these chelates behave as nonpolar solutes.

On the other hand, the solubilities of both *mer*- and *fac*-[Co(aa)$_3$] increase in the presence of NaCl and NaBr.[5–7] These facts indicate that a specific interaction between [Co(aa)$_3$] and the surroundings takes place and is strengthened by the addition of salts. The preceding investigations have suggested that the salting-in effect of NaCl and NaBr on [Co(aa)$_3$] is caused through a hydrophilic interaction other than the hydrogen-bond formation of [Co(aa)$_3$] with the salt

Table 3. Solubilities (m and c) of *mer*-[Co(aiba)$_3$] in Aqueous NaBr, NaCl, $(NH_4)_2SO_4$, and Bu_4NBr Solutions[a)]

$\theta/°C$	NaBr concentration m_s/mol kg^{-1}				NaCl concentration m_s/mol kg^{-1}			
	0.203	0.512	0.768	1.032	0.221	0.510	0.763	1.026
	$m/10^{-3}$ mol kg^{-1}				$m/10^{-3}$ mol kg^{-1}			
5	5.14(0.06)	4.98(0.02)	4.69(0.02)	4.51(0.03)	4.88(0.03)	4.68(0.02)	4.22(0.04)	3.84(0.02)
10	4.79(0.03)	4.65(0.02)	4.49(0.02)	4.24(0.02)	4.57(0.01)	4.42(0.04)	3.97(0.03)	3.62(0.03)
15	4.65(0.04)	4.41(0.03)	4.21(0.06)	3.95(0.03)	4.40(0.02)	4.24(0.01)	3.82(0.03)	3.50(0.02)
20	4.51(0.04)	4.32(0.02)	4.12(0.03)	3.90(0.02)	4.24(0.02)	4.12(0.02)	3.72(0.03)	3.40(0.02)
25	4.34(0.01)	4.22(0.03)	4.06(0.02)	3.82(0.02)	4.16(0.02)	4.02(0.02)	3.61(0.02)	3.34(0.01)
30	4.33(0.06)	4.17(0.02)	3.97(0.07)	3.81(0.01)	4.15(0.02)	3.99(0.02)	3.59(0.02)	3.33(0.02)
35	4.41(0.04)	4.20(0.03)	3.96(0.02)	3.81(0.03)	4.14(0.04)	4.02(0.02)	3.64(0.01)	3.34(0.03)
40	4.39(0.02)	4.25(0.06)	3.99(0.02)	3.85(0.03)	4.18(0.02)	4.07(0.02)	3.68(0.02)	3.40(0.01)
	c_s/mol dm^{-3}				c_s/mol dm^{-3}			
	0.201	0.503	0.750	1.000	0.219	0.504	0.750	1.002
	$c/10^{-3}$ mol dm^{-3}				$c/10^{-3}$ mol dm^{-3}			
25	4.50(0.01)	4.48(0.03)	4.39(0.02)	4.21(0.02)	4.29(0.02)	4.20(0.02)	3.79(0.02)	3.54(0.01)
$\theta/°C$	$(NH_4)_2SO_4$ concentration m_s/mol kg^{-1}				Bu_4NBr concentration m_s/mol kg^{-1}			
	0.207	0.517	0.791	1.070	0.213	0.589	0.966	1.421
	$m/10^{-3}$ mol kg^{-1}				$m/10^{-3}$ mol kg^{-1}			
5	4.06(0.03)	2.89(0.02)	2.15(0.01)	1.49(0.01)	5.12(0.02)	4.68(0.03)		
10	3.83(0.02)	2.73(0.02)	2.05(0.01)	1.45(0.01)	4.90(0.04)	4.58(0.02)	3.86(0.06)	3.14(0.03)
15	3.70(0.05)	2.65(0.01)	2.02(0.01)	1.42(0.01)	4.74(0.03)	4.51(0.03)	3.88(0.02)	3.28(0.03)
20	3.59(0.02)	2.61(0.01)	1.98(0.02)	1.40(0.01)	4.62(0.03)	4.54(0.03)	3.94(0.01)	3.41(0.02)
25	3.58(0.01)	2.58(0.02)	1.96(0.01)	1.39(0.01)	4.56(0.01)	4.56(0.01)	4.11(0.02)	3.57(0.01)
30	3.55(0.02)	2.56(0.01)	1.96(0.01)	1.40(0.01)	4.58(0.03)	4.63(0.03)	4.20(0.01)	3.76(0.02)
35	3.57(0.03)	2.60(0.01)	1.99(0.03)	1.43(0.02)	4.63(0.02)	4.77(0.02)	4.41(0.01)	3.97(0.04)
40	3.65(0.04)	2.67(0.02)	2.01(0.03)	1.45(0.03)	4.74(0.03)	4.95(0.04)	4.61(0.02)	4.23(0.02)
	c_s/mol dm^{-3}				c_s/mol dm^{-3}			
	0.204	0.500	0.752	1.000	0.200	0.501	0.750	1.000
	$c/10^{-3}$ mol dm^{-3}				$c/10^{-3}$ mol dm^{-3}			
25	3.71(0.01)	2.72(0.02)	2.11(0.02)	1.51(0.01)	4.67(0.02)	4.70(0.01)	4.27(0.03)	3.73(0.02)

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

Table 4. Solubilities (m and c) of *mer*-[Co(gly)$_3$], *mer*-(+)-[Co(L-ser)$_3$], and *mer*-(+)-[Co(L-leu)$_3$] in Aqueous NaBr Solutions[a)]

θ/°C	*mer*-[Co(gly)$_3$]				*mer*-(+)-[Co(L-leu)$_3$]			
	m_s/mol kg^{-1}				m_s/mol kg^{-1}			
	0.202	0.534	0.770	1.034	0.510	1.029	1.567	2.123
	$m/10^{-2}$ mol kg^{-1}				$m/10^{-4}$ mol kg^{-1}			
5	1.67(0.02)	2.26(0.01)	2.76(0.03)	3.46(0.03)	5.93(0.07)	6.30(0.05)	6.33(0.08)	6.24(0.02)
10	2.07(0.02)	2.75(0.01)	3.31(0.04)	4.07(0.01)	5.34(0.04)	5.57(0.05)	5.61(0.05)	5.37(0.04)
15	2.53(0.01)	3.35(0.02)	3.97(0.03)	4.87(0.03)	4.83(0.03)	5.04(0.11)	4.98(0.08)	4.91(0.12)
20	3.11(0.01)	4.05(0.02)	4.81(0.02)	5.76(0.08)	4.54(0.11)	4.74(0.09)	4.63(0.05)	4.50(0.04)
25	3.84(0.04)	4.90(0.02)	5.80(0.02)	6.94(0.01)	4.40(0.01)	4.42(0.01)	4.36(0.01)	4.30(0.01)
30	4.69(0.03)	5.69(0.02)	6.92(0.03)		4.47(0.11)	4.36(0.06)	4.29(0.03)	4.11(0.05)
35	5.62(0.05)				4.43(0.10)	4.49(0.10)	4.38(0.07)	4.18(0.03)
40						4.69(0.09)	4.48(0.05)	4.33(0.09)
	c_s/mol dm^{-3}				c_s/mol dm^{-3}			
	0.200	0.524	0.751	1.001	0.502	1.000	1.501	2.002
	$c/10^{-2}$ mol dm^{-3}				$c/10^{-4}$ mol dm^{-3}			
25	3.97(0.05)	5.19(0.04)	6.22(0.03)	7.58(0.01)	4.61(0.01)	4.81(0.01)	4.90(0.01)	5.00(0.01)

θ/°C	*mer*-(+)-[Co(L-ser)$_3$]				
	m_s/mol kg^{-1}				
	0.158	0.210	0.509	0.768	1.034
	$m/10^{-2}$ mol kg^{-1}				
5	0.790(0.009)	0.757(0.002)	0.613(0.004)	0.709(0.009)	0.783(0.004)
10	0.901(0.009)	0.905(0.015)	0.767(0.006)	0.884(0.003)	0.957(0.004)
15	1.07(0.01)	1.06(0.01)	0.949(0.002)	1.09(0.01)	1.19(0.01)
20	1.27(0.01)	1.30(0.01)	1.20(0.01)	1.36(0.01)	1.50(0.01)
25	1.56(0.02)	1.59(0.01)	1.53(0.01)	1.73(0.01)	1.89(0.01)
30	1.91(0.03)	1.98(0.02)			
	c_s/mol dm^{-3}				
	0.157	0.209	0.502	0.751	1.003
	$c/10^{-2}$ mol dm^{-3}				
25	1.61(0.02)	1.66(0.01)	1.62(0.01)	1.86(0.02)	2.08(0.01)

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

components.[5,7]

In order to compare a contribution of enthalpy and entropy factors to the salt effect examined in this study with the previously reported contribution, the standard enthalpy ($\Delta_{tr}H^0$) and entropy of transfer ($\Delta_{tr}S^0$) at 25 °C from water to the aqueous salt solutions for the present chelates were calculated by

$$\Delta_{tr}Y^0 = \Delta_{dis}Y^0(\text{salt}) - \Delta_{dis}Y^0(\text{water}), \tag{1}$$

where Y denotes enthalpy or entropy and $\Delta_{dis}Y^0$(salt) describes $\Delta_{dis}H^0$ or$\Delta_{dis}S^0$ of the chelates in the aqueous salt solutions estimated from the temperature dependence of ln (m). The resulting values for $\Delta_{tr}H^0$ are plotted against $T\Delta_{tr}S^0$ in Fig. 3, where for comparison the data for the salting-out effect of NaCl on tris(2,4-pentanedionato)cobalt(III) ([Co(acac)$_3$])[6] are also displayed.

The data for the effect of NaBr on the *mer*-isomers other than *mer*-(+)-[Co(L-ser)$_3$] seem to constitute a single straight line given by

$$\Delta_{tr}H^0 = 1.6T\Delta_{tr}S^0 \; (\gamma = 0.981), \tag{2}$$

where γ is the correlation coefficient. Equation 2 is consistent with that settled in the previous study for the salting-in effect of NaBr and NH$_4$Br on *mer*-(+)-[Co(L-ala)$_3$].[5] Both $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ for *mer*-[Co(gly)$_3$], *mer*-(+)-[Co(L-ala)$_3$], and *mer*-(+)-[Co(L-leu)$_3$] decrease with increasing m_s, and Eq. 2 indicates that the large decrease in $\Delta_{tr}H^0$ causes the salting-in effect. The $\Delta_{tr}H^0$ values for the transfer to about 0.5 mol kg^{-1} NaBr solution decrease in the order of *mer*-[Co(aiba)$_3$] > *mer*-(+)-[Co(L-leu)$_3$] > *mer*-(+)-[Co-(L-ala)$_3$] > *mer*-[Co(gly)$_3$]. The magnitude of the salting-in effect increases with this decreasing $\Delta_{tr}H^0$ (see Fig. 2).

The data for the salting-out effect of NaCl on [Co(acac)$_3$] do not satisfy Eq. 2. The salting-out effect is obviously produced by the large increase in $\Delta_{tr}H^0$, which can be explained by the above-mentioned idea of McDevit that an increase in the internal pressure in the presence of salt brings about an increase in the energy for the formation of a cavity to accommodate nonelectrolyte.[1]

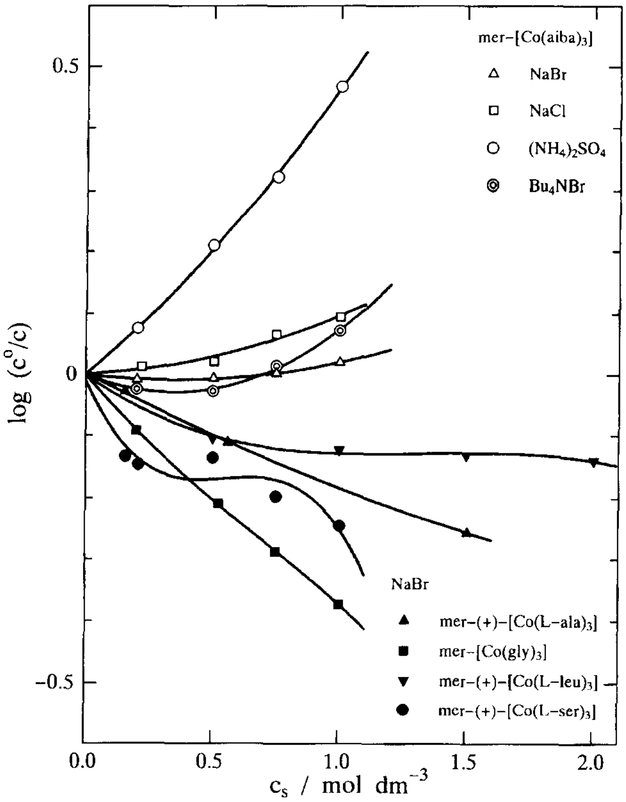

Fig. 2. Effects of various salts on *mer*-[Co(aiba)$_3$], and of NaBr on various *mer*-[Co(aa)$_3$] depicted by plotting $\log(c^0/c)$ against c_s. The data for *mer*-(+)-[Co(L-ala)$_3$] in aqueous NaBr solutions were taken from Ref. 7. The solid lines are tentatively drawn by fitting the $\log(c^0/c)$ values to power series of c_s.

In contrast to the McDevit prediction, the decrease in $\Delta_{tr}H^0$ causes the salting-in effect of NaBr on *mer*-[Co(aa)$_3$]. This fact indicates that a polar part, probably the carbonyl group, in *mer*-[Co(aa)$_3$] may interact with surroundings in a unique fashion. The specific interaction may be strengthened by the addition of NaBr and a decrease in enthalpy due to this effect seems to be superior to the increase in the cavity formation energy in the presence of NaBr.

In the case of *mer*-[Co(aiba)$_3$], the enthalpy changes due to the above two effects produced by the addition of NaBr and NaCl may be mutually compensated. This compensation results in extremely small $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ values. The addition of $(NH_4)_2SO_4$ causes the definite salting-out and the data for $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ deviate from Eq. 2 (see Figs. 2 and 3). A similar result has been also found for the effect of $(NH_4)_2SO_4$ on *mer*-(+)-[Co(L-ala)$_3$].[7] It is well known that sulfate salts bring about large increases in the internal pressure and exhibit large salting-out effects.[1] For *mer*-[Co(aiba)$_3$] also, the large effect of $(NH_4)_2SO_4$ on the internal pressure seems to be superior to the interaction of *mer*-[Co(aiba)$_3$] with surroundings and the salting-out effect is observed. But the salting-out effect of $(NH_4)_2SO_4$ on *mer*-(+)-[Co(L-ala)$_3$][7] is smaller than the effect on *mer*-[Co(aiba)$_3$]. Furthermore, the $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ values for *mer*-(+)-[Co(L-ala)$_3$] are also smaller than those for *mer*-[Co(aiba)$_3$] (for example, in the transfer to about 0.5 mol kg^{-1} $(NH_4)_2SO_4$ solution, for *mer*-(+)-[Co(L-ala)$_3$] $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ are -0.2 and -0.4 kJ mol^{-1}, respectively; while for *mer*-[Co(aiba)$_3$] $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ are 1.7 and 0.4 kJ mol^{-1}, respectively.). These findings indicate that in the case of $(NH_4)_2SO_4$ also the specific interaction of *mer*-(+)-[Co(L-ala)$_3$] is stronger than the interaction of *mer*-[Co(aiba)$_3$].

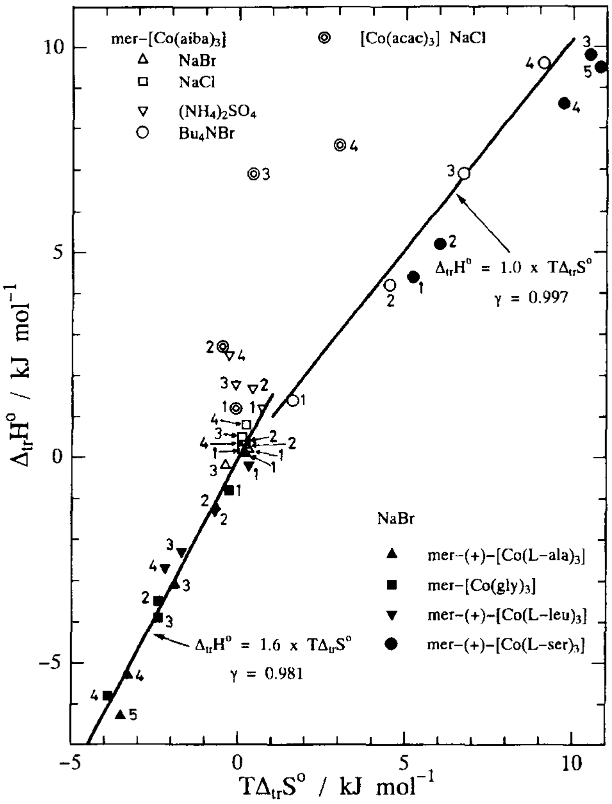

Fig. 3. Correlation between $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ for the transfer process of various *mer*-[Co(aa)$_3$] from water to aqueous salt solutions. The $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ values for the transfer of [Co(acac)$_3$] to NaCl solutions and of *mer*-(+)-[Co(L-ala)$_3$] to NaBr solutions were calculated from the data reported in Refs. 6 and 7, respectively. The number given beside each mark represents increasing sequence of salt concentration m_s.

The above-mentioned argument suggests that an activation of the α-carbon hydrogen atoms in *mer*-[Co(aa)$_3$] enhances the specific interaction of *mer*-[Co(aa)$_3$] with surroundings. Electron-releasing side chains of amino acids, which are expected to weaken the activation of the α-carbon hydrogen, turn out to reduce the enhancement of the specific interaction, that is, to prevent any decrease in $\Delta_{tr}H^0$. Since an alkyl group induces the electron-releasing, $\Delta_{tr}H^0$ to the NaBr solution decreases in the order of *mer*-[Co(aiba)$_3$] > *mer*-(+)-[Co(L-leu)$_3$] > *mer*-(+)-[Co(L-ala)$_3$] > *mer*-[Co(gly)$_3$].

In the preceding work,[5] the effect of tetraalkylammonium bromide on *mer*-[Co(aa)$_3$] has been studied in detail. It has been elucidated that the effect of tetrapropylammonium bromide (Pr_4NBr) and Bu_4NBr should be ascribed to hydrophobic interaction between *mer*-[Co(aa)$_3$] and Pr_4N^+ or Bu_4N^+ ion. In the present study also the effect of Bu_4NBr on *mer*-[Co(aiba)$_3$] was examined to obtain information about the hydrophobicity of the side chain of aibaH.

For the transfer of *mer*-[Co(aiba)$_3$] to the Bu$_4$NBr solutions, $\Delta_{tr}H^0$ is almost completely compensated by $T\Delta_{tr}S^0$ as shown by

$$\Delta_{tr}H^0 = 1.0T\Delta_{tr}S^0 \ (\gamma = 0.997). \tag{3}$$

Equation 3 is closely consistent with the equation created by using the data for the transfer of various *mer*-[Co(aa)$_3$] to Bu$_4$NBr solutions.[5] For *mer*-[Co(aiba)$_3$], the $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ values for the transfer to 0.97 mol kg^{-1} Bu$_4$NBr solution, which have been used to estimate the hydrophobicity of *mer*-[Co(aa)$_3$],[5] are 6.9 and 6.7 kJ mol^{-1}, respectively and these values are consistent with the corresponding values for *mer*-(−+)-[Co(DL-aba)$_3$] (7.7 and 8.4 kJ mol^{-1}, respectively).[5] These results indicate that the activated α-carbon hydrogen does not affect markedly the hydrophobic interaction and that the hydrophobicities of *mer*-[Co(aiba)$_3$] and *mer*-(−+)-[Co(DL-aba)$_3$] are comparable.

The correlation between $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ for the transfer of *mer*-(+)-[Co(L-ser)$_3$] to the NaBr solutions differs markedly from that expressed by Eq. 2 and resembles Eq. 3, indicative of the hydrophobic interaction. The hydrophobicity of serH may be expected to be smaller than that of alaH because of an introduction of hydrophilic hydroxyl group to the methyl group of alaH. In practice, the $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ values of *mer*-(+)-[Co(L-ser)$_3$] and *mer*-(+)-[Co(L-ala)$_3$] to 0.97 mol kg^{-1} Bu$_4$NBr solution verify the above expectation.[5] Thus, occurrence of the hydrophobic interaction between *mer*-(+)-[Co(L-ser)$_3$] and NaBr is unreliable. In order to examine whether the introduction of hydroxyl group results in any peculiar effect, a comparison with tris(L-threoninato)cobalt(III) ([Co(L-thr)$_3$]) is investigated.

Salt Effect on the Solubility of *fac*-[Co(aa)$_3$]. The solubilities (m and c) of *fac*-[Co(aiba)$_3$] and *fac*-[Co(pic)$_3$] in the aqueous NaBr and Bu$_4$NBr solutions, and of *fac*-[Co(gly)$_3$] in the aqueous Bu$_4$NBr solutions are given in Table 5. The values for log (c^0/c) are plotted against c_s in Fig. 4, where

Table 5. Solubilities (m and c) of *fac*-[Co(aiba)$_3$] and *fac*-[Co(pic)$_3$] in Aqueous NaBr and Bu$_4$NBr Solutions, and of *fac*-[Co(gly)$_3$] in Aqueous Bu$_4$NBr Solutions[a)]

θ/°C	NaBr concentration m_s/mol kg^{-1}				Bu$_4$NBr concentration m_s/mol kg^{-1}			
	0.203	0.510	0.768	1.036	0.215	0.589	0.968	1.424
	fac-[Co(aiba)$_3$] m/10^{-3} mol kg^{-1}				*fac*-[Co(aiba)$_3$] m/10^{-3} mol kg^{-1}			
5	3.31(0.03)	3.57(0.02)	3.91(0.03)	4.06(0.03)				
10	2.58(0.02)	3.06(0.01)	3.40(0.04)	3.53(0.02)	2.36(0.02)	2.33(0.01)	2.06(0.02)	1.84(0.02)
15	2.29(0.03)	2.69(0.02)	2.98(0.03)	3.09(0.01)	2.10(0.01)	2.12(0.01)	1.93(0.02)	1.77(0.01)
20	1.98(0.03)	2.39(0.02)	2.64(0.02)	2.76(0.01)	1.90(0.01)	1.98(0.02)	1.82(0.02)	1.72(0.02)
25	1.78(0.02)	2.16(0.02)	2.41(0.01)	2.50(0.01)	1.74(0.01)	1.84(0.01)	1.75(0.02)	1.70(0.03)
30	1.63(0.01)	2.00(0.01)	2.22(0.02)	2.33(0.01)	1.62(0.01)	1.73(0.02)	1.72(0.01)	1.68(0.01)
35	1.51(0.01)	1.88(0.01)	2.08(0.01)	2.16(0.01)	1.50(0.01)	1.68(0.02)	1.66(0.01)	1.66(0.01)
40	1.42(0.01)	1.76(0.02)	1.97(0.03)	2.04(0.02)	1.40(0.01)	1.63(0.01)	1.63(0.02)	1.65(0.01)
	c_s/mol dm^{-3}				c_s/mol dm^{-3}			
	0.201	0.502	0.751	1.005	0.201	0.500	0.751	1.001
	c/10^{-3} mol dm^{-3}				c/10^{-3} mol dm^{-3}			
25	1.84(0.02)	2.29(0.02)	2.60(0.01)	2.75(0.01)	1.78(0.01)	1.90(0.01)	1.82(0.02)	1.78(0.03)

θ/°C	NaBr concentration m_s/mol kg^{-1}				Bu$_4$NBr concentration m_s/mol kg^{-1}				
	0.204	0.508	0.769	1.039	0.966	0.160	0.589	0.967	1.330
	fac-[Co(pic)$_3$] m/10^{-4} mol kg^{-1}				*fac*-[Co(pic)$_3$] m/10^{-3} mol kg^{-1}	*fac*-[Co(gly)$_3$] m/10^{-4} mol kg^{-1}			
5						3.04(0.05)			
10	3.62(0.08)	4.10(0.08)	4.40(0.05)	4.79(0.15)	1.99(0.03)	3.74(0.06)	3.60(0.10)	3.10(0.06)	3.00(0.07)
15	4.30(0.02)	4.78(0.05)	5.07(0.06)	5.53(0.12)	2.54(0.03)	4.54(0.10)	4.38(0.06)	3.89(0.11)	3.70(0.04)
20	5.18(0.05)	5.80(0.06)	6.13(0.10)	6.57(0.09)	3.26(0.04)	5.52(0.13)	5.36(0.04)	4.88(0.10)	4.64(0.08)
25	6.47(0.03)	6.90(0.09)	7.28(0.03)	7.78(0.08)	4.13(0.04)	6.54(0.11)	6.53(0.07)	5.97(0.11)	5.65(0.08)
30	7.59(0.10)	8.10(0.05)	8.66(0.01)	9.03(0.13)	5.17(0.08)	8.00(0.07)	7.88(0.03)	7.18(0.09)	6.97(0.18)
35	9.35(0.07)	9.79(0.07)	10.4(0.2)	10.8(0.2)	6.40(0.09)		9.39(0.06)		
40	11.4(0.1)	11.8(0.1)	12.5(0.1)	13.1(0.1)	8.22(0.16)				
	c_s/mol dm^{-3}				c_s/mol dm^{-3}				
	0.203	0.500	0.751	1.006	0.750	0.152	0.500	0.750	0.952
	c/10^{-4} mol dm^{-3}				c/10^{-3} mol dm^{-3}	c/10^{-4} mol dm^{-3}			
25	6.64(0.01)	7.25(0.10)	7.79(0.01)	8.46(0.10)	4.31(0.04)	6.64(0.12)	6.69(0.07)	6.16(0.11)	5.87(0.11)

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

the data for *fac*-[Co(gly)$_3$] in the NaBr solutions[7]) and for *fac*-(−)-tris(D-prolinato)cobalt(III) (*fac*-(−)-[Co(D-pro)$_3$]) in the NaCl solutions[6] are also illustrated. The information for the salt effect from the standpoint of the correlation between $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ is depicted in Fig. 5.

Figure 5 shows that the correlation of $\Delta_{tr}H^0$ with $T\Delta_{tr}S^0$ for the transfer of *fac*-[Co(gly)$_3$] and *fac*-[Co(aiba)$_3$] to the Bu_4NBr solutions agrees with Eq. 3 arranged for *mer*-[Co(aiba)$_3$] (see Figs. 3 and 5). Thus, the effect of Bu_4NBr on *fac*-[Co(gly)$_3$] and *fac*-[Co(aiba)$_3$] can be also explained from the view of the hydrophobic interaction as well as the effect on *mer*-[Co(aa)$_3$], and it is interesting to compare the $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ values for the *fac*-isomer with the values for the corresponding *mer*-isomer. The $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ values for the transfer to 0.97 mol kg^{-1} Bu_4NBr solution are as follows: ($\Delta_{tr}H^0$/kJ mol^{-1}, $T\Delta_{tr}S^0$/kJ mol^{-1}) for *fac*-[Co(gly)$_3$] ; (4.7, 4.5), for *mer*-[Co(gly)$_3$] ; (−3.7, −3.9), for *fac*-[Co(aiba)$_3$]; (9.6, 10.4), and for *mer*-[Co(aiba)$_3$]; (6.9, 6.7). Evidently, both $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ for the mer-isomers are smaller than those for the corresponding *fac*-isomers. The hydrophobic interaction is caused by overlapping of hydrophobic hydration shells around hydrophobic solutes and brings about an increase in both enthalpy and entropy. Accordingly, the above-mentioned results can be regarded as the indication that the hydrophobic interaction of the *mer*-isomer with Bu_4N^+ ion is weaker than the interaction of the *fac*-isomer.

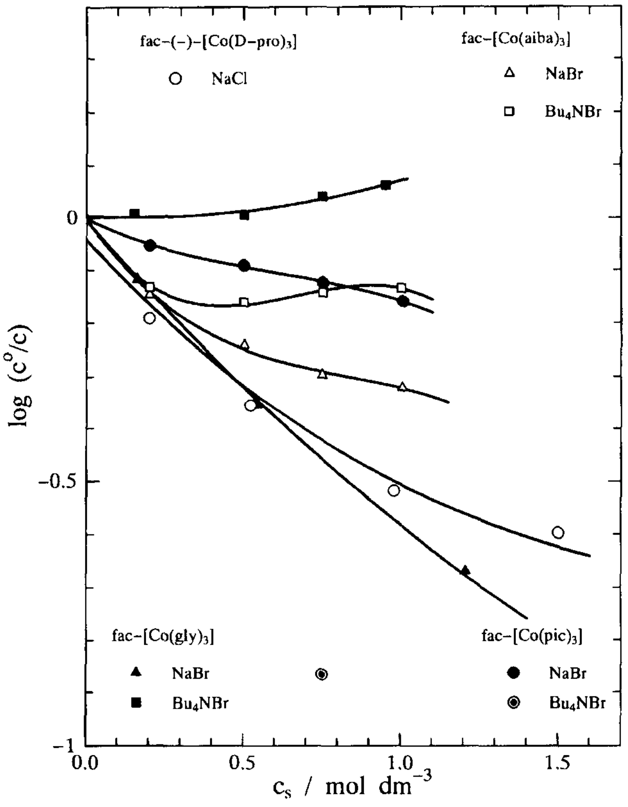

Fig. 4. Salt effect on some *fac*-[Co(aa)$_3$] and *fac*-[Co(pic)$_3$] depicted by plotting log (c^0/c) against c_s. The data for *fac*-(−)-[Co(D-pro)$_3$] in NaCl solutions and for *fac*-[Co(gly)$_3$] in NaBr solutions were taken from Refs. 6 and 7, respectively. The solid lines are tentatively drawn by fitting the log (c^0/c) values to power series of c_s.

In *fac*-[Co(aa)$_3$] three amino groups or carboxylato groups constitute a triangular face of an octahedron, while in *mer*-[Co(aa)$_3$] three amino or carboxylato groups are aligned on a meridian of an octahedron. A comparison of molecular models of the two isomers shows that the distances between the side chains of three amino acids in *fac*-[Co(aa)$_3$] are almost identical with each other, while in *mer*-[Co(aa)$_3$] the distance between the side chains of two amino acids, whose carboxylato groups are *trans*, is somewhat shorter. This suggests that in *mer*-[Co(aa)$_3$] the overlapping of the hydrophobic hydration shells around the side chains occurs. The overlapping may lower the hydrophobic interaction with Bu_4N^+ ion.

The data for *fac*-[Co(gly)$_3$] in the NaBr solutions and for *fac*-(−)-[Co(D-pro)$_3$] in the NaCl solutions construct a single linear correlation given by

$$\Delta_{tr}H^0 = 1.9\,T\Delta_{tr}S^0 - 4.3\ (\gamma = 0.975). \qquad (4)$$

Since the solubilities of *fac*-(+)-[Co(L-ala)$_3$] and *fac*-(+)-[Co(L-leu)$_3$] in water are extremely low, the effect of NaBr on extensive *fac*-[Co(aa)$_3$] could not be examined. Within the

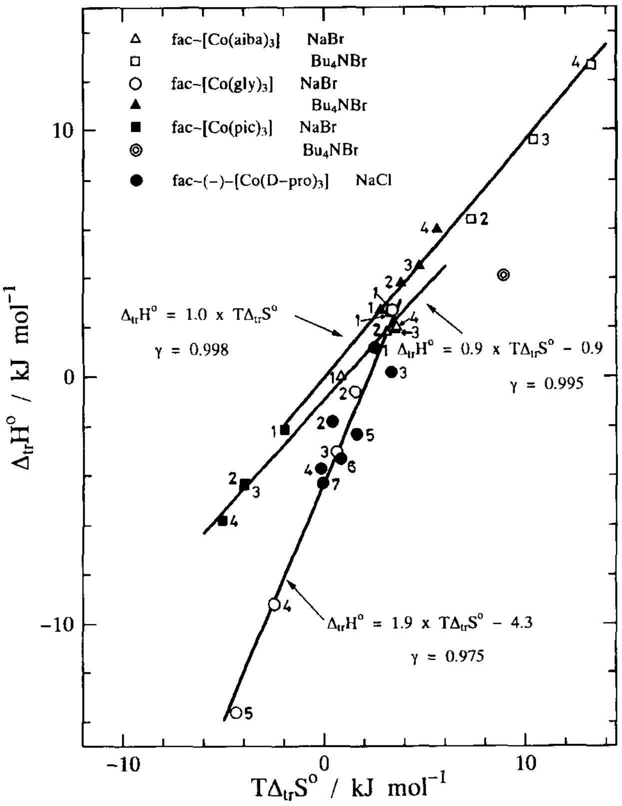

Fig. 5. Correlation between $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ for the transfer process of some *fac*-[Co(aa)$_3$] and *fac*-[Co(pic)$_3$] from water to aqueous salt solutions. The $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ values for the transfer of *fac*-(−)-[Co(D-pro)$_3$] to NaCl solutions and of *fac*-[Co(gly)$_3$] to NaBr solutions were calculated from the data reported in Refs. 6 and 7, respectively. The number given beside each mark represents increasing sequence of salt concentration m_s.

limited data, Eq. 4 indicates that the salting-in effect of NaBr on *fac*-[Co(gly)$_3$] is produced by the decreasing $\Delta_{tr}H^0$ with m_s, and that the larger decrease in $\Delta_{tr}H^0$ for *fac*-[Co(gly)$_3$] is responsible for the larger salting-in effect compared to *mer*-[Co(gly)$_3$] (see Figs. 2 and 4). The large decrease in $\Delta_{tr}H^0$ of *fac*-[Co(gly)$_3$] corresponds to strong hydrophilic interaction. This result may be attributed to the expectation that *fac*-[Co(gly)$_3$] has larger polarity than *mer*-[Co(gly)$_3$], because in *fac*-[Co(aa)$_3$] three polar groups such as carboxylato groups are *cis* to each other. This expectation is also supported by the fact that *fac*-[Co(aa)$_3$] is eluted later than *mer*-[Co(aa)$_3$] from the column of Florisil or alumina.

The data for the transfer of *fac*-[Co(aiba)$_3$] to NaBr solutions also seem to satisfy Eq. 4. On the other hand, these data may be also expressed by

$$\Delta_{tr}H^0 = 0.9T\Delta_{tr}S^0 - 0.9\ (\gamma = 0.995), \tag{5}$$

which is arranged by using the data of *fac*-[Co(pic)$_3$] also. At the present stage, it is difficult to establish which equation expresses the true correlation for the transfer process of *fac*-[Co(aiba)$_3$]. But the magnitude of the $\Delta_{tr}H^0$ and $T\Delta_{tr}S^0$ values for *fac*-[Co(aiba)$_3$] is much smaller than *fac*-[Co(gly)$_3$]. Accordingly, the conclusion that the activated α-carbon hydrogen enhances the interaction of *mer*-[Co(aa)$_3$] with surroundings seems to be valid for *fac*-[Co(aa)$_3$] also.

The data for the transfer of *fac*-[Co(pic)$_3$] to 0.97 mol kg^{-1} Bu$_4$NBr solution deviate from the corresponding correlation line for *fac*-[Co(aa)$_3$]. This deviation suggests that the nature of the hydrophobic interaction of *fac*-[Co(pic)$_3$] with Bu$_4$N$^+$ ion differs from the hydrophobic interaction of *fac*-[Co(aa)$_3$]. The difference in the nature of the hydrophobic interaction may be attributed to a distinction between the aromatic and the aliphatic groups. The synthesis of *mer*-[Co(pic)$_3$] was also attempted though the analytical data of the resulting chelate was not in accord with the theoretical values. At the present stage, a comparative conclusion for the salt effects on [Co(aa)$_3$] and [Co(pic)$_3$] cannot be yet given.

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