Optical Resolution Mechanism in an Optically Active Solvent or Cosolute in an Equilibrium State

Kazuaki Yamanari

Department of Chemistry, Faculty of Science, Osaka University, Toyonaka, Osaka 560, Japan

By crystallization of $\Delta\Lambda$-[Co(aet)(en)$_2$][ClO$_4$]$_2$ in the presence of Δ-Na[Co(edta)]·3H$_2$O or Na$_2$(D-tart)·2H$_2$O [aet = 2-aminoethanethiolate(1−), en = ethylenediamine, edta = ethylenediaminetetraacetate(4−) and D-tart = (*RR*)-tartrate(2−)] the Δ-aet complex always appears as the first crop. The mechanism can be best explained by use of a ternary solubility isotherm: a shift of the eutectic point on the central racemic line into the optically active region is caused by the active cosolute (or solvent); the larger the shift the higher is the percentage resolution. This isotherm has also clarified that the solubility difference between the enantiomers in the binary system is not relevant to the optical resolution. This resolution mechanism is applicable to conglomerates with rapid racemization rates.

A number of examples have been reported where crystallizations of racemates in optically active solvents or cosolutes led to partial optical resolution. Jacques *et al.*[1] have reviewed these resolutions and suggested that the results reflect the operation of a kinetic rather than an equilibrium phenomenon. Addadi *et al.*[2] have clarified systematically the kinetic optical resolutions of organic conglomerates with the assistance of 'tailor-made impurities'. The mechanism is based on stereoselective adsorption of a chiral additive and inhibition of crystal growth. Yamanari and Shimura[3] revealed that the same kinetic resolution mechanism also operates in metal complexes: some racemic conglomerates such as [Co(ox)(en)$_2$]Cl·4H$_2$O and [Co(acet)(en)$_2$][ClO$_4$]$_2$ (ox = oxalate, en = ethylenediamine; aet = 2-aminoethanethiolate) are resolved by direct crystallization in the presence of chiral additives [Co(glyO)(en)$_2$]Cl$_2$·H$_2$O and [Co(pyt)(en)$_2$][ClO$_4$]$_2$ (glyO = glycinate, pyt = pyridine-2-thiolate), respectively, which have the same kind of charge as the conglomerates to be resolved. Thus, the above mechanism can explain many resolutions in optically active solvents or cosolutes. However, no resolution mechanism under equilibrium conditions has been revealed experimentally.

In 1977 Muramoto and Shibata[4] reported a very interesting optical resolution of *cis*-Li[Co(CO$_3$)$_2$(NH$_3$)$_2$]. The Δ-lithium salt directly crystallized in 70% yield from a mixed aqueous solution of the racemic lithium salt and Δ-[Co(ox)(en)$_2$][CH$_3$CO$_2$]. The application of the above kinetic resolution mechanism to this system is impossible because the diastereoisomer was not formed and the chiral cosolute [Co(ox)(en)$_2$]$^+$ cannot be adsorbed on the crystals of the complex *cis*-[Co(CO$_3$)$_2$(NH$_3$)$_2$]$^-$. Therefore, another mechanism is needed to explain the resolution. Owing to the short half-life of racemization (*ca.* 3 min) of Δ- or Λ-*cis*-[Co(CO$_3$)$_2$(NH$_3$)$_2$]$^-$, a detailed mechanistic investigation is not easy using this system. The two pairs $\Delta\Lambda$-[Co(aet)(en)$_2$][ClO$_4$]$_2$–Δ-Na[Co(edta)]·3H$_2$O (edta = ethylenediaminetetraacetate) and $\Delta\Lambda$-[Co(aet)(en)$_2$][ClO$_4$]$_2$–Na$_2$(D-tart)·2H$_2$O (tart = tartrate(2−)] were chosen as such model systems, where both systems have enough inertness to protect the racemization and do not form any diastereoisomeric salt. In this paper the optical resolution and its mechanism for $\Delta\Lambda$-[Co(aet)(en)$_2$][ClO$_4$]$_2$ in the presence of a chiral cosolute Δ-Na[Co(edta)]·3H$_2$O or Na$_2$(D-tart)·2H$_2$O are described. The role of the optically active environmental material will be reported in detail and the resolution mechanism will be applied to other experiments.

Experimental

Preparation of Metal Complexes.—The following cobalt(III) complexes were prepared and resolved according to methods described in the literature: $\Delta\Lambda$-, Δ- and Λ-[Co(aet)(en)$_2$][ClO$_4$]$_2$;[5] $\Delta\Lambda$-, Δ- and Λ-Na[Co(edta)]·nH$_2$O (n = 4 for $\Delta\Lambda$, 3 for Δ and Λ);[6] $\Delta\Lambda$-*cis*-M[Co(CO$_3$)$_2$(NH$_3$)$_2$]·nH$_2$O (n = 0 for M = Li, 1 for M = K).[7] **CAUTION**: The solid aet perchlorate salt ignites in a Bunsen-burner flame or on contact with a hot surface, but presents no hazard in solution.

Estimation of Induced Circular Dichroism (CD) Contribution.—The molar absorption coefficients of [Co(aet)(en)$_2$]$^{2+}$ for the first d–d band region are almost constant in the concentration ranges of 1×10^{-4}–2×10^{-2} mol dm^{-3} Δ-Na[Co(edta)] or Na$_2$(D-tart). However, the CD spectrum is slightly affected by these cosolutes and the extent was examined in each case.

In the case of Δ-Na[Co(edta)]·3H$_2$O, the differential CD (ICD) between a solution A ($\Delta\Lambda$-aet, 3.5×10^{-2} mol dm^{-3}; Δ-edta, 1.75×10^{-2} mol dm^{-3}) and a solution B (Δ-edta, 1.75×10^{-2} mol dm^{-3}) was measured using a 1 mm quartz cell. The ICD contains two contributions: ICD (Λ-aet + Δ-edta) and ICD (Δ-aet + Δ-edta). Another differential CD spectrum between a solution C (Λ-aet, 1.75×10^{-2} mol dm^{-3}; $\Delta\Lambda$-edta, 3.5×10^{-2} mol dm^{-3}) and a solution D (Λ-aet, 1.75×10^{-2} mol dm^{-3}) was obtained. This ICD contains also two contributions: ICD (Λ-aet + Δ-edta) and ICD (Λ-aet + Λ-edta). Since ICD (Δ-aet + Δ-edta) is equal to −ICD (Λ-aet + Λ-edta), the contributions ICD (Λ-aet + Δ-edta) and ICD (Δ-aet + Δ-edta) can be obtained from half of the addition and the subtraction of the two ICD spectra, respectively. Fig. 1 shows these induced CD spectra. The contribution due to a (Δ-aet + Δ-edta) ion pair is somewhat larger than that due to a (Λ-aet + Δ-edta) ion pair. Thus, the $\Delta\varepsilon$ values of the Δ and Λ enantiomers at 510 nm, which were used to determine the Δ/Λ ratio of [Co(aet)(en)$_2$]$^{2+}$, became 3 and 0.7% lower than the authentic value [$|\Delta\varepsilon\ (510\ \text{nm})| = 1.22$], respectively, because of the induced CD contributions. The actual CD measurements of the ternary isotherm were carried out in the concentration ranges 2×10^{-3}–6×10^{-3} mol dm^{-3} of the aet and edta complexes. The induced CD spectra are almost negligible in such concentrations because the contributions were one-third of the above values.

In the case of Na$_2$(D-tart)·2H$_2$O the $\Delta\varepsilon$ values of [Co(aet)(en)$_2$]$^{2+}$ ($c = 5.504 \times 10^{-3}$ mol dm^{-3}) were examined in the

Table 1 Optical resolution of ΔΛ-$[Co(aet)(en)_2][ClO_4]_2$ in the presence of a chiral cosolute

Experiment	Chiral cosolute	Amount*	e.e. configuration [yield (%)] First crop	e.e. configuration [yield (%)] Second crop
1	Δ-$Na[Co(edta)]\cdot 3H_2O$	5	30 Δ (7)	
2	Δ-$Na[Co(edta)]\cdot 3H_2O$	5	15 Δ (17)	
3	Δ-$Na[Co(edta)]\cdot 3H_2O$	5	7 Δ (33)	
4	Δ-$Na[Co(edta)]\cdot 3H_2O$	5	4 Δ (50)	
5	Δ-$Na[Co(edta)]\cdot 3H_2O$	25	43 Δ (3)	10 Λ (8)
6	Δ-$Na[Co(edta)]\cdot 3H_2O$	25	61 Δ (12)	
7	Δ-$Na[Co(edta)]\cdot 3H_2O$	25	23 Δ (13)	9 Λ (34)
8	Δ-$Na[Co(edta)]\cdot 3H_2O$	25	3 Δ (44)	
9	Δ-$Na[Co(edta)]\cdot 3H_2O$	42	98 Δ (4)	13 Λ (44)
10	Δ-$Na[Co(edta)]\cdot 3H_2O$	42	27 Δ (27)	88 Λ (7)
11	Δ-$Na[Co(edta)]\cdot 3H_2O$	42	16 Δ (33)	84 Λ (8)
12	Na_2(D-tart)·$2H_2O$	100	13 Δ (6)	2 Λ (25)
13	Na_2(D-tart)·$2H_2O$	100	6 Δ (11)	11 Λ (2)
14	Na_2(D-tart)·$2H_2O$	100	3 Δ (26)	46 Λ (14)

* In mg of chiral cosolute per 100 mg of ΔΛ-$[Co(aet)(en)_2][ClO_4]_2$.

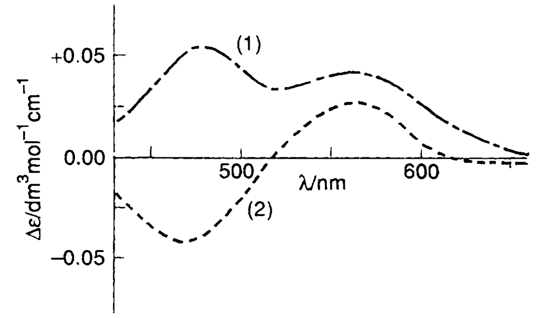

Fig. 1 Calculated induced circular dichroism (ICD) spectra of Δ- and Λ-$[Co(aet)(en)_2][ClO_4]_2$ in Δ-$Na[Co(edta)]$ (concentrations: ΔΛ-aet, 3.5×10^{-2}; Δ-edta, 1.75×10^{-2} mol dm^{-3}): (1) ICD (Δ-aet + Δ-edta); (2) ICD (Λ-aet + Δ-edta)

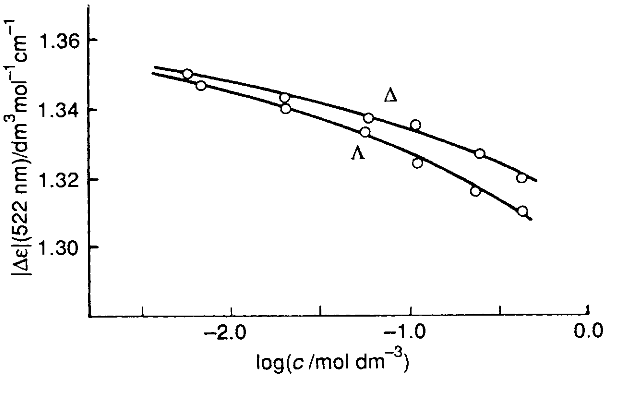

Fig. 2 Plots of Δε of Δ- and Λ-$[Co(aet)(en)_2][ClO_4]_2$ (c = 5.504×10^{-3} mol dm^{-3}) at 522 nm in Na_2(D-tart) aqueous solution

concentration range 5.8×10^{-3}–4.4×10^{-1} mol dm^{-3} of Na_2(D-tart). The absolute values of the enantiomers decreased with increasing Na_2(D-tart) concentration as shown in Fig. 2: the decrements are 1.5% for the Δ enantiomer and 2.5% for the Λ one near 2×10^{-2}–4×10^{-2} mol dm^{-3}, the concentration range used in the measurements of the ternary isotherm described below. The pair ΔΛ-aet and Na_2(D-tart) showed a negative induced CD spectrum in the first d–d absorption band region. This is in agreement with the larger CD contribution due to a [Λ-aet + Na_2(D-tart)] ion pair.

Optical Resolutions of ΔΛ-$[Co(aet)(en)_2][ClO_4]_2$ *in Optically Active Cosolutes.*—The general resolution procedure is as follows. The complex ΔΛ-$[Co(aet)(en)_2][ClO_4]_2$ (500 mg) was dissolved in an aqueous solution containing an optically active cosolute, Δ-$Na[Co(edta)]$ or Na_2(D-tart). The mixture was kept standing at room temperature (*ca.* 22 °C). After partial crystallization of the aet complex, the solution was decanted and the crystals were washed with a small amount of water and dried on filter-paper. These crystals were redissolved in water, and the crystal yield and enantiomeric excess (e.e.) were determined from the absorption and CD spectra of the solution. In both systems the partially active aet complex crystallized directly without forming any diastereoisomeric salt. The results are collected in Table 1 and the plots of the e.e. of the first crop against crystal yield in the system ΔΛ-$[Co(aet)(en)_2][ClO_4]_2$–Δ-$Na[Co(edta)]\cdot 3H_2O$ are shown in Fig. 3.

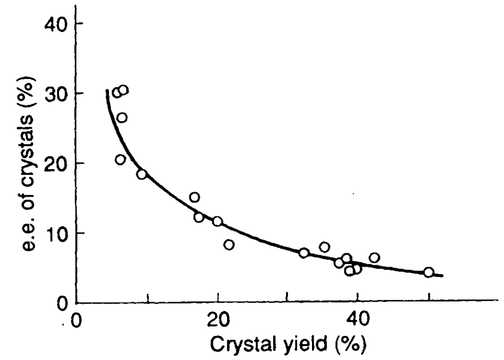

Fig. 3 Plots of the enantiomeric excess of the first crop against the crystal yield in the system ΔΛ-$[Co(aet)(en)_2][ClO_4]_2$–Δ-$Na[Co(edta)]\cdot 3H_2O$. Amount of a chiral cosolute: 5 mg per 100 mg of ΔΛ-$[Co(aet)(en)_2][ClO_4]_2$

Determination of Ternary Isotherms in Optically Active Cosolutes.—Ternary solubility isotherms were determined in two systems, Δ-$[Co(aet)(en)_2][ClO_4]_2$–Λ-$[Co(aet)(en)_2][ClO_4]_2$–4.5% Δ-$Na[Co(edta)]$ (aqueous solution) and Δ-$[Co(aet)(en)_2][ClO_4]_2$–Λ-$[Co(aet)(en)_2][ClO_4]_2$–15% Na_2(D-tart) (aqueous solution), at 25 °C. These systems are considered approximately as ternary ones because the active cosolute Δ-$Na[Co(edta)]\cdot 3H_2O$ or Na_2(D-tart)·$2H_2O$ does not crystallize with the aet complex in both systems and can be treated as an optically active solvent. Solubility in water was determined in % w/w. A saturated solution was weighed and diluted with water to a certain volume. Optical densities and CD spectra were measured under the calibrated conditions described above.

In the Δ-$Na[Co(edta)]\cdot 3H_2O$ system the concentrations of the aet and edta complexes were determined from the two

Table 2 Solubility (in % w/w of anhydrous salt) in the ternary system Δ-[Co(aet)(en)$_2$][ClO$_4$]$_2$–Λ-[Co(aet)(en)$_2$][ClO$_4$]$_2$–X at 25 °C. Abbreviations: Δ-[Co(aet)(en)$_2$][ClO$_4$]$_2$ = [Δ] and Λ-[Co(aet)(en)$_2$]-[ClO$_4$]$_2$ = [Λ]

X	Position of point*	Liquid phase (% w/w)		Solid phase
		[Δ]	[Λ]	
Water	D	8.05	0	[Δ]
		7.68	0.89	[Δ]
		7.36	1.76	[Δ]
		6.95	2.67	[Δ]
		6.32	4.59	[Δ]
	↓	6.08	5.70	[Δ]
	C	5.97	5.97	[Δ] + [Λ]
4.5% Δ-Na[Co(edta)] aqueous solution	E	0	10.0	[Λ]
		1.70	9.21	[Λ]
		2.49	9.18	[Λ]
	↓	4.98	8.22	[Λ]
	F	6.87	7.47	[Λ] + [Δ]
	H	10.3	0	[Δ]
		9.18	2.32	[Δ]
		8.43	3.67	[Δ]
		8.27	4.26	[Δ]
	↓	7.87	5.09	[Δ]
	F	6.87	7.47	[Δ] + [Λ]
15% Na$_2$(D-tart) aqueous solution	B′	0	8.34	[Λ]
		1.97	7.02	[Λ]
	↓	3.43	6.38	[Λ]
	C′	5.32	5.65	[Λ] + [Δ]
	E′	8.26	0	[Δ]
		6.43	3.29	[Δ]
	↓	5.92	4.47	[Δ]
	C′	5.32	5.65	[Δ] + [Λ]

* Positions of the points in Fig. 4.

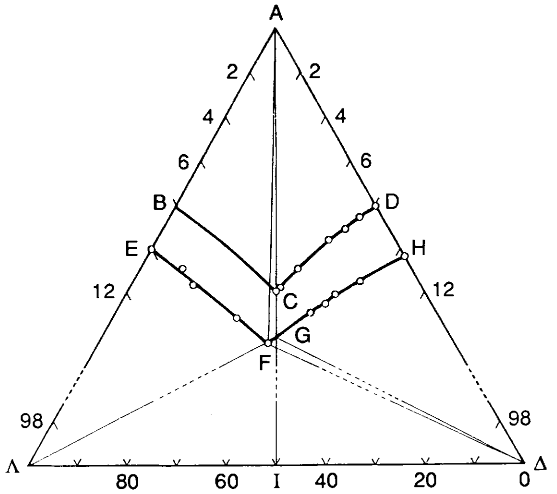

Fig. 4 The ternary isotherm (% w/w) of Δ-[Co(aet)(en)$_2$][ClO$_4$]$_2$ (abbreviated Δ)–Λ-[Co(aet)(en)$_2$][ClO$_4$]$_2$ (abbreviated Λ)–A {water or 4.5% Δ-Na[Co(edta)]} (aqueous solution) at 25 °C

absorbances at 534 ($\varepsilon_{edta} = 320$, $\varepsilon_{aet} = 77.0$) and 482 nm ($\varepsilon_{edta} = 138$, $\varepsilon_{aet} = 144$ dm^3 mol^{-1} cm^{-1}). The Δ/Λ ratio of the aet complex was obtained by subtracting the edta contribution from the total CD intensity at 510 nm ($\Delta\varepsilon_{aet} = \pm 1.22$, $\Delta\varepsilon_{edta} = +0.754$). The induced CD contribution is negligible at concentrations of the order of 10^{-3} mol dm^{-3}, but in the eutectic this contribution is measured by reconstituting the eutectic composition from the racemic aet complex and Δ-Na[Co(edta)]·3H$_2$O. The original concentration of the Δ-edta complex was 4.18% and the measured concentrations were 4.40–4.67% in the ternary system, which means the spontaneous evaporation of *ca.* 7% of water during the measurements. The position of the eutectic was also determined in 11.6% Δ-Na[Co(edta)] aqueous solution. The e.e. values are 4.2 and 7.1% Λ in 4.5 and 11.6% Δ-Na[Co(edta)] solution, respectively. The results are shown in Table 2 and Fig. 4.

In the Na$_2$(D-tart)·2H$_2$O system the concentration of the aet complex was determined from the absorbance at 482 nm because the effect of Na$_2$(D-tart) on the molar absorption coefficient is negligible in the measured concentration ranges. The Δ/Λ ratio was determined by referring to the calibrated Δε values at 522 nm [$\Delta\varepsilon(\Delta) = -1.33$ and $\Delta\varepsilon(\Lambda) = +1.32$]. In the eutectic the induced CD contribution was measured by reconstituting the eutectic composition from the racemic aet complex and Na$_2$(D-tart). The initial concentration of Na$_2$(D-tart) was 14.4% but the actual concentration is estimated as 15.3% by considering the spontaneous evaporation of water during the measurements. The results are shown in Table 2.

Conglomerate Crystallization of cis-Li[Co(CO$_3$)$_2$(NH$_3$)$_2$].—A saturated aqueous solution of the racemic lithium salt was kept standing in a refrigerator for 1 d to give columnar crystals. Circular dichroism measurements were carried out for an aqueous solution of each crystal and the enantiomeric CD patterns were observed, which indicates the conglomerate crystallization of *cis*-Li[Co(CO$_3$)$_2$(NH$_3$)$_2$]. The same experiment was done for the potassium salt but the crystals did not show any CD spectrum.

Spectral Measurements.—The absorbances were measured with a Hitachi 330 spectrophotometer and the CD spectra with a JASCO J-500 spectropolarimeter.

Results and Discussion

Optical Resolution of ΔΛ-[Co(aet)(en)$_2$][ClO$_4$]$_2$.—The optical resolutions of ΔΛ-[Co(aet)(en)$_2$][ClO$_4$]$_2$ were performed in the presence of a chiral cosolute Δ-Na[Co(edta)]·3H$_2$O or Na$_2$(D-tart). The results are shown in Table 1. With Δ-Na[Co(edta)]·3H$_2$O the Δ-rich aet complex always crystallizes first and each second crop shows the opposite absolute configuration. High enantiomeric excesses are observed in cases of low crystal yields because prolonged crystallization induces the coappearance of crystals having the opposite absolute configuration. Fig. 3 shows the plots of the enantiomeric excesses of the first crops against the crystal yields. The resolution percentages gradually decrease with increasing crystal yield, but it should be noted that the configuration of the first crystals is always Δ irrespective of the crystal yield. Table 1 also shows that the resolution percentages clearly increase in proportion to the quantity of the chiral cosolute Δ-Na[Co(edta)]·3H$_2$O.

With Na$_2$(D-tart)·2H$_2$O the Δ-rich crystals appear as the first crop, too. However, the enantiomeric excesses are relatively lower compared with the above system even though the concentration of Na$_2$(D-tart)·2H$_2$O is considerably higher. This means that Δ-Na[Co(edta)]·3H$_2$O is a more efficient chiral cosolute than is Na$_2$(D-tart)·2H$_2$O in the optical resolution of ΔΛ-[Co(aet)(en)$_2$][ClO$_4$]$_2$.

Resolution Mechanism.—To clarify the above resolution mechanism, the binary solubilities of Δ- or Λ-[Co(aet)(en)$_2$]-[ClO$_4$]$_2$ in 100 g of 4.5% Δ-Na[Co(edta)] aqueous solution were measured. The values are 11.5 g for the Δ enantiomer and 11.1 g for the Λ. This is contradictory to the above resolutions because the more soluble Δ enantiomer always crystallizes as the first crop.

The ternary isotherms were measured in the two systems Δ-[Co(aet)(en)$_2$][ClO$_4$]$_2$–Λ-[Co(aet)(en)$_2$][ClO$_4$]$_2$–4.5% Δ-Na[Co(edta)] (aqueous solution) and Δ-[Co(aet)(en)$_2$]-[ClO$_4$]$_2$–Λ-[Co(aet)(en)$_2$][ClO$_4$]$_2$–15% Na$_2$(D-tart) (aqueous solution) at 25 °C. Fig. 4 shows the isotherms in the absence and presence of Δ-Na[Co(edta)]·3H$_2$O. The line AI represents the

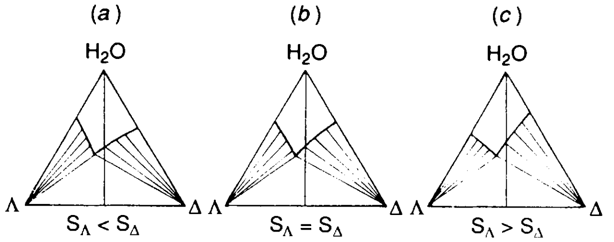

Fig. 5 Proposed ternary isotherms which can explain the first appearance of the Δ enantiomer in the system *cis*-Li[Co(CO_3)$_2$-(NH_3)$_2$]–Δ-[Co(ox)(en)$_2$][CH_3CO_2]

racemic composition. In the absence of a chiral cosolute, the isotherm of Δ- and Λ-[Co(aet)(en)$_2$][ClO_4]$_2$ consists of two solubility curves BC and CD. Since there is no isotherm corresponding to a racemic compound, the aet complex shows the conglomerate crystallization. The eutectic C is located on the line AI, the isotherm being symmetrical.

On the other hand, the existence of a chiral cosolute changes this symmetrical nature. That is, in the presence of 4.5% Δ-Na[Co(edta)], the solubilities of the Δ- and Λ-aet complex increase by 35 and 31%, respectively, and the solubility of the ΔΛ-aet complex increases by *ca.* 25%. The isotherm becomes EFGH and the eutectic point F is shifted into the Λ-region. In optical resolution an unsaturated racemic solution is concentrated along the line AI and reaches the point G. At this point the saturated solution is in equilibrium with the solid of the Δ enantiomer and therefore the Δ-aet complex always crystallizes as the first crop irrespective of its higher solubility in the binary system. After the appearance of the Δ enantiomer, the liquid composition moves along the line GF and finally reaches the point F where both enantiomers will appear simultaneously. Since the GF interval is considerably short, only partial resolution is possible. It should be noted that the binary solubility difference between two enantiomers (points E and H) is irrelevant to optical resolution and the shifting of the eutectic into the Λ region is the essential origin of the first appearance of the Δ cryatals.

The data for Δ-[Co(aet)(en)$_2$][ClO_4]$_2$–Λ-[Co(aet)(en)$_2$]-[ClO_4]$_2$–15% Na_2(D-tart) (solution) at 25 °C are summarized in Table 2. The solubilities of the Δ- and Λ-aet complexes increase by 17–18%, while the solubility of the ΔΛ-aet one increases only by 1.5%. The isotherm B′C′D′E′ becomes more flat and also unsymmetrical compared with the original isotherm BCD in Fig. 4. The eutectic C′ is not on the racemic line A′F′ and is located in the Λ region. In resolution, the Δ-aet complex crystallizes as the first crop in this system, too. These are the first isotherms to demonstrate the shifted eutectic of the conglomerate system experimentally.

Amaya[8] has theoretically shown that the solubilities of enantiomers differ from each other in an optically active solvent or cosolute and there have been many experiments designed to reveal such solubility differences.[1] However, it must be emphasized that such a solubility difference cannot be related to optical resolution. Apparent resolution is carried out along the central racemic line in a ternary isotherm and never along the side axes which represent a binary system.

Resolution Efficiency.—As stated above the percentage resolutions of the aet complex are higher in 4.5% Δ-Na[Co(edta)] solution than those in 15% Na_2(D-tart) solution. This is relevant to the extent of shift of the eutectic point from the central racemic line: the e.e. of the eutectic is 4.2% for the former system and 3.0% for the latter. In 11.6% Δ-Na[Co(edta)] solution the eutectic composition becomes 7.1% Λ-rich. These facts indicate that the extent of shift of the eutectic depends upon the properties and quantity of the chiral cosolute. A superior chiral cosolute means the induction of a larger eutectic shift. Monosodium (*S*)-glutamate monohydrate was also examined as a chiral cosolute but no shift of the eutectic in the aet complex was observed.

Application of the Present Resolution Mechanism to Other Resolutions.—Muramoto and Shibata[4] have directly obtained Δ-lithium crystals in 70% yield from a mixture of ΔΛ-*cis*-Li[Co(CO_3)$_2$(NH_3)$_2$] and Δ-[Co(ox)(en)$_2$][CH_3CO_2], and reported that the solubilities of the racemic, Λ-, and Δ-Li[Co(CO_3)$_2$(NH_3)$_2$] in 0.2 mol dm^{-3} Δ-[Co(ox)(en)$_2$]-[CH_3CO_2] aqueous solution are approximately 0.35, 0.26 and 0.24 mol dm^{-3}, respectively. They concluded that the lower solubilities of the active salts than that of the racemate, the different solubilities between the enantiomeric salts, and the rapid racemization of the enantiomers are responsible for the above phenomemon. Their interpretation, however, seems to be a little questionable. First, the short half-life of racemization (*ca.* 3 min) reduces the reliability of the solubility data. Secondly, they cannot explain that the above resolution is only possible in the lithium salt but impossible in the sodium and potassium salts.

I examined the crystallization types of the racemic lithium and potassium salts: the crystals grown from the racemic lithium salt showed enantiomeric CD spectra and therefore the salt forms a conglomerate, whereas the potassium salt did not show any CD spectrum and seems to be a racemic compound. Three kinds of ternary isotherms (Fig. 5) are proposed. All isotherms can explain the first appearance of the Δ enantiomer irrespective of the binary solubility relationship and isotherm (*c*) corresponds to the above system by considering their solubility measurements. The eutectic point of the lithium salt exists in the Λ region owing to the effect of the chiral cosolute Δ-[Co(ox)(en)$_2$][CH_3CO_2]. In resolution, the saturated solution is in equilibrium with the Δ enantiomer and the Δ complex will appear first. Rapid racemization of the system would keep the solution composition always racemic. Thus, even a small dissymmetry could account for the 70% crystal yield of the Δ-lithium salt. In the case of the potassium salt the saturated solution is in equilibrium with the racemic compound and therefore this kind of resolution would be impossible. It is thought that the present resolution mechanism is especially effective for the conglomerate with a rapid racemization rate. In such a system, high enantiomeric excess and high yield will be achieved.

In conclusion, two conditions are necessary for successful optical resolution in an optically active cosolute (or solvent) in an equilibrium state. First, the complex to be resolved shows conglomerate crystallization. Since the shifting of the eutectic by a chiral cosolute is at best 10% e.e., this resolution mechanism cannot be applied to most racemic compounds. Secondly, a shift of the eutectic of the conglomerate on the racemic line into the optically active region caused by a chiral cosolute is necessary: larger shifts give higher resolutions.

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