Temperature-dependent Conglomerate Crystallization of Carbonatobis(ethylenediamine)cobalt(III) Bromide and Its Application to Kinetic Optical Resolution†

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The binary and ternary solubility diagrams of $[Co(CO_3)(en)_2]Br$ (en = ethylenediamine) have been determined at 5–70 °C. It was found that the bromide exists as a racemic compound dihydrate below 15.0 °C and as an anhydrous conglomerate above this temperature. The conglomerate is kinetically resolved by crystallization in the presence of chiral additives, Δ-$[Co(glyO)(en)_2]Br_2$ (glyO = glycinate) and Λ-$[Co(ox)(en)_2]Br$ (ox = oxalate), at room temperature. The same resolutions utilizing racemization of $[Co(CO_3)(en)_2]Br$ were also attempted at 40 °C.

As a special method of optical resolution, conglomerates can be optically resolved with the assistance of 'tailor-made impurities'.[1] The mechanism is based on stereoselective adsorption of a chiral additive and inhibition of crystal growth. We applied this method to optical resolution of $M'X$ and $M'X_2$ type metal complexes where M' and X denote a racemic complex and its counter ion, respectively.[2] For example, in the presence of a small amount of Λ-$[Co(glyO)(en)_2]Cl_2$ (glyO = glycinate, en = ethylenediamine), the additive is adsorbed on the Λ crystals of $[Co(ox)(en)_2]Cl$ (ox = oxalate) and inhibits their crystal growth, leading to different crystallization rates, $k_\Delta > k_\Lambda$. Therefore, the enantiomer Δ-$[Co(ox)(en)_2]Cl$ having the opposite absolute configuration to that of the chiral additive crystallizes first in excess. Such resolutions are effective in a dozen cobalt(III) complex systems.[2] In other words, this resolution procedure becomes a useful criterion to know whether the complex to be resolved crystallizes as a conglomerate or a racemic compound because only conglomerates showed relatively high enantiomeric excesses.

Preliminary experiments showed that the bromide of $[Co(CO_3)(en)_2]^+$ is effectively resolvable by this procedure. Therefore, the binary and ternary solubility phase diagrams have been reinvestigated at various temperatures,[3] and the above kinetic resolution experiments utilizing racemization of $[Co(CO_3)(en)_2]Br$ at 40 °C, the second-order asymmetric transformation, in addition to ones at room temperature, attempted.

Experimental

Preparations of Metal Complexes.—The following cobalt(III) complexes used in this study were prepared and/or resolved according to the methods described in the literature and were converted into the desired salts on a QAE-Sephadex A-25 column: $\Delta\Lambda$-, Δ- and Λ-$[Co(CO_3)(en)_2]Br$,[4] -$[Co(ox)(en)_2]Br$;[5] -$[Co(en)_3]X_3$ (X = Cl or Br),[6] -$[Co(glyO)(en)_2]X_2$ (X = Cl or Br),[7,8] and -$[Co(NO_2)_2(en)_2]Br$.[9]

Solubility Measurements.—The solubilities of complexes in water were determined as previously reported:[3,10] weighed saturated solutions were diluted with water to a certain volume. The solubility was determined on the basis of the optical density and circular dichroism (CD) spectrum. The binary and ternary values in weight (%) are presented in SUP 56847. The solid phases were identified by elemental analysis, infrared, absorption and CD spectra and X-ray powder diffraction patterns. The absorbances were measured with a Hitachi 330 spectrophotometer and the CD spectra with a JASCO J-500 spectropolarimeter. X-Ray powder diffraction was recorded on a Rigaku model RAD-ROC instrument at the X-Ray diffraction Service of the Department of Chemistry, using Cu-Kα radiation.

Resolution of Metal Complexes with the Assistance of Chiral Additives.—The racemic bromide $[Co(CO_3)(en)_2]Br$ and a small amount of a chiral additive were dissolved in an appropriate amount of water. The mixed solution was allowed to stand at room temperature (*ca.* 22 °C). After partial crystallization of the bromide, the solution was decanted and the crystals were dried on filter-paper. All crystals were redissolved in water, and the crystal yield and enantiomeric excess (e.e.) were determined by measuring the absorption and CD spectra of the solution. The results are collected in Table 1.

Racemization-crystallization Experiments.—A mixed solution of the racemic bromide and a chiral additive was allowed to stand at 40 °C. After crystallization of most of the carbonato complex, spontaneous evaporation was stopped. The crystals obtained were redissolved in water, and the amount and e.e. were determined by absorption and CD spectral measurements. In the system Δ- or Λ-$[Co(glyO)(en)_2]X_2$ (X = Cl or Br), the solution of the racemic bromide and the chiral additive was allowed to evaporate to dryness at 35 or 40 °C. The residue redissolved in water was chromatographed on a column of SP-Sephadex C-25 and then the optical purity of $[Co(CO_3)(en)_2]Br$ was determined. In this case, the recovery of the starting carbonato complex was complete. The results are collected in Table 2.

Results and Discussion

Fig. 1 shows the binary solubility curves at 5–70 °C; the curves of the enantiomer above 35 °C cannot be determined because of the racemization. The racemate shows polymorphism: it exists as a dihydrate below 15 °C and an anhydrate above 15 °C. The enantiomer exists as an anhydrate over the entire measured region 5–35 °C. We previously clarified that the racemate crystallizes as a conglomerate, when the solubility of the racemate is $\geqslant 2^{\frac{1}{2}}$ times larger than that of the pure enantiomer in a $M'X$ type metal complex.[3] The ratio of the solubilities of the anhydrous racemate and the enantiomer $S_{\Delta\Lambda}:S_\Delta$ is 1.55:1 at

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† *Supplementary data available* (No. SUP 56847, 6 pp): solubility data. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1991, Issue 1, pp. xviii–xxii.

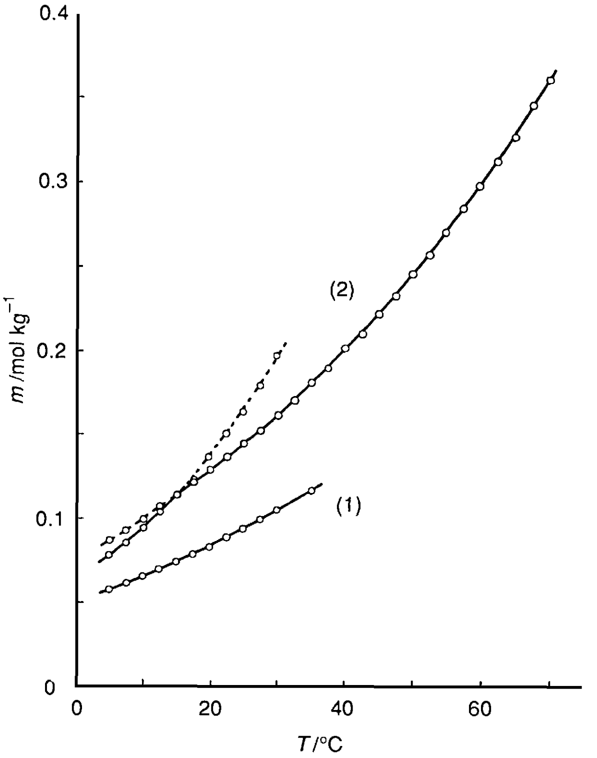

Fig. 1 Solubility curves, where solubility is presented in molality *m* of anhydrous salt: (1) Δ-$[Co(CO_3)(en)_2]Br$ and (2) ΔΛ-$[Co(CO_3)(en)_2]Br{\cdot}nH_2O$, $n = 2$ ($\leqslant$15.0 °C) or 0 ($\geqslant$15.0 °C)

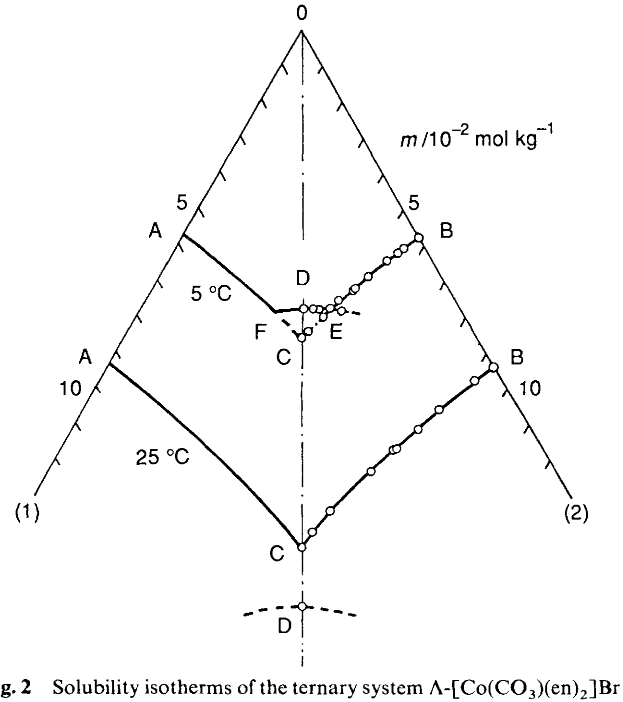

Fig. 2 Solubility isotherms of the ternary system Λ-$[Co(CO_3)(en)_2]Br$ (1)–Δ-$[Co(CO_3)(en)_2]Br$ (2)–water, at 5.0 and 25.0 °C. -----, Metastable state

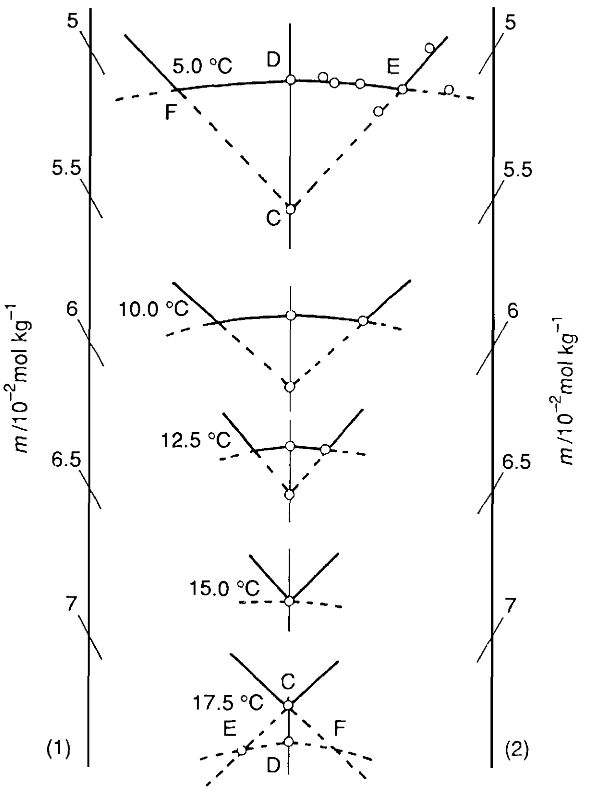

Fig. 3 Temperature dependence of the invariant points, C, E and F, and the point D corresponding to the racemic compound in the ternary isotherm. ----, Metastable state

20 °C and 1.54:1 at 35 °C and therefore the present system satisfies the above condition. To confirm the conglomerate crystallization, the racemic bromide was crystallized at 21 and 60 °C. Each aqueous solution of one crystal at both temperatures showed a CD spectrum. The optical purities were between 0.3 and 31% of the pure enantiomer. The infrared spectrum of the anhydrous racemate was the same as that of the pure enantiomer. The same situation was found in the X-ray powder patterns. Thus, it is concluded that the racemate forms a racemic compound below 15 °C and a conglomerate above this temperature as a stable phase.

These results were supported by the ternary solubility diagrams at 5 and 25 °C shown in Fig. 2. At 5 °C the racemic compound corresponding to the line FDE is a stable phase in equilibrium because there are two invariant points F and E, and the conglomerate corresponding to point C appears only as a metastable state. On the other hand, the situation is reversed at 25 °C: the conglomerate becomes a stable phase and the racemic compound corresponding to point D is a metastable state. Thus, the temperature-dependent conglomerate crystallization is confirmed for the present $[Co(CO_3)(en)_2]Br$ system by the binary and ternary solubility phase diagrams. This is extremely rare in metal complexes and the only precedent is $[Co(glyO)(en)_2]SO_4$.[7]

The temperature for transition of the racemic compound to the conglomerate can be determined more accurately using the ternary isotherms. Fig. 3 shows only the central part of the ternary diagrams at various temperatures. The range of the line FDE showing the racemic compound dihydrate at 5.0 °C gradually diminishes with increasing temperature and is finally superimposed on the point C representing the anhydrous conglomerate at 15.0 °C. This temperature corresponds to the intersection between the dihydrate and the anhydrate in the binary system. Above it the line FDE appears only as a metastable state as shown in the isotherm at 17.5 °C.

The racemic compound dihydrate easily effloresces to the anhydrate in air. This anhydrate is clearly different from the anhydrous conglomerate, as is confirmed by their infrared spectra and X-ray powder patterns.

Kinetic Optical Resolution.—Since the present complex $[Co(CO_3)(en)_2]Br$ forms a conglomerate above 15.0 °C, kinetic optical resolution by a chiral additive which is stereochemically similar to one enantiomer of the conglomerate to be resolved is possible. Table 1 shows the results of such resolution experiments. We found that two kinds of chiral additives,

Table 1 Resolution of $\Delta\Lambda$-$[Co(CO_3)(en)_2]Br$ in the presence of a chiral additive[a]

Experiment	Chiral additive	Amount[b]	e.e. (%)	Configuration	Yield (%)
1	Λ-$[Co(ox)(en)_2]Br$	0.4	3.7	Δ	35
2	Λ-$[Co(ox)(en)_2]Br$	0.8	6.1	Δ	33
3	Λ-$[Co(ox)(en)_2]Br$	2	12	Δ	22
4	Δ-$[Co(ox)(en)_2]Br$	2	29	Λ	17
5	Λ-$[Co(ox)(en)_2]Br$	4	59	Δ	17
6	Δ-$[Co(glyO)(en)_2]Br_2$	2	27	Λ	18
7	Δ-$[Co(glyO)(en)_2]Br_2$	5	37	Λ	18
8	Δ-$[Co(glyO)(en)_2]Br_2$	5	27	Λ	22
9	Δ-$[Co(glyO)(en)_2]Br_2$	5	21	Λ	29
10	Δ-$[Co(glyO)(en)_2]Br_2$	5	2	Λ	51

[a] Crystallization was performed by allowing the solution to stand at room temperature for 1–3 d. [b] In mg of additive per 100 mg of $\Delta\Lambda$-$[Co(CO_3)(en)_2]Br$.

Table 2 Second-order asymmetric transformation of $\Delta\Lambda$-$[Co(CO_3)(en)_2]Br$ in the presence of a chiral additive

Experiment	Chiral additive	Amount*	T/°C	Crystallization time/d	e.e. (%)	Configuration	Yield (%)
1	Λ-$[Co(ox)(en)_2]Br$	4	40	2	6.2	Δ	81
2	Λ-$[Co(glyO)(en)_2]Cl_2$	4	40	2	4.6	Δ	82
3	Δ-$[Co(glyO)(en)_2]Br_2$	16	35	3	4.5	Λ	100
4	Δ-$[Co(glyO)(en)_2]Br_2$	20	40	2	6.1	Λ	100
5	Δ-$[Co(glyO)(en)_2]Br_2$	40	40	2	7.1	Λ	100
6	Δ-$[Co(glyO)(en)_2]Br_2$	75	35	3	11	Λ	100

* In mg of additive per 100 mg of $\Delta\Lambda$-$[Co(CO_3)(en)_2]Br$.

Δ (or Λ)-$[Co(ox)(en)_2]Br$ and -$[Co(glyO)(en)_2]Br_2$, are very effective. These systems show relatively high e.e. It should be noted that the absolute configuration of the first crop is always opposite to that of the chiral additive and even a small amount of chiral additive works effectively. We previously showed that a high e.e. is obtained when the first crystal yield is kept below *ca.* 15% because the second crop having the opposite absolute configuration to that of the first crop will appear at *ca.* 15–35% crystal yield and compensates the optical purity of the first crop.[2] The best e.e. of $[Co(CO_3)(en)_2]Br$ is 59% Δ (17% yield) in the case of Λ-$[Co(ox)(en)_2]Br$ as a chiral additive, and 37% Λ (18% yield) in the case of Δ-$[Co(glyO)(en)_2]Br_2$.

Second-order Asymmetric Transformation.—In contrast to most resolutions, which employ low temperature to keep racemization to a minimum, the technique of second-order asymmetric transformation involves warming the solution during crystallization in order to induce racemization. The present carbonato complex Δ (or Λ)-$[Co(CO_3)(en)_2]Br$ racemizes with a moderate rate above 35 °C without decomposition. The half-life of racemization is $t_{\frac{1}{2}} = 3.6$ h at 40 °C under neutral conditions. Therefore, when the above kinetic resolution is carried out in 2 or 3 d at 40 °C, the combination of racemization-crystallization is realized, leading to the second-order asymmetric transformation. The results are collected in Table 2. Both systems containing Λ-$[Co(ox)(en)_2]$-Br or Δ (or Λ)-$[Co(glyO)(en)_2]X_2$ (X = Cl or Br) as a chiral additive are found to be effective. The e.e. values are between *ca.* 5 and 11%. In each experiment, the absolute configuration of the total crystals is always opposite to that of the chiral additive, which means the operation of the same resolution mechanism as described above. The realization of a second-order asymmetric transformation, though the e.e. values are not so high, should be noticeable because most other chiral additives such as Λ-$[Co(NO_2)_2(en)_2]Br$ and Λ-$[Co(en)_3]Br_3$ cannot induce any positive effect. Some examples of diastereomer crystallization are known[11] but the direct crystallization of the enantiomer is extremely rare in metal complexes.[12]

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