

CHREV. 183

MECHANISM OF CHROMATOGRAPHIC SEPARATION OF OPTICALLY ACTIVE METAL COMPLEXES

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1. INTRODUCTION

Chromatographic techniques have been widely used for the separation of various metal complexes, and have been recognized by coordination chemists as indispensable for the separation and purification of various kinds of isomers (geometric, diastereomeric, enantiomeric, etc.) of a wide variety of coordination compounds. A vast number of studies have been carried out in this area. Most of them, however, had as their aim the isolation of pure isomers, with a discussion of the correlation between properties and structures, so that their efforts were mainly concentrated on the search for appropriate separation conditions. From the chromatographic viewpoint the data are diverse and non-systematic.

We therefore attempted to elucidate the mechanism of the chromatographic

separation of complexes, with emphasis on the elucidation of the mechanism of chiral discrimination from a stereochemical viewpoint. Our approach to this problem was to measure the retention volumes for enantiomeric pairs of a series of complexes having related structures with a chiral selector as the eluent, to obtain their difference and ratio for each enantiomeric pair and to deduce the structure of the favourable ion pair formed between either one of the enantiomers and chiral selector ions. To achieve this aim, we did not confine ourselves to the chromatographic study for its own sake. We determined the crystal structures of diastereomeric salts and examined the NMR and circular dichroism (CD) spectra of chiral complex ions in solutions containing chiral selector ions and deduced the structure of the ion pair in solution.

The results revealed that the *d*-tartrate ion approaches a $[\text{Co}(\text{N})_6]^{3+}$ -type complex along its C_3 axis and discriminates the two enantiomers through the intimate ion-pair formation with the *A* enantiomer.

Concerning the mechanism of optical resolution by another chiral selector, the antimony *d*-tartrate ion, the importance of the shape of the opening between the chelate rings was noticed and the L-J model was intuitively proposed. A series of chromatographic studies was performed to verify this model. These studies have been published mainly in *Journal of Chromatography*, and a review has been published in *Journal of Liquid Chromatography* on stereochemical aspects of optical resolution of octahedral metal chelates¹. Since then, progress has been made concerning the chromatographic separation of optically active complexes. High-performance liquid chromatography (HPLC) and reversed-phase ion-pair chromatography began to be applied to the separation of metal complexes and the complete resolution of anionic complexes was achieved in several instances. As an extension of the study of the Pfeiffer effect, the mode of interaction between the chiral complex cation and anion has been studied, which might lead to the exploitation of a new chiral selector. The effect of chiral selector ions, such as *d*-tartrate and antimony *d*-tartrate ions, on the CD spectra of the $[\text{Co}(\text{N})_6]^{3+}$ -type complexes was studied and the mode of chiral interaction has been more clearly visualized.

This review outlines work carried out mainly in the author's laboratory to elucidate the mechanism of the chromatographic separation of optically active complexes. Emphasis is placed not on the individual experimental details but on an explanation of how the individual facts are combined to lead to visualization of the mode of chiral discrimination.

2 HISTORICAL BACKGROUND

Since Tsuchida *et al.*² reported in 1935 the asymmetric adsorption of metal complexes by quartz powder, many attempts have been made to achieve optical resolution by chromatography using as adsorbents optically active substances, such as quartz^{3,4}, starch⁵⁻⁸, cellulose^{9,10}, lactose^{11,12}, alumina treated with lactose¹³ and with *d*-tartaric acid¹⁴ and ion-exchange resins saturated with optically active complex ions¹⁵. These adsorbents, however, had such weak adsorbing powers that the optical resolution achieved was far from complete. There are two ways of improving the efficiency of optical resolution, as follows. When the adsorbent has only a weak affinity towards the samples to be separated, an eluent having a similarly weak affinity towards the samples should improve the efficiency of separation. A remarkable

example of the chromatographic separation of optically active complexes was presented by Dwyer *et al*¹⁶ in 1963. They chromatographed the mixed-ligand cobalt(III) complexes of ethylenediamine and (–)-propylenediamine through a column packed with cellulose powder using water-saturated *n*-butanol–hydrochloric acid as the eluent and separated a series of diastereomeric salts of the type $[\text{Co}(\text{en})_{3-n}(\text{l-pn})_n]\text{Cl}_3$ ($n = 3, 2, 1$ and 0). This technique was soon applied to the separation of isomers of $[\text{Co}(\text{d,l-pn})_3]\text{Cl}_3$ and a series of diastereomeric pairs were obtained¹⁷. In these two instances, the chirality of the cellulose skeleton does not seem to make any contribution, as no enantiomeric separation was achieved. The separation was attained here by partition chromatography.

Another way of improving the efficiency of optical resolution is to use a packing material having a sufficient adsorbing power. As most coordination compounds are ionic, an ion-exchange resin will meet this requirement.

It was in 1952 when King and Walters¹⁸ reported the separation of the *cis*- and *trans*- $[\text{Co}(\text{NO}_2)_2(\text{NH}_3)_4]^+$ using a column packed with a strongly acidic cation-exchange resin (Amberlite IR-120) using 1 and 3 *M* NaCl solutions as the eluent. From then until the mid 1970s, coordination chemists concentrated their efforts on the chromatographic separation of geometrical isomers of various complexes of relatively simple chelating ligands. In these separations, the *trans* isomer having no dipole moment is always eluted faster than the *cis* isomer having a dipole moment. The situation is not changed even when there are more than two isomers to be separated. The retention volume increases with increase in the polarity of the isomer, irrespective of whether they are cations or anions¹⁹ (Fig. 1).

It is therefore clear that the separation of isomers depends on the difference in adsorption strengths on the ion-exchange resin, that is, the separation is governed by adsorption. A common ion-exchange resin is the three-dimensional network of

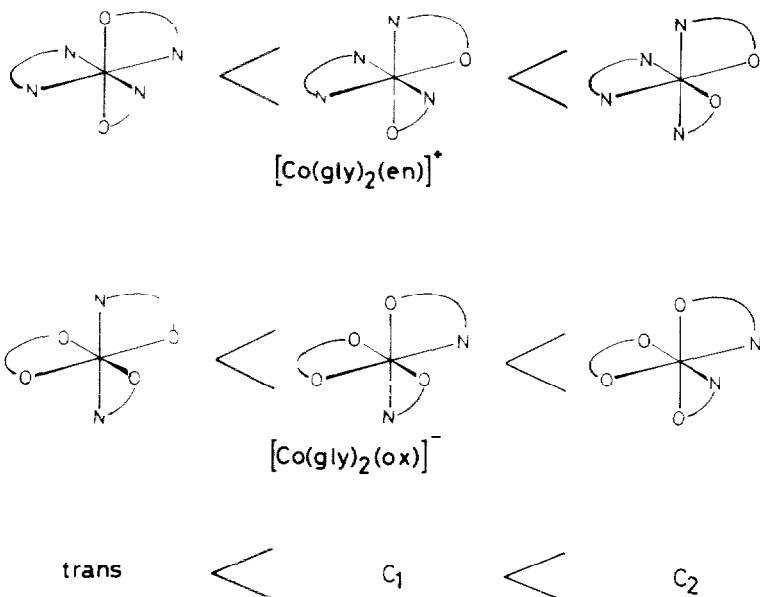


Fig. 1 Polarity order of geometrical isomers of $[\text{Co}(\text{gly})_2(\text{en})]^+$ and $[\text{Co}(\text{gly})_2(\text{ox})]^-$

styrene-divinylbenzene copolymer with ionized functional groups. The environment of the functional group is hydrophobic and the electrostatic interaction between ions should be much stronger here than in an aqueous solution as the eluent. This explains why the separation is governed by adsorption. It must be noted that almost all examples of such successful separations of geometrical isomers reported so far are separations of univalent cations or anions. This type of resin is not suitable for the separation of highly charged ions. Coordination chemists whose aim is optical resolution by chromatography for its own sake take $[\text{Co}(\text{en})_3]^{3+}$ as the first target because it has a simple structure of high symmetry and is the prototype of chiral complex ions. However, this complex is adsorbed so strongly on ion-exchange resins that elution itself is very difficult.

To elute highly charged complex ions, it is desirable to use an ion-exchange resin whose functional group is surrounded not by a hydrophobic environment but by a somewhat hydrophilic environment. Cellulose ion exchangers may satisfy this condition. In fact, the first report of the complete resolution of complex ions was made in 1962 by Brubaker *et al.*²⁰, who eluted tripositive trinuclear complex ions of the type $[\text{Co}_3(\text{NH}_2\text{CH}_2\text{CH}_2\text{S})_6]^{3+}$ on a column packed with cellulose ion exchanger using 0.1 M NaCl solution as the eluent and separated one type of enantiomer in a pure state. In this instance, however, optical resolution is presumed to have been achieved by the chirality of the cellulose skeleton. This success was attributed to the high charge and large size of the complex cation. Following this, they showed that partial resolution could easily be achieved for several kinds of racemic complexes, such as $[\text{Co}(\text{edta})]^-$, $[\text{Co}(\text{trdta})]^-$, *cis*- $[\text{Co}(\text{ida})_2]^-$ and $[\text{Co}(\text{en})\text{A}]^-$, where trdta and ida represent trimethylenediaminetetraacetate and iminodiacetate, respectively, and A is N,N'-dimethyl- or N,N'-diethylethylenediamine-N,N'-diacetate, and $[\text{Co}(\text{edta})\text{B}]^+$, where B is N-methyl-, N-ethyl-, N,N'-dimethyl- or N,N'-diethylethylenediamine.²¹ These resolutions are partial. The exchange capacity of cellulose ion exchanger was not so high as to allow an efficient resolution. For efficient and easy operation of chromatographic separations, a new type of ion-exchange resin was desired that contains the ionizable functional groups more densely in a hydrophilic environment. Sephadex ion exchanger meets such requirements.

After several attempts at optical resolution with insufficient efficiency using cellulose and ion-exchange cellulose,²² Yoshikawa and Yamasaki²³ achieved the complete resolution of $[\text{Co}(\text{en})_3]^{3+}$ on a column of Sephadex ion exchanger using an

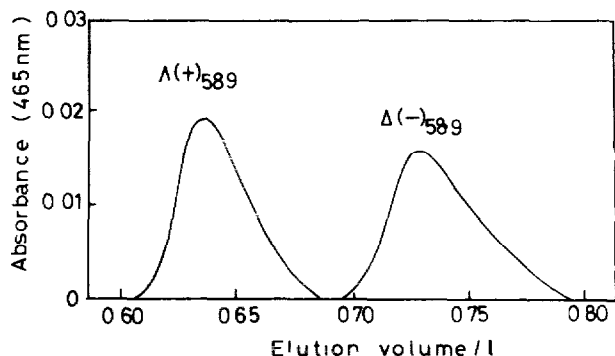


Fig. 2. Elution curve of $[\text{Co}(\text{en})_3]^{3+}$ eluted by 0.15 M sodium *d*-tartrate on an SE-Sephadex column.

aqueous solution of sodium *d*-tartrate as the eluent (Fig 2) They also succeeded in separating three geometrical isomers of $[\text{Co}(\text{dien})_2]^{3+}$ and showed that Sephadex ion exchanger is a suitable packing material for the chromatographic separation of various kinds of highly charged isomers With this report as a starting point, chromatographic separations of a wide variety of isomers (geometric, diastereomeric and enantiomeric or conformational) have been performed, and now chromatographic separation and purification have become a necessary technique in preparative coordination chemistry²⁴

3 OPTICAL RESOLUTION OF CATIONIC COMPLEXES

3.1 Optical resolution by *d*-tartrate

3.1.1 Resolution of $[\text{Co}(\text{en})_3]^{3+}$

Since $[\text{Co}(\text{en})_3]^{3+}$ is a prototype of chiral metal complexes, attempts to achieve the complete resolution of this complex were made before any other racemic complexes In the same year as Yoshikawa and Yamasaki achieved the complete resolution of this complex, Yoneda and co-workers also achieved the complete resolution of this complex by paper electrophoresis²⁵ and later by thin-layer chromatography²⁶ using an aqueous $\text{Na}_2(\textit{d}\text{-tart})$ solution mixed with AlCl_3 as a supporting electrolyte or developer The idea of adding AlCl_3 to the $\text{Na}_2(\textit{d}\text{-tart})$ solution came from the expectation that the Al^{3+} ion would deprive the hydrated $[\text{Co}(\text{en})_3]^{3+}$ of water molecules so that the *d*-tartrate ion could come close to the complex to recognize the chirality more clearly This expectation soon proved to be wrong, however If this expectation were realized, the Δ cation should migrate through the supporting electrolyte solution more slowly than the Λ cation, because the Δ cation associates with the *d*-tartrate ion more strongly than the Λ cation and should be decelerated by the *d*-tartrate ion to a greater extent than the Λ cation However, this is not the case²⁷ In actual electrophoresis, the Λ cation showed a longer migration than the Δ cation (see Fig 3) It was therefore concluded that the separation of the Λ and Δ isomers was achieved by the anionic $\text{Al-}d\text{-tartrate}$ complex Optical resolution by the $\text{Na}_2(\textit{d}\text{-tart})$ and AlCl_3 solution was a special case that cannot be applied to any complexes other than $[\text{M}(\text{en})_3]^{3+}$

3.1.2 Crystal structures of diastereomeric salts containing $[\text{M}(\text{en})_3]^{3+}$ and *d*-tartrate ions

Our strategy for the elucidation of the mechanism of optical resolution of $[\text{Co}(\text{en})_3]^{3+}$ by the *d*-tartrate ion is first to obtain information on how $[\text{Co}(\text{en})_3]^{3+}$ and *d*-tart²⁻ ions are packed in the diastereomeric salt, $\Lambda\text{-}[\text{Co}(\text{en})_3]\text{Br } d\text{-tart } 5\text{H}_2\text{O}$ It is well known that the $\Lambda\text{-}[\text{Co}(\text{en})_3]^{3+}$ ions form crystals with halide and *d*-tartrate ions, but the $\Delta\text{-}[\text{Co}(\text{en})_3]^{3+}$ ions do not Some clue with respect to the elucidation of chiral discrimination should be found in the packing mode of the Λ cation and *d*-tartrate anion Crystal structure analysis²⁸ revealed that a unique face-to-face close contact mode of the two ions exists in this crystal Fig 4 shows this face-to-face ion-pair structure viewed along the C_3 axis of the complex cation Here, four carbon atoms of the *d*-tartrate ion make a plane that is perpendicular to the C_3 axis of the complex, and four oxygen atoms of the *d*-tartrate ion are projecting towards the

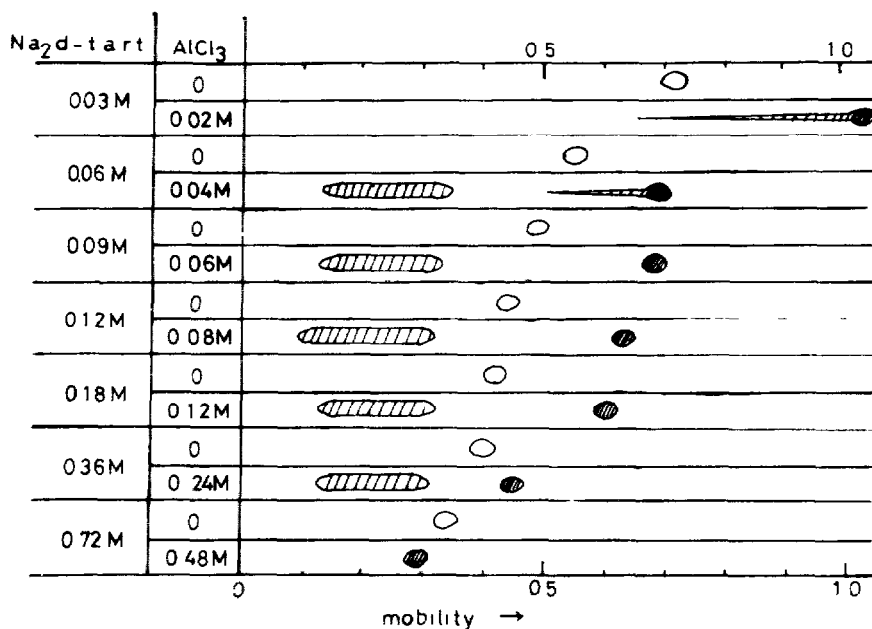


Fig 3 Electrophoresis pattern of the racemic $[\text{Co}(\text{en})_3]^{3+}$ complex in sodium *d*-tartrate with and without aluminum chloride

complex and facing the triangular facet composed of three NH_2 groups. Interestingly, this face-to-face intimate ion-pair structure was also found in other two diastereomeric salts composed of Δ - $[\text{M}(\text{en})_3]^{3+}$ and d - tart^{2-} ions, $\text{Li } \Delta$ - $[\text{Cr}(\text{en})_3](d\text{-tart})_2 \cdot 3\text{H}_2\text{O}$ ²⁹ and $\text{H } \Delta$ - $[\text{Co}(\text{en})_3](d\text{-tart})_2 \cdot 3\text{H}_2\text{O}$ ³⁰

It is remarkable to find this unique face-to-face ion-pair structure in these three diastereomeric crystals, which are different in composition, cell dimensions and space group symmetry. Therefore, it is reasonable to assume that the origin of discrimination by $d\text{-tart}^{2-}$ lies in this face-to-face ion-pair structure. This ion pair is presumed to be fairly stable and to exist even in solution. The combination of the Δ cation and $d\text{-tart}$ anion does not seem to produce such a stable ion pair. In this way, the chromatographic elution order (the Δ ion is eluted faster than the Λ ion) can be explained

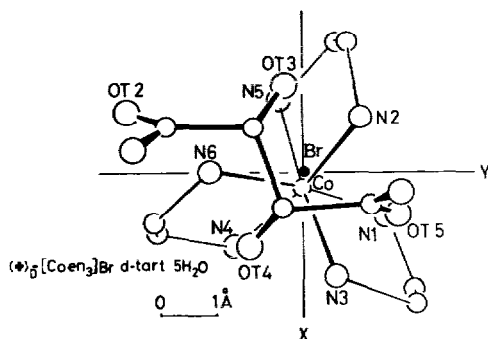
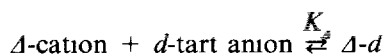
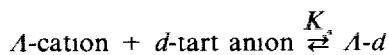


Fig 4 Face-to-face ion-pair structure of Δ - $(+)$ - D - $[\text{Co}(\text{en})_3]\text{Br} \cdot d\text{-tart} \cdot 5\text{H}_2\text{O}$

by the different degrees of ion association. The association constants, K_A and K_d , for the two equilibria



have been obtained by several workers³¹⁻³⁴ and all of the results indicate that $K_A > K_d$.

A similar kind of face-to-face close contact mode was found recently in the crystal structure of a more soluble diastereomeric salt, Λ -[Co(sen)]Cl d -tart $6\text{H}_2\text{O}$, where sen represents $\text{CH}_3\text{C}(\text{CH}_2\text{NHCH}_2\text{CH}_2\text{NH}_2)_3$ ³⁵. The racemic [Co(sen)]³⁺ was found to be completely resolved on an SP-Sephadex C-25 column with sodium d -tartrate solution as the eluent. In this instance also, the Λ cation is eluted first. Hence it appears likely that the unique face-to-face close contact mode found in crystals may also exist in solution and play a decisive role in the chiral discrimination of trigonal [Co(N)₆]³⁺ complexes.

3.1.3 Chromatographic evidence for a face-to-face ion association

It was Searle³⁶ who first demonstrated the significance of ion association in chromatographic separations on an SP-Sephadex column. He chromatographed a set of closely related [Co(N)₆]³⁺-type complexes, [Co(dien)₂]³⁺, [Co(dien)(medien)]³⁺ and [Co(medien)₂]³⁺, where dien and medien represent diethylenetriamine and N -methyl-diethylenetriamine, respectively, on an SP-Sephadex C-25 column with different eluents, such as NaClO_4 , NaNO_3 , NaCl , Na_2SO_4 , $\text{Na}_2(d\text{-tart})$ and Na_3PO_4 . From a consideration of the elution order, he drew several conclusions, as follows.

The separations obtained with highly charged eluent anions appear to be due primarily to differences in the degrees of ion association between the complex ions and the eluent anions rather than to differences in the strengths of adsorption of the free complex cations on the resin. The strength of ion association depends on (1) the basicity of the eluent anion in the order $\text{PO}_4^{3-} > \text{SO}_4^{2-} > d\text{-tart}^{2-} > \text{Cl}^- > \text{NO}_3^-$, and (2) the availability of appropriately disposed N-H bonds for hydrogen bonding to the oxyanion and the acidity of the N-H hydrogens (secondary NH > primary NH₂).

Especially important is the appropriate disposition of the N-H bonds. The oxyanion, such as PO_4^{3-} , SO_4^{2-} and $d\text{-tart}^{2-}$, has a strong tendency to form an especially stable ion pair with the complex having three axial N-H bonds along the C_3 or pseudo- C_3 axis of the complex (see Fig. 5). This is just what we call a face-to-face ion association. A typical example of a separation to support this association mode is found in the elution order of the three symmetric facial isomers of [Co(dien)₂]³⁺, [Co(dien)(medien)]³⁺ and [Co(medien)₂]³⁺ with the strongly associating eluent anion PO_4^{3-} . The elution order is [Co(dien)₂]³⁺ > [Co(dien)(medien)]³⁺ > [Co(medien)₂]³⁺, which corresponds exactly to the decreasing numbers (2, 1, 0) of sites available for triple hydrogen bonding.

Although $s\text{-fac}$ -[Co(medien)₂]³⁺ has no sites for triple hydrogen bonding, it does have sites for double hydrogen bonding. In contrast, $u\text{-fac}$ -[Co(amam)]³⁺ (see

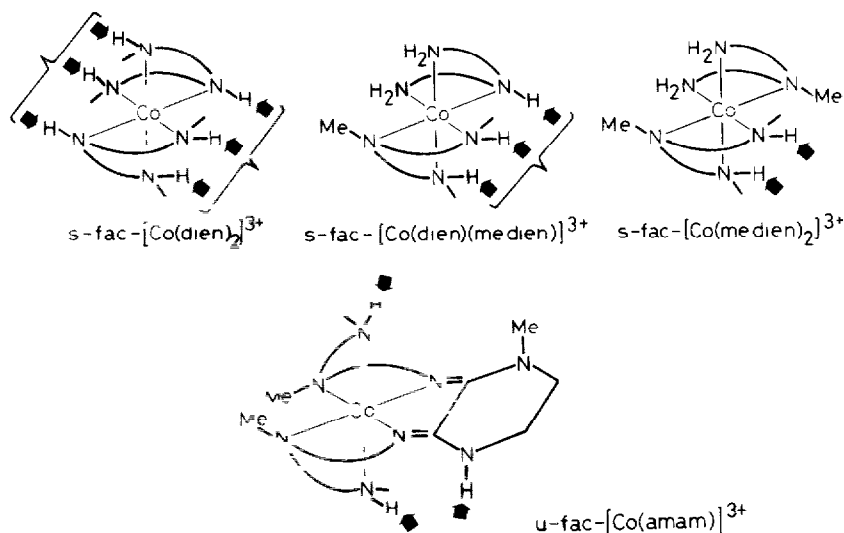


Fig 5 Structures of $[\text{Co}(\text{dien})_2]^{3+}$, $[\text{Co}(\text{dien})(\text{medien})]^{3+}$, $[\text{Co}(\text{medien})_2]^{3+}$ and $[\text{Co}(\text{amam})]^{3+}$

Fig 5) has only three separately disposed N-H bonds available only for single hydrogen bonding, so that this complex is eluted much slower than $s\text{-fac-}[\text{Co}(\text{medien})_2]^{3+}$. Hence we have the elution order $s\text{-fac-}[\text{Co}(\text{dien})_2]^{3+} > s\text{-fac-}[\text{Co}(\text{medien})_2]^{3+} > u\text{-fac-}[\text{Co}(\text{amam})]^{3+}$. This elution order is reversed with the singly charged eluent anions Cl^- , NO_3^- and ClO_4^- , and the degree of separation increases with these anions in the order $\text{Cl}^- < \text{NO}_3^- < \text{ClO}_4^-$.

The reversal of the elution order can be rationalized in terms of two opposing factors, cation-eluent anion interaction (ion association) and cation-resin interaction (adsorption). The former interaction decreases along the anion series from PO_4^{3-} , via SO_4^{2-} and $d\text{-tart}^{2-}$ to Cl^- , NO_3^- and ClO_4^- . With ClO_4^- , the factor that governs the separation should be electrostatic interaction between the cation and the negative sites of the resin. The magnitudes of this interaction for various complex cations should be in the same order as those of the interaction with the eluent anions, *viz*, greatest for $s\text{-fac-}[\text{Co}(\text{dien})_2]^{3+}$, so that this complex is the most retained by the resin and the least retained is $u\text{-fac-}[\text{Co}(\text{amam})]^{3+}$, which is eluted first. It was also pointed out that the acidity difference of N-H hydrogens affects the ion association so that it determines the elution order. Whereas $s\text{-fac-}[\text{Co}(\text{dien})_2]^{3+}$ associates with PO_4^{3-} through two primary amine hydrogens and one secondary amine hydrogen, $u\text{-fac-}[\text{Co}(\text{dien})_2]^{3+}$ associates with PO_4^{3-} through three primary amine hydrogens. Hence the *s-fac* isomer associates more strongly than the *u-fac* isomer with PO_4^{3-} , so that the former is eluted with PO_4^{3-} faster than the latter.

3.1.4 Nature of chiral discrimination by the *d*-tartrate ion

Since the unique ion-pair is found in solution as well as in crystal, it should be fairly stable. However, for a complete understanding of the mechanism of chiral discrimination by the *d*-tartrate ion, the structure of the Δ -*d* ion pair is also needed, which cannot be obtained from crystal structure analysis. To avoid this difficulty, the

hypothetical structure of the Δ - d ion pair was imagined based on the real structure of the Λ - d ion pair

The characteristic feature of the Λ - d ion pair structure can be visualized by looking only at the interacting parts of the ions that are in direct contact with each other. As the part of the complex that is directly involved in association is its upper half (see Fig. 6), we need to consider only its upper half, that is, the shoulders of the three chelate rings. On the other hand, as the d -tart ion associates with the complex ion with its four oxygen atoms, it is sufficient to consider the configuration of these four oxygen atoms. By superimposing these two parts, we obtain the pattern of a stable Λ - d ion pair, as shown in Fig. 6a. Here, the four large circles drawn by broken lines each represent the effective atomic radius of the oxygen atom. These four oxygen circles are placed in the space formed by three chelate rings. A good fit can be experienced between the two ions. However, if we replace the Λ with the Δ ion, as shown in Fig. 6b, such a good fit is not obtained. Three oxygen circles are placed in the space between the chelate rings, but the fourth oxygen circle comes on to the shoulder of the chelate ring so that the Δ - d combination does not form the intimate ion pair structure like the Λ - d combination. Therefore, instead of the three-point attachment model proposed for organic compounds, a four-point attachment model

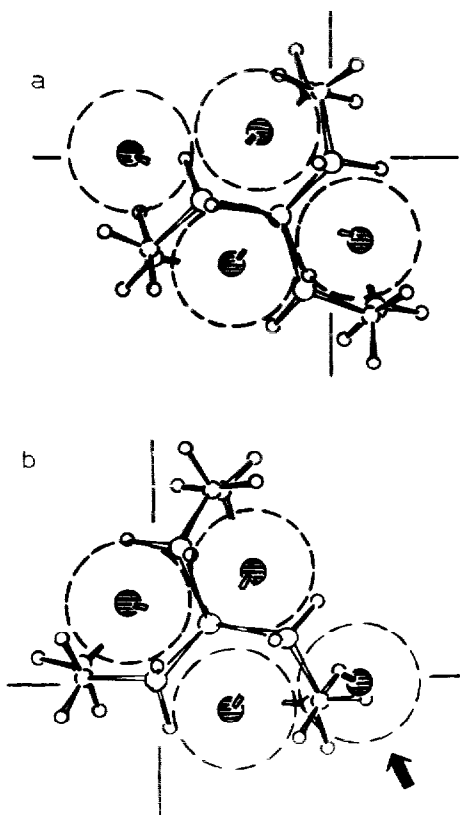


Fig. 6 Schematic representation of the mode of association between d -tart and $[\text{Co}(\text{en})_3]^{3+}$ (a) The compact fit between d -tart and Λ -complex, (b) the non-compact fit between d -tart and Δ -complex

was proposed in which the *d*-tart ion discriminates the complex cation with its four oxygen atoms, that is, with three oxygen atoms hydrogen-bonded to the three NH groups and with the fourth oxygen not involved in hydrogen bonding with the NH group

3.1.5 Application of the three-fold axis association model

The above discussion suggests that the complex having three NH bonds in a triangular facet of the octahedral configuration should be optically resolved with the *d*-tart ion as the eluent. In fact, total resolution by *d*-tart was reported for $[\text{Co}(\text{en})_2(\text{AA})]^{2+}$, where AA represents glycine³⁷, β -alanine³⁷, ethanolamine³⁸ or thioethanolamine³⁸. Even the electrically neutral complex *fac*- $[\text{Co}(\beta\text{-ala})_3]^{39}$ should be resolved with *d*-tart as the eluent. Although this complex is electrically neutral, its three NH_2 groups are disposed in a triangular facet and three COO^- groups are situated in another triangular facet, so that the complex should have a dipole moment. It should be retained fairly firmly by the negative sites of the ion-exchange resin, and associated with *d*-tart fairly strongly. In fact, the complex was completely resolved on the Na^+ form of CM-Sephadex ion exchanger with an ethanol-water solution of $\text{Na}_2(\textit{d}\text{-tart})$ as the eluent (see Fig. 7). As a solution of sodium chloride or sodium sulphate did not give two elution bands, the separation of two elution bands is considered to be effected by *d*-tart and not by the chiral skeleton of the Sephadex.

The separation of four isomers of $[\text{Co}(\text{D/L-phe})(\text{en})_2]$, where phe represents phenylalanine, Δ -L-phe, Λ -L-phe, Δ -D-phe or Λ -D-phe with *d*-tart is worth noting⁴⁰. Fig. 8 shows the structures of these four isomers in their most populated conformers. Here A and B are enantiomers and C and D are also enantiomers, but (A,B) and (C,D) are diastereomers. The phenyl group in C and D is directed along the pseudo- C_3 axis and prevents the approach of *d*-tart to the complex. In contrast, the phenyl group in A and B is directed away from the pseudo- C_3 axis and does not reject the approach of *d*-tart along the pseudo- C_3 axis. The difference in the disposition of the phenyl group between (A,B) and (C,D) should be reflected in the difference in association constants with *d*-tart. In fact, the association constants with

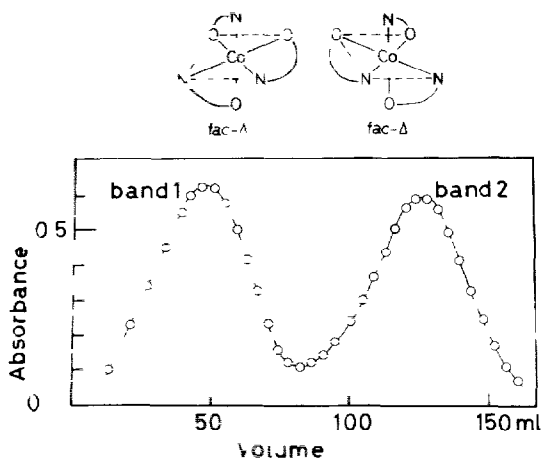


Fig. 7 Two enantiomers and elution curve of *fac*- $[\text{Co}(\beta\text{-ala})_3]$

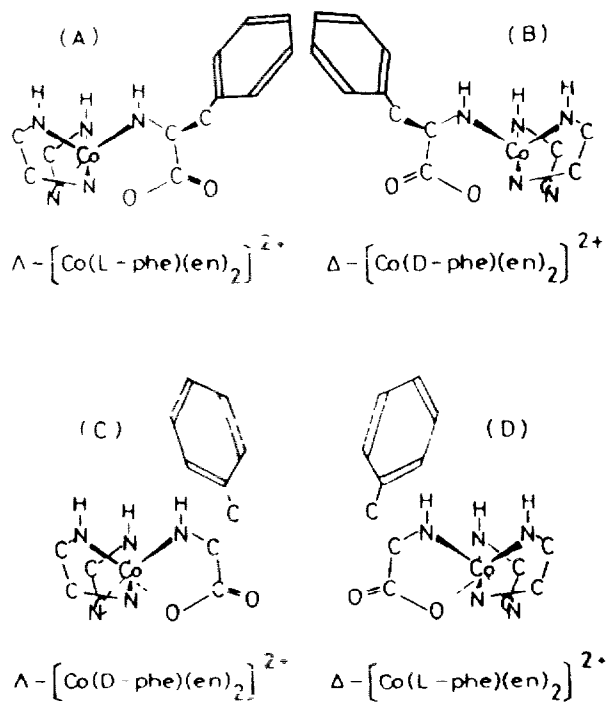


Fig 8 Molecular models for the phenylalaninato complexes

d-tart are smaller in C and D than in A and B. The association constants in A and B are nearly equal to those in [Co(gly)(en)₂]²⁺, for which steric repulsion against the oncoming *d*-tart is not expected (see Table 1). In addition, the *d*-tart ion coming along the pseudo-C₃ axis should discriminate the Λ from the Δ ions. The situation is clearly reflected in the elution curve obtained using an SP-Sephadex column with

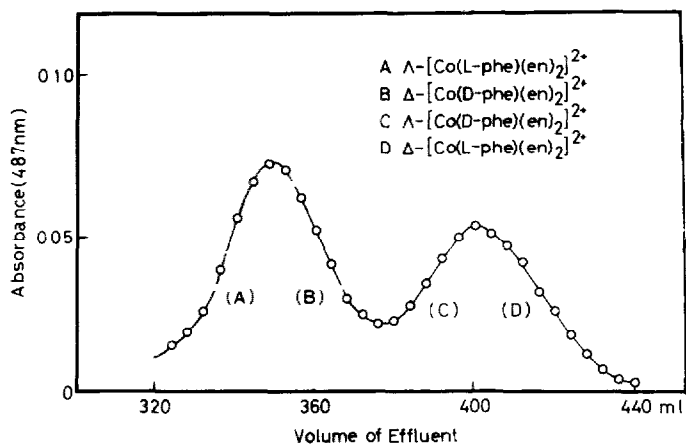
Fig 9 Elution curve of [Co(D,L-phe)(en)₂]²⁺ with *d*-tartrate

TABLE 1

ASSOCIATION CONSTANTS FOR Λ - AND Δ -[Co(am)(en)₂]²⁺ AT 25°C AND $\mu = 0.1$

Complex	<i>L</i> -tart ²⁻	<i>D</i> -tart ²⁻
Λ -[Co(gly)(en) ₂] ²⁺	43 ± 0.2	
Δ -[Co(gly)(en) ₂] ²⁻	39 ± 0.3	
Λ -[Co(<i>L</i> -phe)(en) ₂] ²⁺	43 ± 0.1	40 ± 0.1
Δ -[Co(<i>D</i> -phe)(en) ₂] ²⁺	(40 ± 0.1)	
Λ -[Co(<i>D</i> -phe)(en) ₂] ²⁺	(27 ± 0.3)	
Δ -[Co(<i>L</i> -phe)(en) ₂] ²⁺	12 ± 0.6	27 ± 0.3
Λ -[Co(en) ₃] ³⁺	13.6 ± 0.2	
Δ -[Co(en) ₃] ³⁺	11.7 ± 0.4	

d-tart as the eluent, as shown in Fig 9. It is worth noting that the separation of diastereomers is greater than the separation of enantiomers.

3.1.6 Resolution of [Co(tn)₃]³⁺

Fujita *et al.*^{41,42} prepared a new modification of Sephadex resin with D(-)-tartrate groups of an ester type D-TA(ES)-Sephadex. They employed this cation exchanger in the optical resolution of [Co(tn)₃]³⁺ and also [Co(en)₃]³⁺ with aqueous L(+)-tartrate as the eluent, with the expectation that chiral tartrate groups in both stationary (D) and mobile (D) phases would contribute additively to chiral discrimination of the complex. This technique actually enabled them to isolate optically pure [Co(tn)₃]³⁺, complete resolution of which has not yet been accomplished by conventional chromatographic techniques. However, the D-TA(ES)-Sephadex resin is not suitable for HPLC because its volume varies with variations in the applied pressure.

Subsequently, Fujita *et al.*⁴³ synthesized another cation exchanger suitable for HPLC by allowing Toyopearl HW-40 (a polyvinyl gel having hydroxy groups like Sephadex) to react with D-tartaric acid. The D-tartrate group is introduced as its ester with the OH group in the gel as in a D-TA(ES)-Sephadex, and the resulting gel, called D-TA(ES)-Toyopearl, was successfully used for the optical resolution of several Co(III) complexes. Fig 10 shows the elution curve for [Co(tn)₃]³⁺ obtained by elution with aqueous L-tartrate on a column (40 × 1.6 cm I.D.) packed with D-TA(ES)-Toyopearl. A recycling chromatographic technique is employed here. Efficient reso-

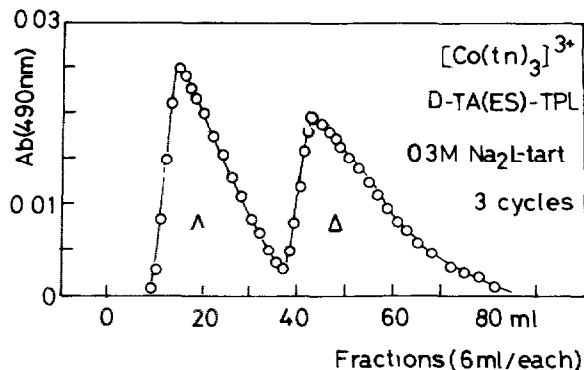


Fig 10 Elution curve of [Co(tn)₃]³⁺ on a D-TA(ES)-Toyopearl column

lution of the complex is achieved by the use of the doubly stereoselective effect of D-TA(ES)-Toyopearl and an L-tartrate eluent on the complex. The *A* enantiomer is eluted faster, as expected. They also accomplished the complete resolution of a neutral complex, *fac*-[Co(β -ala)₃], on this column by eluting with water.

3.2 Optical resolution by the antimony *d*-tartrate ion

3.2.1 Resolution of [Co(N)₆]³⁺ complexes

Antimony *d*-tartrate [more precisely bis(μ -*d*-tartrato)diantimonate(III) ion and abbreviated hereafter to Sb(*d*-tart)] is a divalent anion having a dimeric structure as shown in Fig. 11.^{44, 45} This ion is a versatile resolving agent for many metal complex cations with widely different structures and properties. It can also be used as a chiral selector in the chromatographic separation of many metal complex cations. The association constants of [Co(en)₃]³⁺ are greater with Sb(*d*-tart)²⁻ than with *d*-tart²⁻, and the ratio of the association constants of *A*- and Δ -[Co(en)₃]³⁺ with these chiral selector ions, K_A/K_Δ , is also considerably greater for Sb(*d*-tart)²⁻ than *d*-tart²⁻.⁴⁶ The separation factor of [Co(en)₃]³⁺ on an SP-Sephadex cation-exchange column (90 × 1.2 cm I.D.) with 0.1 M K₂Sb(*d*-tart) is 1.42 and is greater than that with 0.1 M Na₂(*d*-tart) (1.21).³⁸ These data indicate that Sb(*d*-tart) is a more efficient chiral selector than *d*-tart for [Co(en)₃]³⁺. It is well known that Sb(*d*-tart) can resolve more types of complexes than *d*-tart can. These facts suggest that the mode of chiral discrimination by Sb(*d*-tart) should be quite different from that by *d*-tart.

As already discussed, the mode of chiral discrimination by *d*-tart has been established, based on the crystal structures of the diastereomeric salts. However, it should be considered fortunate that a unique face-to-face ion pair was found in common in all diastereomeric crystals. Such chance cannot be expected in crystals of diastereomeric salts containing Sb(*d*-tart) ions. Therefore, a different approach should be adopted. The results of chromatographic separations of Co(III) amine complexes that had been reported to be optically resolved with Sb(*d*-tart) revealed that the first eluted isomers all have the *A* configuration (with a few exceptions). These first eluted isomers are presumed to have a special topography in common.

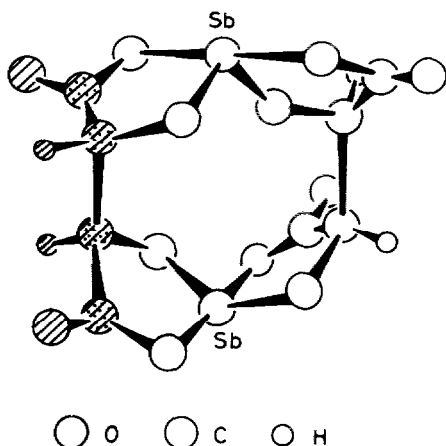


Fig. 11 Dimeric structure of antimony *a*-tartrate

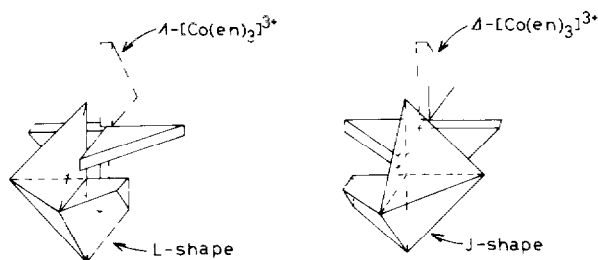


Fig 12 Schematic representation of the Λ -[Co(en)₃]³⁺-L-shaped counter-ion pair (left) and the Δ -[Co(en)₃]³⁺-J-shaped counter-ion pair (right). The L(J)-shaped counter ion fits well the L(J)-shaped channels of $\Lambda(\Delta)$ -[Co(en)₃]³⁺.

that is not found in the Δ isomers. Fig 12 shows schematic representations of the Λ and Δ configurations. The Λ and Δ configurations are characterized not only by the mode of coordination of the three chelate rings but also by the shape of the opening between the chelate rings. The opening formed by the chelate rings of the Λ configuration is L-shaped, and that formed by the chelate rings of the Δ configuration is J-shaped. For the mechanism of discrimination of Λ -[Co(en)₃]³⁺ by Sb(*d*-tart), the key-and-lock model was proposed⁴⁷, in which Sb(*d*-tart) associates with the complex by setting its skeleton in the L-shaped channel. The skeleton which makes a good fit to the L-shaped channel cannot make a good fit to the J-shaped channel. As Sb(*d*-tart) has such a skeleton which makes a good fit to the L-shaped channel, it can associate with the Λ -[Co(en)₃]³⁺ cation firmly and with the Δ -[Co(en)₃]³⁺ loosely.

This L-J model is a result of intuition and should be verified by experimental data. To obtain the experimental support for this model, chromatographic separations were attempted for a series of Co(III) amine complexes that satisfy certain conditions, and the retention volumes of both enantiomers and their ratios were measured. The conditions that should be satisfied are as follows: (1) they should have the same charge (3+), which is not localized at some special sites, (2) they should

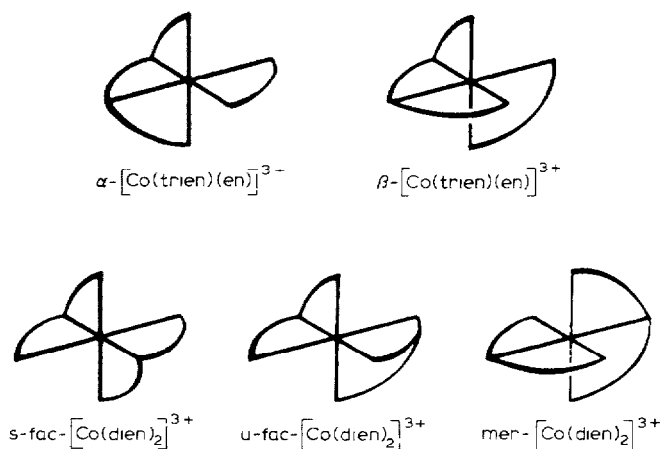


Fig 13 The five complexes examined, including geometric isomers.

TABLE 2
ADJUSTED RETENTION VOLUMES AND SEPARATION FACTORS

L and J are the number of L- and J-shaped channels in the first eluted enantiomer Vol(I) = retention volume of the first band eluted with $K_2[Sb_2(d-tart)_2]$, Vol(II) = retention volume of the second band eluted with $K_2[Sb_2(d-tart)_2]$ Vol(III) = retention volume of the band eluted with KCl Diff = Vol(II) - Vol(I) α = Separation factor

Complex	L	J	Vol(I) (ml)	Vol(II) (ml)	Vol(III) (ml)	Diff	α
(A) $[Co(en)_3]^{3+}$	6	0	200.1	289.3	113.9	89.2	1.45
(B) $\alpha-[Co(trien)(en)]^{3+}$	4	0	199.1	272.6	104.3	73.5	1.37
(C) $\beta-[Co(trien)(en)]^{3+}$	3	0	214.5	275.0	106.7	60.5	1.28
(D) $u-fac-[Co(dien)_2]^{3+}$	2	0	236.4	283.7	110.4	47.3	1.20
(E) $s-fac-[Co(dien)_2]^{3+}$	2	2	238.9	—	104.8	—	—
(F) $mer-[Co(dien)_2]^{3+}$	0	0	265.2	(298.8)*	108.6	(33.6)	(1.13)

* Estimated, because of a partial resolution

have the same number of the ethylene bridges, and (3) they should differ in the number of L-shaped channels

As complexes that satisfy these conditions, three geometric isomers of $[Co(dien)_2]^{3+}$ and two geometric isomers of $cis-[Co(en)(trien)]^{3+}$ were selected (see Fig 13). The complex $[Co(en)_3]^{3+}$ was also selected because it is the prototype of chiral Co(III) complexes having the largest number of L-shaped channels. The results are shown in Table 2. As can be seen, the separation factor shows a stepwise decrease with a decrease in the number of L-shaped channels. $s-fac-[Co(dien)_2]^{3+}$ is not chiral and is not resolved into enantiomers, but its retention volume is equal to Vol(I) of $u-fac-[Co(dien)_2]^{3+}$ and shows the behaviour of the two L-shaped channels. Further, it is noteworthy that the Vol(II) values of complexes B, C and D are nearly equal, which corresponds to zero L-shaped channels. Therefore, as far as these data are concerned, the L-J model proved to be valid.

3.2.2 Resolution of $cis(O)_2(N)_4]^+$ complexes

The above argument is valid only for complexes of the type $[Co(N)_6]^{3+}$ whose ligands are all electrically neutral. For such complexes, access of the eluent anion from any direction can occur with equal probability. Therefore, any L-shaped channels may be assumed to make an equal contribution to ion association. The separation factor as a measure of the efficiency of optical resolution is considered to be proportional to the number of L-shaped channels. In contrast, for complexes in which negatively charged donor atoms occupy some of the six coordination sites, access of the eluent anion to the L-shaped channels occurs with different probabilities according to their accessibilities. L-shaped channels are ranked according to their accessibilities.

Nakazawa *et al.*⁴⁸ chromatographed four complexes of the type $cis-[Co(O)_2(N)_4]^+$ with 0.1 M $K_2Sb(d-tart)$ as the eluent, and explained their separation patterns in terms of ranked L-shaped channels. As shown in Fig 14, the $cis-[Co(O)_2(N)_4]^+$ -type complex has five kinds of L-shaped channels, which are represented by one edge of an octahedron. Here rank 1 is electrostatically the best position

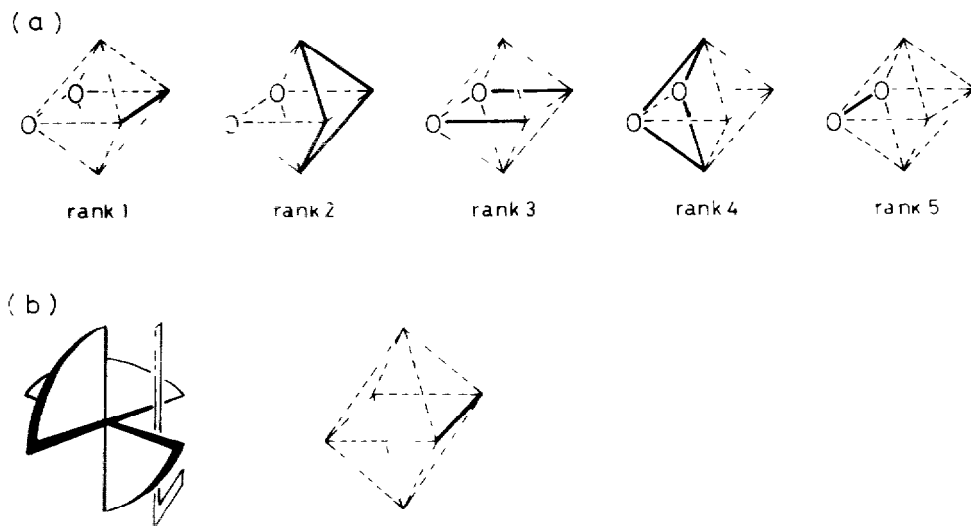


Fig 14 (a) Stereochemically different edges (solid line) of the $cis-[Co(O)_2(N)_4]^+$ -type complex (b) The L-shaped channel is represented as one edge (solid line) of an octahedron

to accept the anion, and the ease of access of the anion toward the complex cation decreases successively from rank 1 to rank 5

The complexes tested were $cis(O)$, $cis(N)$, $cis(NH_3)$ - and $cis(O)$, $trans(N)$, $cis(NH_3)$ - $[Co(gly)_2(NH_3)_2]^+$ and C_1 - cis - and C_2 - cis - $[Co(gly)_2(en)]^+$ (see Fig 15) Because the Δ form of the latter two complexes have only L-shaped channels, the Δ form is expected to be eluted first For the $cis(O)$, $cis(N)$, $cis(NH_3)$ complex also, the Δ form is expected to be eluted first because it has two L-shaped channels and one J-shaped channels, both of rank 2 In contrast, for the $cis(O)$, $trans(N)$, $cis(NH_3)$ complex, the Δ form is expected to be eluted first because it has two L-shaped channels of rank 2 Further, the separation factor for the C_1 - cis complex is better than that for the C_2 - cis complex, because the former has L-shaped channels of higher rank than the C_2 - cis complex These expectations were all fulfilled (see Table 3)

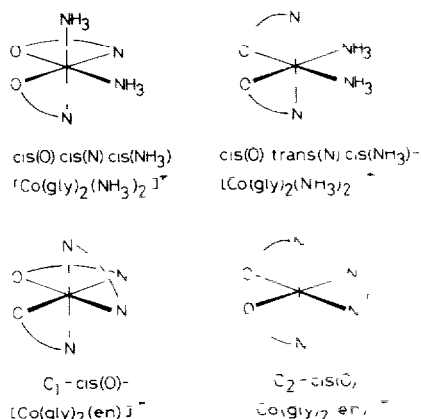


Fig 15 Schematic structures of some $cis-[Co(O)_2(N)_4]^+$ -type complexes

TABLE 3

NUMBER AND POSITION OF L- AND J-SHAPED CHANNELS OF *A*-ENANTIOMERS AND RETENTION VOLUMES OF THE COMPLEXES

Complex	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
<i>cis</i> (O), <i>cis</i> (N), <i>cis</i> (NH ₃)-[Co(gly) ₂ (NH ₃) ₂] ⁺ (13.83 ml)	1 LJ	2 L 1 J 1 LJ	1 J	1 LJ	1 L
<i>cis</i> (O), <i>trans</i> (N), <i>cis</i> (NH ₃)-[Co(gly) ₂ (NH ₃) ₂] ⁺ [12.20 ml (<i>A</i>), 14.03 ml (<i>A</i>)]	1 LJ	2 J 2 LJ	2 L	2 L	—
<i>C</i> ₁ - <i>cis</i> (O)-[Co(gly) ₂ (en)] ⁺ [13.29 ml (<i>A</i>), 15.75 ml (<i>A</i>)]	1 L	2 L	—	—	1 L
<i>C</i> ₂ - <i>cis</i> (O)-[Co(gly) ₂ (en)] ⁺ (15.79 ml)	—	—	2 L	2 L	—

3.2.3 Resolution of *cis*-[Co(X)₂(en)₂]⁺ and *cis-α*-[Co(X)₂(trien)]⁺

Although many examples of complete resolution by ion-exchange chromatography have been reported for tripositive [Co(N)₆]³⁺-type complexes, examples of the resolution of *cis*-[Co(X)₂(en)₂]⁺ are rare. Yamazaki and Yoneda^{4,9} attempted to resolve *cis*-[Co(X)₂(en)₂]⁺ and *cis-α*-[Co(X)₂(trien)]⁺, where X = NO₂⁻, NCS⁻ and N₃⁻, and found a slight resolution for dinitro and disorhodanato complexes and fairly good resolution for diazido complexes. Complete resolution was attained for *cis-α*-[Co(N₃)₂(trien)]⁺. These results could be explained in terms of the L-J model with directional ion association, as shown in Fig. 16.

The *A* form of *cis*-[Co(X)₂(en)₂]⁺ has L-shaped channels that are adjacent to the anionic ligands X. Consequently, the Sb(*d*-tart) anion experiences difficulty in associating with the complex using the L-shaped channels. Rather, the anion associates with the complex from the direction opposite to X⁻. It is not surprising that most *cis*-dianiono complexes are not resolved by Sb(*d*-tart). In the diazido complexes, the negative charge of X⁻ is presumed to be diluted in three N atoms owing to resonance, so that there is some possibility for the Sb(*d*-tart) anion to associate with the cation using the L-shaped channels. A fairly good separation of *cis*-[Co(N₃)₂(en)₂]⁺ is thus understood.

In trien complexes, the ion association along the C₂ direction is prohibited, so that the Sb(*d*-tart) anion is forced to take other directions in associating with the

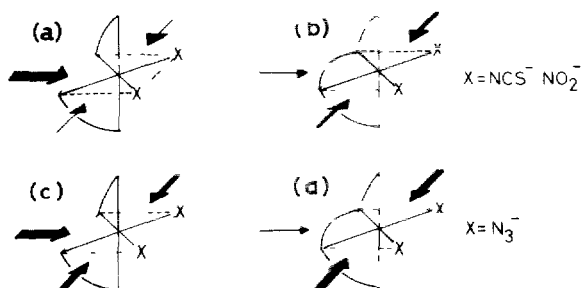


Fig. 16 Access of Sb(*d*-tart)²⁻ towards *cis*-[Co(X)₂(N)₄]⁺ (a) *cis*-[Co(X)₂(en)₂]⁺, (b) *cis-α*-[Co(X)₂(trien)]⁺ (X = NCS and NO₂), (c) *cis*-[Co(N₃)₂(en)₂]⁺, (d) *cis-α*-[Co(N₃)₂(trien)]⁺

complex. Consequently, the probability of the Sb(*d*-tart) anion using the L-shaped channel should increase. In fact, the efficiency of optical resolution was improved in all three trien complexes investigated. Even the dinitro and disorhodanato complexes were partially resolved, and the diazido complex was completely resolved.

3.2.4 Resolution of $[\text{Co}(\text{N})_6]^{3+}$ by reversed-phase ion-pair chromatography

Izumoto and Yoneda⁵⁰ showed that antimony *d*-tartrate salts $\text{M}_2\text{Sb}(\textit{d}\text{-tart})$, where $\text{M} = \text{Na}^+, \text{K}^+, \text{NH}_4^+, \text{N}(\text{CH}_3)_4^+$ and $\text{N}(\text{C}_2\text{H}_5)_4^+$, can be used successfully as ion-pairing reagents for optical resolution by reversed-phase ion-pair chromatography and achieved the complete resolution of $[\text{Co}(\text{en})_3]^{3+}$, $[\text{Co}(\text{tn})_3]^{3+}$, $[\text{Co}(\text{sen})]^{3+}$ and $[\text{Co}(\text{sep})]^{3+}$ and the partial resolution of $[\text{Co}(\text{stn})]^{3+}$ and $[\text{Co}(\text{Hbg})_3]^{3+}$, where stn and Hbg represent $\text{CH}_3\text{C}(\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{NH}_2)_3$ and biguanide ($\text{C}_2\text{H}_7\text{N}_5$), respectively. Some of the results are shown in Table 4. Several points can be noted, as follows:

(1) The efficiency of resolution is improved compared with that obtained by conventional normal-phase chromatography, $[\text{Co}(\text{tn})_3]^{3+}$ being completely resolved with ease.

(2) In all instances except with $[\text{Co}(\text{Hbg})_3]^{3+}$, whose skeleton is quite different from those of the other amine complexes, the Δ isomer is eluted later, which means that the Sb(*d*-tart) ion associates favourably with the Δ isomer. This coincides with the result obtained by normal-phase ion-exchange chromatography. One exception is $[\text{Co}(\text{tn})_3]^{3+}$, which is resolved only slightly with the Sb(*d*-tart) ion as the eluent in normal-phase chromatography⁵¹. Here the Δ is eluted faster than the Δ isomer, which means that Sb(*d*-tart) prefers the Δ to the Δ isomer. In the present reversed-phase chromatography, the Sb(*d*-tart) ion prefers the Δ to the Δ isomer. This contradiction is explained by assuming that this complex may take different conformations (chair and skew-boat) in different environments.

(3) The retention volumes for small-sized complexes, such as $[\text{Co}(\text{en})_3]^{3+}$, $[\text{Co}(\text{tn})_3]^{3+}$ or $[\text{Co}(\text{sen})]^{3+}$, are small and are not much affected by variation of the eluent counter ion M^- . In contrast, the retention volumes for large-sized complexes, such as $[\text{Co}(\text{sep})]^{3+}$, $[\text{Co}(\text{stn})]^{3+}$ or $[\text{Co}(\text{chxn})]^{3+}$ (chxn = cyclohexanediamine), are three to four times greater than those for small-sized complexes, especially when the eluent counter ion M^- is Na^+ , K^+ or NH_4^+ and decrease with increasing size of the eluent counter ions, $\text{N}(\text{CH}_3)_4^+$ and $\text{N}(\text{C}_2\text{H}_5)_4^+$ (see Fig. 17).

TABLE 4

RETENTION VOLUME OF THE LATER ELUTED ENANTIOMER AND THE SEPARATION FACTOR (α), OBTAINED WITH 0.05 M $\text{M}_2\text{Sb}(\textit{d}\text{-tart})$ SOLUTION AS THE ELUENT

Complex	Na^+		K^+		NH_4^+		$\text{N}(\text{CH}_3)_4^+$		$\text{N}(\text{C}_2\text{H}_5)_4^+$	
	V	α	V	α	V	α	V	α	V	α
$[\text{Co}(\text{en})_3]\text{Cl}_3$	10.85	1.99	12.18	2.00	11.18	1.97	12.18	2.27	13.58	2.65
$[\text{Co}(\text{tn})_3]\text{Cl}_3$	10.08	1.25	10.85	1.23	10.00	1.22	7.75	1.25	7.30	1.24
$[\text{Co}(\text{sen})]\text{Cl}_3$	10.75	1.97	11.98	2.01	11.50	2.04	12.23	2.33	14.98	2.65
$[\text{Co}(\text{sep})]\text{Cl}_3$	27.38	1.18	33.85	1.32	34.38	1.30	24.75	1.34	19.50	1.34
$[\text{Co}(\text{stn})]\text{Cl}_3$	38.00	1.00	40.00	1.00	38.25	1.00	27.75	1.00	17.55	1.00

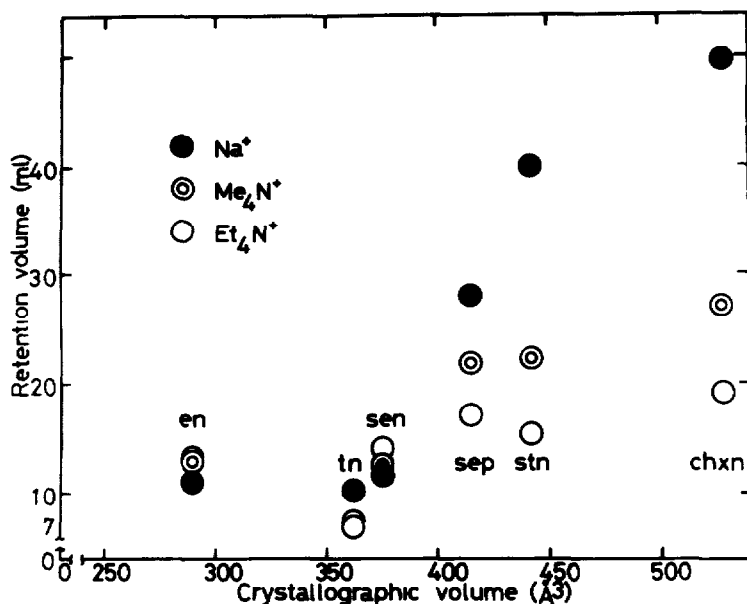


Fig 17 Dependence of the retention volume on the size of the complex ion [Eluted with $M_2Sb(d\text{-tart})$, $M = Na^+$ (●), Me_4N^+ (⊙), and Et_4N^+ (○)]

These trends can be interpreted as follows. The $Sb(d\text{-tart})$ ion is adsorbed on the long alkyl chain with its counter ion M^+ . When the small-sized complex ion approaches the adsorbed $Sb(d\text{-tart})$ ion it does not expel M^+ , because the small-sized complex ion is fairly hydrophilic, so that it stays for a while near the $Sb(d\text{-tart})$ ion, then moves away. In contrast, when the large-sized complex ion arrives at the adsorbed $Sb(d\text{-tart})$ ion, it can displace the counter ion M^+ and stay near the adsorbed $Sb(d\text{-tart})$ ion for a longer time, so that the retention volume is large. However, when the eluent counter ion M^+ is a large hydrophobic ion, such as $N(CH_3)_4^+$ or $N(C_2H_5)_4^+$, the complex ion cannot replace the counter ion so that the complex ion cannot stay for long and the retention volume decreases.

3.3 Spectroscopic evidence for directional ion association

The effect of *d*- and *l*-tartrate ions and antimony *d*- and *l*-tartrate ions⁵³ on the CD spectra of several $[Co(N)_6]^{3+}$ complexes of trigonal symmetry was investigated by Sakaguchi *et al*. As the first ligand-field band of the $[Co(N)_6]^{3+}$ complex consists of only two transitions, A_2 and E_a , which are polarized along the C_3 and C_2 axes, respectively, the problem here is to confirm which rotational strength, $R(A_2)$ or $R(E_a)$, changes primarily by the addition of tartrate and antimony tartrate ions, provided that these anions approach along the C_3 axis or C_2 axis. The complexes tested were the Δ enantiomers of $[Co(en)_3]^{3+}$ and its analogues, *fac*- and *mer*- $[Co(l\text{-pn})_3]^{3+}$, $[Co(sen)]^{3+}$, $[Co(sep)]^{3+}$ and $[Co(chxn)_3]^{3+}$ (Fig 18). These complexes contain substituent groups in the direction of the C_3 and C_2 axes of $[Co(en)_3]^{3+}$ in such a way that they prevent the access of an anion in that direction. The difference CD spectra (DCD spectra), defined as the CD spectra with the anion

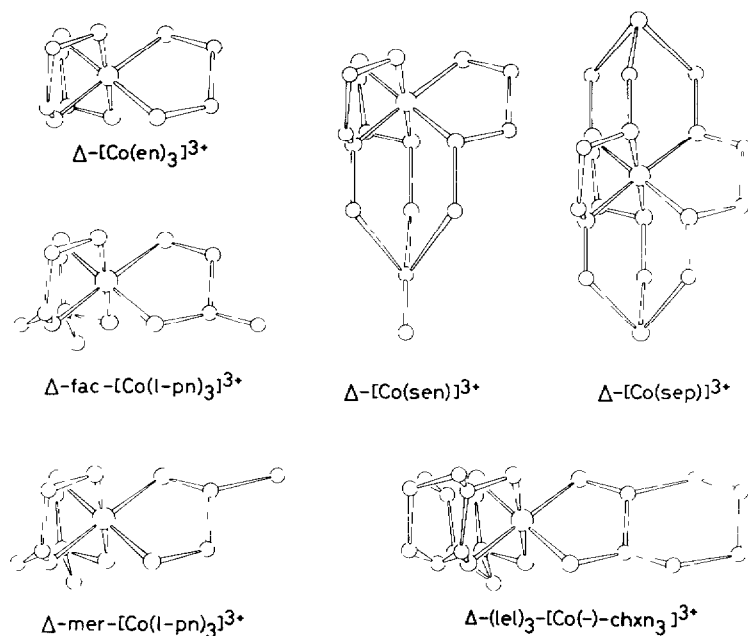


Fig 18 Structures of Δ -[Co(N)₆]³⁺ complexes

minus the CD spectra without the anion, were measured. From the DCD data, the association constant K and the CD spectrum of the ion pair were obtained. Table 5 shows the values of K_d , K_l and the degree of chiral discrimination, α , defined as the ration of $K_l - K_d$ and $K_l + K_d$.

It is worth noting that the value of α is zero for [Co(sep)]³⁺-tart²⁻, in which the access of the tart²⁻ ion is allowed along the C_2 axis but not along the C_3 axis. This means that the d -tart²⁻ ion cannot discriminate the chirality of [Co(sep)]³⁺ along the C_2 axis. Other [Co(N)₆]³⁺ complexes can accept the tart²⁻ ion approaching along the C_3 axis. The value of α is not zero. Therefore, it can be said that the tart²⁻ ion can discriminate the chirality of [Co(N)₆]³⁺ by association along the C_3 axis.

Concerning the CD change, the association of the tart²⁻ ion induces an increase in the E_a component for [Co(sep)]³⁺ and an increase in the A_2 component for the other complexes (see Fig. 19). The pattern of the CD change corresponds exactly to the direction of access of the anion.

A similar interpretation is applied to the ion association with the Sb(tart)²⁻ ion (see Fig. 20). As shown in Table 4, the value of α is not zero in the system [Co(sep)]³⁺-Sb(tart)²⁻, which means that the Sb(tart)²⁻ ion can discriminate the chirality of [Co(sep)]³⁺ through association along the C_2 axis. In accordance with this, the CD spectrum of [Co(sep)]³⁺ changes on addition of the Sb(tart)²⁻ ion in such a way as the E_a component increases. For complexes with two triangular facets composed of three NH hydrogens, the A_2 component is enhanced on ion association, which may be taken to indicate that the Sb(tart)²⁻ ion exerts axial perturbation in the ion pair. It is inferred that such an axial perturbation arises from hydrogen bonding between axial NH hydrogens on both trigonal facets of the complex and the

TABLE 5

ASSOCIATION CONSTANTS WITH $d\text{-tart}^{2-}$ AND $\text{Sb}(d\text{-tart})^{2-}$

Complex	$d\text{-tart}^{2-}$			$\text{Sb}(d\text{-tart})^{2-}$		
	K_1	K_d	$\alpha^*(\%)$	K_1	K_d	$\alpha^*(\%)$
$\Delta\text{-}[\text{Co}(\text{en})_3]^{3+}$	13.4	11.7	7	47.3	26.8	28
$\Delta\text{-}[\text{Co}(\text{sen})]^{3+}$	71.7	49.6	18	75.0	ca 5	90
$\Delta\text{-}[\text{Co}(\text{sep})]^{3+}$	39.3	38.3	0	52.4	39.0	15
$\Delta\text{-mer-}[\text{Co}(l\text{-pn})_3]^{3+}$	26.7	21.2	15	27.9	19.5	18
$\Delta\text{-fac-}[\text{Co}(l\text{-pn})_3]^{3+}$	30.3	22.5	11	24.1	16.8	18
$\Delta\text{-}[\text{Co}(l\text{-chxn})_3]^{3+}$	21.4	15.4	16	21.3	14.0	21

$$* \alpha = (K_1 - K_d)/(K_1 + K_d) \cdot 100$$

oxygen atoms of the $\text{Sb}(\text{tart})^{2-}$ ion, as shown in Fig. 21. This model can also explain equally well the results of the chromatographic separations. The difference between the L-J model and the present model lies in the orientation of the anion. In the L-J model, the anion was assumed to face the complex cation with the tartrate backbone in front. This model of access is not favoured electrostatically over that of the present model.

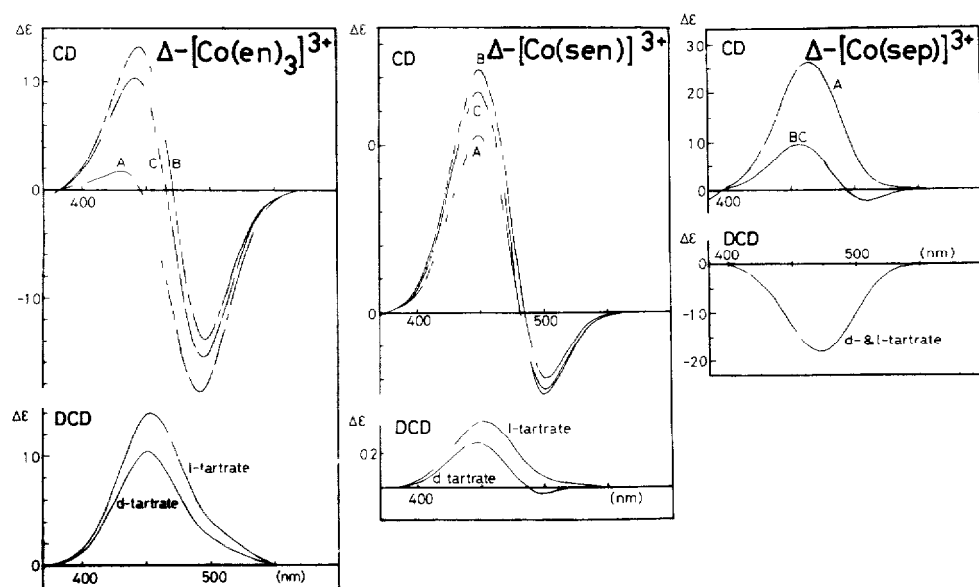


Fig. 19 (Above) CD spectra of (A) the metal complex and of the ion pairs with (B) l -tartrate and (C) d -tartrate (Below) DCD spectra due to l - and d -tartrates

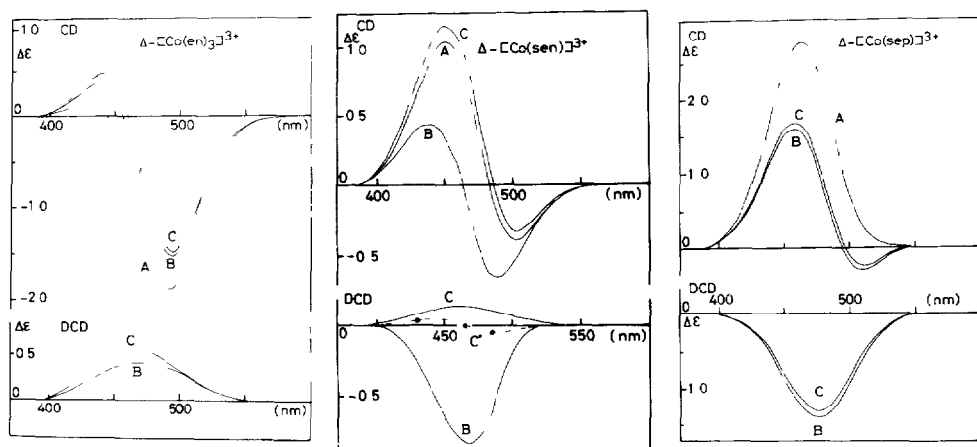


Fig 20 (Above) CD spectra of (A) the metal complex and of the ion pairs with (B) $\text{Sb}(d\text{-tart})^{2-}$ and (C) $\text{Sb}(l\text{-tart})^{2-}$ (Below) DCD spectra to $\text{Sb}(d\text{-tart})^{2-}$ and $\text{Sb}(l\text{-tart})^{2-}$



Fig 21 Proposed model for the favourable pair $\Delta\text{-}[\text{Co}(\text{en})_3]^{3+}\text{-Sb}(l\text{-tart})^{2-}$ For clarity, only the relevant hydrogens are shown for the cation. Solid lines are situated in front.

4 RESOLUTION OF NEUTRAL COMPLEXES

4.1 Resolution of $\text{fac-}[\text{Co}(\alpha\text{-AA})_{3-n}(\beta\text{-Ala})_n]$

In order to establish the detailed features of the optical resolution of facial tris(aminoacidato)chelates by $d\text{-tart}^{2-}$ and by $\text{Sb}(d\text{-tart})^{2-}$ ions, a series of enantiomeric pairs of $\text{fac-}[\text{Co}(\text{gly})_{3-n}(\beta\text{-ala})_n]$ and two series of diastereomeric pairs of $\text{fac-}[\text{Co}(L\text{-ala})_{3-n}(\beta\text{-ala})_n]$ and $\text{fac-}[\text{Co}(D\text{-ala})_{3-n}(\beta\text{-ala})_n]$ were prepared. Each pair corresponding to $n = 3, 2, 1$ and 0 was loaded on a column of an anion-exchange

resin saturated with Cl^- , SO_4^{2-} , $d\text{-tart}^{2-}$ and $\text{Sb}(d\text{-tart})^{2-}$ and eluted with water⁵⁴ Fig 22 shows schematic representations of the retention volumes obtained When eluted through the Cl^- form of the resin, the retention volumes are similar with a variation of n from 3 to 0 In contrast, when eluted through the SO_4^{2-} and $d\text{-tart}^{2-}$ forms of the resin, the retention volume decreases with the decreasing n The trend of the retention volume on going from $n = 3$ to 0 is nearly the same with the SO_4^{2-} and $d\text{-tart}^{2-}$ forms of the resin, which strongly suggests that the association takes place along the C_3 axis The NH_2 group of the chelated $\beta\text{-ala}$ in $\text{fac}[\text{Co}(\beta\text{-ala})_3]$ has two types of N-H bonds, axial and equatorial Three axial N-H bonds form hydrogen bonds with three oxygen atoms of SO_4^{2-} and $d\text{-tart}^{2-}$ ions which are coming along the C_3 axis, so that a relatively stable association product is formed However, substitution of the five-membered chelate ring ($\alpha\text{-ala}$) for the six-membered chelate ring ($\beta\text{-ala}$) results in a decrease in the number of the axial N-H bonds which provide suitable sites for association along the C_3 axis Hence the complex decreases its ability to associate with SO_4^{2-} and $d\text{-tart}^{2-}$ with increasing number of $\alpha\text{-ala}$ substituents, so that the retention volume and the efficiency of discrimination also decrease As the $d\text{-tart}^{2-}$ ion associates favourably with the Δ isomer, as with $[\text{Co}(\text{en})_3]^{3+}$, the Δ isomer is eluted faster through the $d\text{-tart}^{2-}$ form of the resin

A different pattern of optical resolution was obtained on elution through the $\text{Sb}(d\text{-tart})^{2-}$ form of the resin, as shown in Fig 23 In a series of glycine complexes, the retention volume increases with increase in the number of five-membered chelate rings (gly) The separation of two enantiomers also increases with increasing number of five-membered chelate rings In contrast, the retention volume for a series of $\alpha\text{-ala}$ complexes decreases with increasing number of five-membered chelate rings According to the L-J model, the methyl group in $\alpha\text{-ala}$ chelate complexes narrows the L-shaped channel and reduces the opportunity for the anion to associate, and at the same time sharpens the discrimination between the L and J shapes Hence the separation increases with increasing number of five-membered chelate rings

Similar trends were observed in the retention volumes and their ratios for a series of enantiomeric and diastereomeric pairs of $\text{fac}[\text{Co}(\text{D/L-ser})_{3-n}(\beta\text{-ala})_n]$, where D/L-ser represents D- and L-serine⁵⁵

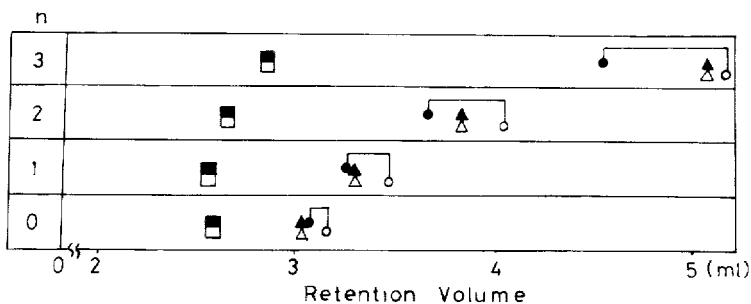


Fig 22 Retention volumes of $\Delta[\text{Co}(\beta\text{-ala})_n(\text{L-ala})_{3-n}]$ and $\Delta[\text{Co}(\beta\text{-ala})_n(\text{D-ala})_{3-n}]$ ($n = 0-3$) ■ and □, elution through the Cl^- form of the resin, ▲ and △, elution through the SO_4^{2-} form of the resin, ● and ○, elution through the tart^{2-} form of the resin (closed and open symbols correspond to the Δ - and Λ -enantiomers respectively)

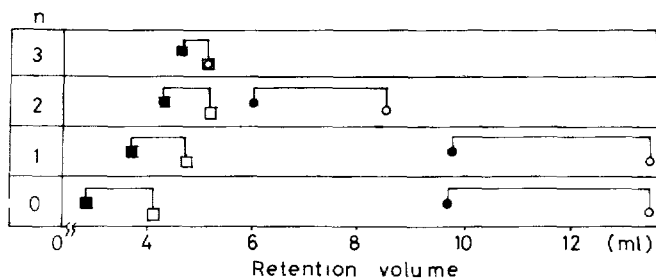


Fig 23 Retention volumes of two series of enantiomeric pairs of *fac*-[Co(β -ala) $_n$ (gly) $_3$ - $_n$] (● and ○) and *fac*-[Co(β -ala) $_n$ (α -ala) $_3$ - $_n$] (■ and □) eluted through a column containing Sb(tart) $^{2-}$. Closed and open symbols correspond to the Δ and Λ enantiomers, respectively

4.2 Resolution of *mer*-[Co(AA) $_3$] complexes

Meridional isomers of [Co(β -ala) $_3$] were also completely resolved through the Sb(*d*-tart) $^{2-}$ form of QAE-Sephadex resin with ethanol-water as the solvent⁵⁶ (see Fig 24). Structural analysis of the crystal obtained from the second-eluted fraction revealed that the absolute configuration is Δ ⁵⁷. Therefore, it became clear that the Δ isomer of *mer*-[Co(β -ala) $_3$] associates more favourably than the Λ isomer with the Sb(*d*-tart) $^{2-}$ ion. The diastereomeric pairs of *mer*-[Co(L-ala) $_3$] and *mer*-[Co(D-ala) $_3$] were also completely resolved through the Sb(*d*-tart) $^{2-}$ form of the anion-exchange resin with water as the eluent⁵⁶. *mer*-[Co(gly) $_3$] was also resolved into enantiomers, although only partially. In all these instances, the Λ were eluted faster than the Δ isomer, which indicates that the Sb(*d*-tart) $^{2-}$ ion prefers the Δ to the Λ isomer. Hence the L-J model cannot explain the separation order in the meridional chelates.

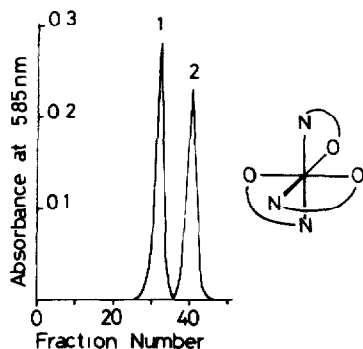


Fig 24 Elution curve of *mer*-[Co(β -ala) $_3$]. Eluent, 50% ethanol-water, column, Sb(*d*-tart) $^{2-}$ form of QAE-Sephadex A-25 (54 \times 2 cm I.D.)

4.3 Resolution of [M(acac) $_3$]

A variety of chromatographic techniques⁵⁸⁻⁶¹ have been applied for the resolution of tris(acetylacetonato)M(III) complexes, which are otherwise not easily resolved by conventional diastereomer formation. It seems timely to review recent developments in the chromatographic resolution of [M(acac) $_3$].

Yamagishi⁶² reported the partial resolution of $[M(\text{acac})_3]$ ($M = \text{Co}, \text{Cr}$ or Ru) on a column of montmorillonite whose cation-exchange site had been replaced with $\Delta\text{-}[\text{Ni}(\text{phen})_3]^{2+}$. His results indicated that $\Delta\text{-}[M(\text{acac})_3]$ is preferentially adsorbed on $\Delta\text{-}[\text{Ni}(\text{phen})_3]$ in the stationary phase, suggesting the importance of hydrophobic interactions between $[M(\text{acac})_3]$ and $[M(\text{phen})_3]^{2+}$. He applied this unique technique to the resolution of various hydrophobic metal complexes. For example, he investigated the optical resolution of a series of neutral complexes of the type $[\text{Co}(\text{acac})_n(\text{gly})_{3-n}]$ ($n = 3, 2, 1$ and 0) with water as the eluent and achieved partial resolution for $[\text{Co}(\text{acac})_3]$, $[\text{Co}(\text{acac})_2(\text{gly})]$ and $[\text{Co}(\text{acac})(\text{gly})_2]$.⁶³

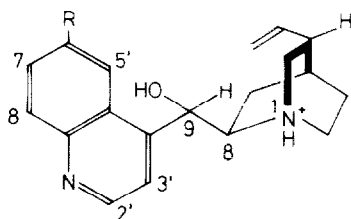
Another notable study was made by Okamoto and Yuki⁶⁴, who showed that optically active poly(triphenylmethyl methacrylate) (PTrMA) coated on silica gel serves as a useful packing material for the chromatographic resolution of $[\text{Co}(\text{acac})_3]$ and $[\text{Cr}(\text{acac})_3]$. They were, to our knowledge, the first to achieve the complete resolution of these neutral complexes by chromatography. The separation factors were 1.32 and 1.37 for $[\text{Co}(\text{acac})_3]$ with methanol and methanol-water (80/20), respectively, as the eluent. They proposed that chiral discrimination is effected through hydrophobic interactions between acac ligands and the triphenyl group in the chiral polymer.

5 RESOLUTION OF ANIONIC COMPLEXES

5.1 Resolution by alkaloid cations

5.1.1 Resolution of $[\text{Co}(\text{O})_4(\text{N})_2]^-$ type hydrophilic complexes

Although many examples of successful resolution by chromatography have been reported for cationic complexes, few examples have been published for anionic complexes. This can probably be attributed to the lack of appropriate chiral selectors. Cinchona alkaloids, *e.g.*, cinchonine, cinchonidine, quinidine and quinine, are well known to be very effective for shifting the chiral equilibrium of an initially racemic labile complex (see Fig. 25). This suggests that these alkaloid cations interact differently with the two enantiomers of the complex and can be used as a chiral selector in chromatographic separations. As alkaloids are fairly soluble in water, yet have a hydrophobic character, they can be used as ion-pairing reagents. Yamazaki⁶⁵



$R = \text{H}$

d-(8R,9S)-cinchoninium ion

l-(8S,9R)-cinchonidinium ion

$R = \text{OMe}$

d-(8R,9S)-quinidinium ion

l-(8S,9R)-quininium ion

Fig. 25 Structure of the alkaloid cations

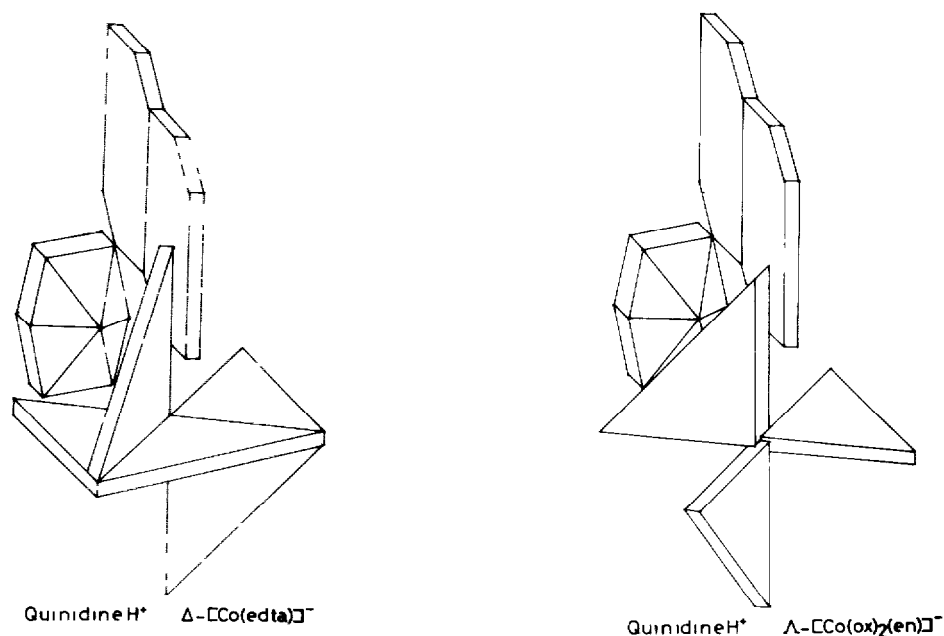


Fig 26 Proposed mode of chiral discrimination between the quininium cation and Δ -[Co(edta)]⁻ (left) and between the quininium cation and Λ -[Co(ox)₂(en)]⁻ (right)

achieved the complete resolution of [Co(edta)]⁻, *cis*-[Co(ida)₂]⁻, etc, by reversed-phase ion-pair chromatography using quinine as an ion-pairing reagent⁵⁻⁸. Izumoto *et al*⁶⁶ applied this technique to the optical resolution of several anionic complexes of the type *cis*-[Co(O)₄(N)₂]⁻, such as [Co(edta)]⁻, [Co(cydt)₂]⁻, [Co(ida)₂]⁻, [Co(ox)₂(en)]⁻ and *cis*- α -[Co(ox)(edda)]⁻, where cydt and edda are cyclohexanediaminetetraacetate and ethylenediaminediacetate, respectively. With quinine, quin-

TABLE 6

CHROMATOGRAPHIC RESOLUTION OF [Co(ox)₂(phen)]⁻ WITH CINCHONA ALKALOID CATIONS AS A CHIRAL ELUENT

Eluent	Distance (cm)	Enantiomer eluted fastest
(8 <i>R</i> ,9 <i>S</i>)-cinchonine	3.1	Δ
(8 <i>S</i> ,9 <i>R</i>)-cinchonidine	1.9	Δ
(8 <i>R</i> ,9 <i>S</i>)-quinidine	> 4	Δ
(8 <i>S</i> ,9 <i>R</i>)-quinine	4.0	Δ
N(1)-Me-(8 <i>S</i> ,9 <i>R</i>)-quinine	3.4	Δ
9-AcO-(8 <i>R</i> ,9 <i>S</i>)-cinchonine	3.4	Δ
9-AcO-(8 <i>S</i> ,9 <i>R</i>)-cinchonidine	2.2	Δ
9-AcO-(8 <i>R</i> ,9 <i>S</i>)-quinidine	5.3, 9.1*	Δ
9-AcO-(8 <i>S</i> ,9 <i>R</i>)-quinine	4.9, 8.9*	Δ

* Complete resolution achieved

idine and cinchonidine, complete resolution was achieved for all these complexes. It was found that the efficiency of chiral discrimination by cinchonine is not sufficient for complete resolution. The proposed mode of chiral discrimination is shown in Fig 26

5.1.2 Resolution of $[Co(O)_4(N)_2]^-$ type hydrophobic complex

Miyoshi *et al*⁶⁷ found that the (8*S*,9*R*)-quinine cation shifts considerably the chiral equilibrium of initially racemic $[Cr(ox)_2(phen)]^-$ in water, and attempted to resolve the corresponding inert Co(III) complex by ion-exchange chromatography using various alkaloid cations as the eluent⁶⁸. The results obtained were examined thoroughly from a stereochemical viewpoint, and the features of chiral discrimination were vividly illustrated.

Table 6 gives the distances (cm) from the top of the resin to the band(s) developed when racemic $K[Co(ox)_2(phen)]$ was eluted with 200 ml of each eluent (20 mM). When complete resolution is attained, two figures are given for each. The absolute configuration of the faster eluted enantiomer is also listed in Table 6. The following characteristics can be extracted from the table: (1) the elution order is governed by the configuration around the C-8 and C-9 atoms of each alkaloid, (2) alkaloids having a methoxy group at the 6'-position of the quinoline ring, *i.e.*, quinine and quinidine, have a greater eluting ability than cinchonidine and cinchonine, respectively, (3) N(1)-methylation of each alkaloid diminishes its eluting ability, whereas acetylation of the OH group at the C-9 atom enhances it, the elution order being completely inverted, (4) complete resolution is attainable with 9-AcO derivatives, and (5) alkaloids having an (8*R*,9*S*) configuration have a greater eluting ability than those having an (8*S*,9*R*) configuration.

A detailed study of the kinetic aspects of the Pfeiffer effect of $[Cr(ox)_2(phen)]^-$ and PMR spectral changes of each alkaloid on addition of $[Co(ox)_2(phen)]^-$ demonstrated that both of the N(1)-H⁺ and the C(9)-OH groups are hydrogen-bonded to the ox part of the complex, and that the quinoline ring bearing an MeO group is stacked with the phen ligand of the complex. Coupled with these experimental observations, Miyoshi *et al* explained the five characteristics in Table 6 on the basis of the two concomitant interaction modes.

Figs 27 and 28 depict the two association models they proposed (types 1 and 2, respectively), where hydrophobic stacking interactions between the quinoline ring

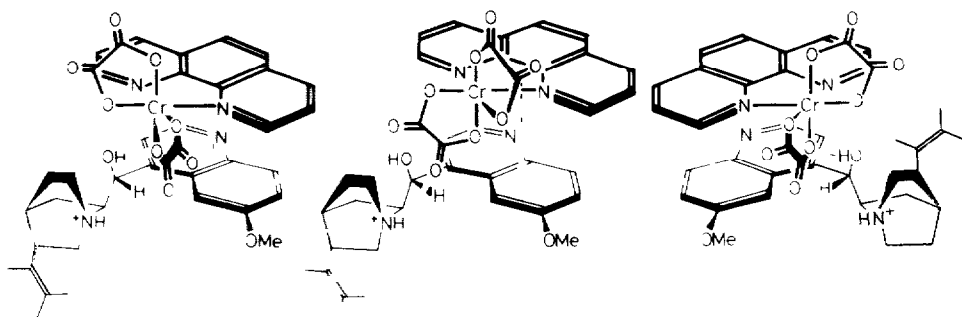


Fig 27 Type 1 association models between $[Cr(ox)_2(phen)]^-$ and alkaloid ions. Left, (8*S*,9*R*)-quininium-*A*-complex; middle, (8*S*,9*R*)-quininium-*D*-complex; right, (8*R*,9*S*)-quinidinium-*D*-complex.

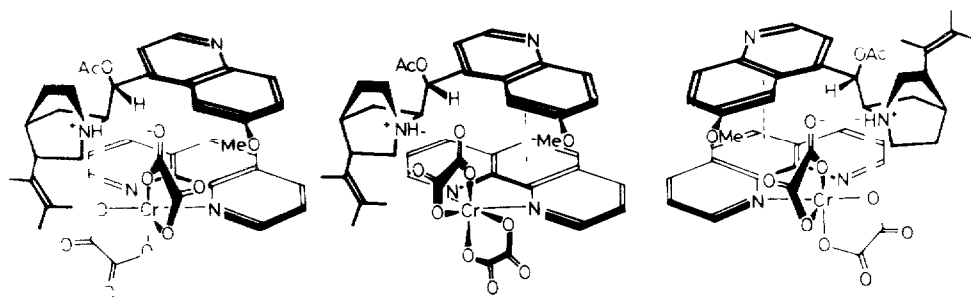


Fig 28 Type 2 association model between $[\text{Cr}(\text{ox})_2(\text{phen})]^-$ and acetylated alkaloid ions Left, (8*S*,9*R*)-AcO-quininium Δ -complex, middle, (8*S*,9*R*)-AcO-quininium Δ -complex, right, (8*R*,9*S*)-quinidinium- Δ -complex

and the phen ligand contribute appreciably in addition to the hydrogen-bonding interactions mentioned above. If (8*S*,9*R*)-quinine is taken as an example, it associates with the Δ complex more firmly (left model) than with the antipode (middle) in the type 1 mode, as quinine is hydrogen-bonded to both of the two ox ligands for the former complex. Similarly, (8*R*,9*S*)-quinidine associates more favourably with the Δ complex (right) in this way, the elution orders obtained can be interpreted easily, except for 9-acetoxy derivatives. However, these alkaloids can adopt the type 2 mode simultaneously when the OH group is not involved in the interaction with the complex, but the quinoline ring is stacked with the phen ligand as before. In this mode, quinine interacts with the Δ complex (left model in Fig 28) more intimately than with the antipode, as the N(1)-H⁺ group is hydrogen-bonded to both of the ox ligands for the Δ complex. Similarly, (8*R*,9*S*)-quinidine favours the Δ complex over its antipode in the type 2 mode. In addition, a close examination of Figs 27 and 28 reveals that the ox part of the complex experiences steric hindrance from the vinyl group at the C-3 atom for (8*S*,9*R*)-quinine but not for (8*R*,9*S*)-quinidine. The steric hindrance explains why (8*R*,9*S*)-alkaloids have a greater eluting ability than their (8*S*,9*R*)-diastereomers. However, as opposite enantiomers are favoured in the two interactions modes by a particular alkaloid, the efficiency of chiral discrimination is naturally low. As a result, complete resolution is not achieved with these alkaloids.

On the other hand, if the alkaloid is acetylated, it is forced to adopt the type 2 mode exclusively, as the OH group is not available for hydrogen bonding. Hence complete resolution is attained with 9-AcO derivatives.

5.2 Chiral discrimination by complex ions

The chromatographic resolution of anionic complexes has rarely been attempted because appropriate chiral cationic eluents are not readily available. However, optically active metal complexes have been successfully utilized as resolving agents for metal complexes of opposite charge. For example, $[\text{Co}(\text{ox})_2(\text{en})]^-$ is easily resolved with optically active *cis*- $[\text{Co}(\text{NO}_2)_2(\text{en})_2]^+$ via diastereomeric salt formation. In addition, Miyoshi and co-workers found that asymmetric complex cations of the type *cis*- $[\text{M}(\text{X})(\text{Y})(\text{diamine})_2]^{n+}$ (X and/or Y = anionic ligand) displace the chiral equilibrium of initially racemic $[\text{Cr}(\text{ox})_3]^{3-}$ in dioxane-water mixtures^{69,70}. These observations suggest that chiral cationic complexes effectively recognize the chirality

TABLE 7

ENANTIOMERS OF ANIONIC COMPLEXES FORMING FAVOURABLE PAIRS WITH Δ CATIONIC COMPLEXES

Complex	Δ -[Co(sep)] ³⁺ (C ₂)	Δ -[Co(chxn) ₃] ³⁺ (C ₃)	Δ -[Co(en) ₃] ³⁺ (C ₂ and C ₃)
[Co(edta)] ⁻ (C ₃)	Δ	Δ	Δ
[Co(ox) ₂ (en)] ⁻ (C ₂)	Δ	Δ	Δ
[Co(ox) ₂ (gly)] ²⁻ (C ₂ and C ₃)	Δ	Δ	Δ
[Cr(mal) ₃] ³⁻ (C ₂ and C ₃)	Δ	Δ	Δ
<i>fac</i> -[Co(β -ala) ₃] (C ₃)	Δ	Δ	Δ

of anionic complexes in solution, and therefore they are potentially used as chiral selectors in the chromatographic resolution of anionic complexes

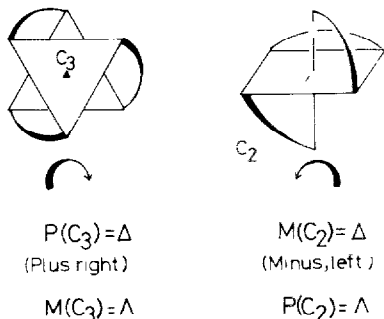
Tatehata *et al*⁷¹ achieved the complete resolution of [Co(ox)₂(gly)]²⁻ with a DEAE-Sephadex column, using 30% aqueous ethanol containing Δ -[Co(en)₃]³⁺ as the eluent. Δ -(+)₅₄₆-[Co(ox)₂(gly)]²⁻ was eluted faster. They proposed a model of a favourable pair, Δ -[Co(en)₃]³⁺- Δ -[Co(ox)₂(gly)]²⁻, in which the anionic complex is attached to the triangular face of Δ -[Co(en)₃]³⁺ in the direction of the C₃ axis and makes a face-to-face close contact through hydrogen bonds.

Although this model seems to explain the strong association between the two complex ions, it is difficult to explain the mechanism of chiral discrimination and why the Δ cation prefers the Δ anion to the Λ anion in this type of ion pairing. Sakaguchi *et al*⁷² expressed doubts about the mechanism proposed by Tatehata *et al* and attempted to study the mode of interaction between chiral complex ions more generally. They eluted several anionic complexes with water on SP-Sephadex saturated with various optically active [Co(N)₆]³⁺-type complexes, and also chromatographed these anionic complexes on an anion exchanger (IEX 220) with aqueous solutions of chiral [Co(N)₆]³⁺-type complexes as the eluent. Both sets of results were consistent with respect to favourable diastereomeric combinations. Table 7 shows the chirality of the anionic complexes that form favourable pairs with the cationic complexes (Δ).

The chirality of these selector cations (Δ) is specified by looking at the complexes either along the C₃ axis as P(C₃) or along the C₂ axis as M(C₂). These notations define the chirality by the handedness of the mutual spatial disposition of three or two chelate rings (see Fig. 30). Hence the anionic complexes to be resolved will experience P(C₃) chirality (right-handed propellers) when they approach the Δ cation from the cation's C₃ axis, whereas they will experience M(C₂) chirality (left-handed propellers) in the case of the C₂ access (access along the cation's C₂ axis from the side opposite to one chelate ring). The chirality of anionic complexes felt by cationic complexes is described similarly. Sakaguchi *et al* assumed that favourable pairs are formed between those complexes which have the same handedness of chelate rings when viewed along the axis that each complex ion directs to the counterpart complex, *i.e.*, the combinations M⁺(C₂ or C₃)-M⁻(C₂ or C₃) and P⁺(C₂ or C₃)-P⁻(C₂ or C₃) form favourable pairs, where the first chirality refers to the cation and the second to the anion.

For example, Δ -[Co(sep)]³⁺ will direct its C₂ axis to anionic complexes on

Handedness of Chelate Rings

 Δ Complex $M(\text{ch})_3$ Fig 29 Handedness of chelate rings of the Δ -complex $[M(\text{ch})_3]$

association, as its C_3 axis is blocked by bulky covalent caps. Then, anionic complexes always feel $M(C_2)$ chirality and Δ -[Co(sep)]³⁺ therefore forms a favourable pair with those anionic complexes which have $M(C_2) = \Delta$ or $M(C_3) = \Lambda$ chirality. In other words, if anionic complexes "use" the C_3 axis, their Λ enantiomers are favoured by Δ -[Co(sep)]³⁺, whereas the Δ enantiomers are favoured if they use the C_2 axis. Steric and electrostatic requirements lead us to suppose that [Co(edta)]⁻, [Co(ox)₂(gly)]²⁻, [Cr(ox)₃]³⁻ and *fac*-[Co(β -ala)₃] tend to direct their C_3 (or pseudo- C_3) axes towards cationic complexes, so that their Λ [*l.e.*, $M(C_3)$] enantiomers form favourable pairs with Δ -[Co(sep)]³⁺, as is actually found.

On the other hand, Δ -[Co(chxn)₃]³⁺ is forced to use only its C_3 axis owing to its bulky chxn rings, the chirality felt by anionic complexes being $P(C_3)$. Then, the Δ enantiomers [$P(C_3)$] of the above anionic complexes are favoured by Δ -[Co(chxn)₃]³⁺. [Co(en)₃]³⁺ has to use its C_2 axis exclusively to be consistent with the experimental results, although both the C_3 and C_2 axes are available.

The interpretations presented above, however, do not accommodate the results obtained for [Co(ox)₂(en)]⁻ which judging from electrostatic considerations should use its C_2 axis only. Miyoshi *et al.*⁷³ proposed another mechanism of chiral discrimination in which hydrogen bonds between the associating complex ions play an essential role. According to their mechanism (see Fig 29), a homochiral combination, $\Delta^+ - \Delta^-$ (or $\Lambda^+ - \Lambda^-$), is a favourable pair when the cationic complex uses the C_3^+ axis, whereas a heterochiral combination $\Delta^+ - \Lambda^-$ (or $\Lambda^+ - \Delta^-$) is a favourable pair when it uses the C_2^- axis, irrespective of which axis (C_3^- or C_2^-) is directed by the anionic complex. Hence it follows that Δ -[Co(sep)]³⁺, which uses only the C_2 axis, forms favourable pairs always with the Λ anionic complexes, whereas the opposite enantiomers (Δ) are favoured by Δ -[Co(chxn)₃]³⁺, which uses the C_3 axis exclusively.

It is necessary to discuss Δ -[Co(en)₃]³⁺ separately, as it can use both the C_3 and C_2 axes for hydrogen bonding to anionic complexes. For this complex, all the modes conceivable are possible: $C_3^+ - C_3^-$ ($\Delta^+ - \Delta^-$), $C_3^+ - C_2^-$ ($\Delta^+ - \Delta^-$), $C_2^+ - C_3^-$ ($\Delta^+ - \Lambda^-$) and $C_2^+ - C_2^-$ ($\Delta^+ - \Lambda^-$). Miyoshi *et al.* considered that the first interaction mode contributes appreciably to the overall interaction, but not effectively to chiral discrimination, as no definite difference in the interaction is discernible between the

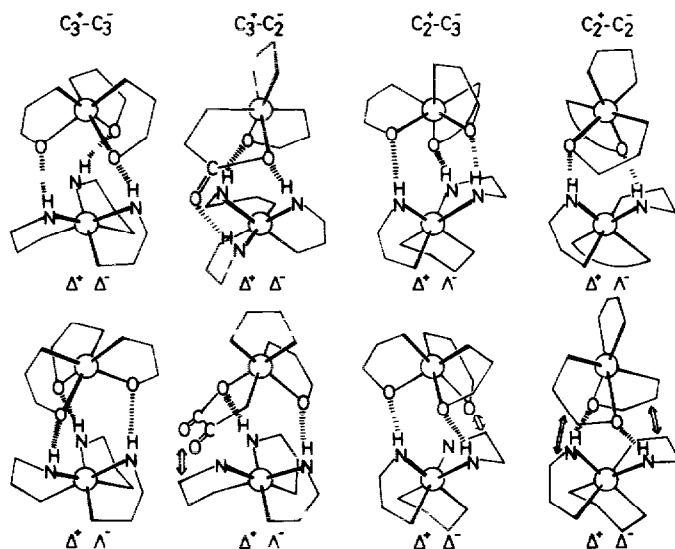


Fig 30 Four types of hydrogen bonding interactions between the complex cation and anion relevant to chiral discrimination

$\Delta^+ - \Delta^-$ and $\Delta^+ - \Lambda^-$ combinations (for the $C_3^+ - C_3^-$ mode) However, the $C_3^+ - C_2^-$ and $C_2^+ - C_3^-$ modes serve effectively in chiral discrimination because three hydrogen bonds are possible for favourable pairs, whereas only two hydrogen bonds are formed for unfavourable pairs. The $C_2^+ - C_2^-$ mode is also effective, but contributes to a lesser extent than the $C_3^+ - C_2^-$ and $C_2^+ - C_3^-$ modes because chiral discrimination is effected through the steric repulsion of chelate rings between the complex ions, two hydrogen bonds are possible for both the favourable and unfavourable pairs.

With the above considerations, the results obtained for $[\text{Co}(\text{en})_3]^{3+}$ can be interpreted as follows. When the anionic complexes use the C_3 axis only, as with $[\text{Co}(\text{edta})]^-$ and *fac*- $[\text{Co}(\beta\text{-ala})_3]$, the $C_2^+ - C_3^-$ mode ($\Delta^+ - \Lambda^-$) predominates over the $C_3^+ - C_3^-$ mode ($\Delta^+ - \Delta^-$), Δ - $[\text{Co}(\text{en})_3]^{3+}$ forming favourable pairs with the Λ enantiomers of these anionic complexes. When the anionic complexes use the C_2 axis, as with $[\text{Co}(\text{ox})_2(\text{en})]^-$, the $C_3^+ - C_2^-$ mode predominates over the $C_2^+ - C_2^-$ mode, Λ - $[\text{Co}(\text{ox})_2(\text{en})]^-$ being favoured by Δ - $[\text{Co}(\text{en})_3]^{3+}$.

On the other hand, if an anionic complex can use both of the C_3 and C_2 axes, e.g., $[\text{Co}(\text{ox})_2(\text{gly})]^{2-}$ and $[\text{Cr}(\text{mal})_3]^{3-}$, the $C_3^+ - C_2^-$ ($\Delta^+ - \Delta^-$), $C_2^+ - C_3^-$ ($\Delta^+ - \Lambda^-$) and $C_2^+ - C_2^-$ ($\Delta^+ - \Lambda^-$) modes contribute dominantly to chiral discrimination, as the contribution of the $C_3^+ - C_3^-$ ($\Delta^+ - \Delta^-$) mode is negligible. It follows that then Δ - $[\text{Co}(\text{en})_3]^{3+}$ prefers the Λ enantiomers of $[\text{Co}(\text{ox})_2(\text{gly})]^{2-}$ and $[\text{Cr}(\text{mal})_3]^{3-}$, although the efficiency of chiral discrimination is naturally low.

As discussed above, $[\text{Co}(\text{en})_3]^{3+}$ is not an effective discriminator of the anionic complexes listed in Table 7, because it can direct both the C_3 and C_2 axes to anionic complexes. Further, $[\text{Co}(\text{chxn})_3]^{3+}$ is not expected to discriminate effectively the chirality of those anionic complexes which can use the C_3 axis only, as the discrimination is effected here by the $C_3^+ - C_3^-$ mode. These discussions lead us to conclude that efficient discrimination occurs when only the $C_3^+ - C_2^-$ or $C_2^+ - C_3^-$ interaction mode

is possible. For example, $[\text{Co}(\text{sep})]^{3+}$ should serve as a good chiral selector for those anionic complexes which can direct the C_3 axis to the selector cationic complexes, e.g., $[\text{Co}(\text{edta})]^-$, $[\text{Co}(\text{ox})_2(\text{gly})]^{2-}$, $[\text{Cr}(\text{ox})_3]^{3-}$ and $\text{fac-}[\text{Co}(\beta\text{-ala})_3]$. On the other hand, it is not recommended to use $[\text{Co}(\text{en})_3]^{3+}$ as a chiral selector. In fact, complete resolution is attained for $\text{fac-}[\text{Co}(\beta\text{-ala})_3]$ when it is eluted with water on a very short column packed with Δ - $[\text{Co}(\text{sep})]^{3+}$ -saturated SP-Sephadex C-25 resin, but not with Δ - $[\text{Co}(\text{en})_3]^{3+}$. Of course, the Δ enantiomer is eluted faster here, in keeping with the proposed mechanism. However, if $[\text{Co}(\text{en})_3]^{3+}$ is forced to use the C_2 axis only (or the C_3 axis only), its discriminating ability should be greatly increased, as exemplified by $[\text{Co}(\text{sep})]^{3+}$. It is desirable and probably possible to design the structures of chiral selector complexes so that they will be effective in the chromatographic resolution of a particular metal complex if the electrostatic interaction between complex ions, which is not discussed here, is properly taken into account.

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