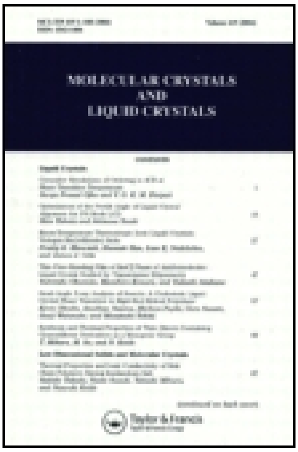

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Chiral Discrimination in the Solid and the Solution States

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CHIRAL DISCRIMINATION IN THE SOLID AND THE SOLUTION STATES

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Abstract Crystal packing modes were compared for the active and the corresponding racemic crystals obtained for various representative compounds. In the case of 1,1'-binaphthyl, the molecular conformation itself was different in the two crystal forms. For metal complexes of D_3 symmetry with three-bladed propeller shape, there appear to be only a few favoured crystal packing modes, which is in good agreement with our dispersion energy calculations. Using CD spectroscopy and X-ray crystallography, chiral discriminations of optically labile chromium complexes of D_3 symmetry have been investigated in the solid and the solution states.

INTRODUCTION

Racemic compounds sometimes crystallize into a conglomerate of optical active crystals each containing only one of the optical isomers. However, this phenomenon of so-called spontaneous optical resolution on crystallization does not occur frequently. Most chiral compounds crystallize to form true racemates, accommodating equal amounts of optical antipodes. Wallach[1] presented a rule which states that racemic crystals tend to be denser than their chiral counterparts. Our simple survey[2] however has indicated that the combination of optical antipodes to form a racemate is not necessarily accompanied by a volume contraction. The reason for the rareness of spontaneous optical resolution can be explained by the packing arrangement[2] based on Kitaigorodsky's pure geometric models[3] who investigated the high frequency of some space groups in molecular crystals and the virtual absence of others. A recent thorough analysis by Brock *et al*[4] supported this idea, based on data for 129 racemic/active pairs extracted from the Cambridge Structural Data Base.

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We have studied chiral discrimination of organic compounds such as 1,1'-binaphthyl,[5] helicenes[6] and their derivatives,[7-8] sodium ammonium tartrate,[9] and metal complexes chelated with organic ligands.[10-14] We have also investigated chiral discrimination of optically labile metal complexes using CD spectroscopy.[15-16] In this paper, we summarize our work on chiral discriminations of 1,1'-binaphthyl and metal complexes of D_3 symmetry and report our latest work on optically labile chromium complexes in the crystalline and in the solution states.

1,1'-BINAPHYTHYL

1,1'-binaphthyl exists as the R-(-)- and the S-(+)- isomers due to a restricted rotation around the central C-C bond. The racemic crystal which is much denser than the corresponding active form melts at 145 °C, while the active form melts at 158 °C. Thermodynamically, the racemic crystal is the more stable up to a transition temperature at 76 °C. Above the temperature, the racemic crystals undergo a solid-state transformation to a conglomerate of active crystals. The crystal structure of the racemate, determined by Kerr and Robertson[17] shows that the molecule adopts the cisoid conformation with a dihedral angle between the two naphthalene ring planes of 68°. Our structure analysis of the optically active crystal has shown[5] that the molecular conformation is transoid with the corresponding dihedral angle of 103°. This difference in the molecular conformation must contribute to the unusually large density difference for the active and the racemic crystals.

METAL COMPLEXES OF D_3 SYMMETRY

Tris-bidentate metal complexes with octahedral coordination exhibit the highest chiral symmetry, D_3, which facilitates spectroscopic and theoretical analysis of chiral discriminations. All the complexes we have studied possess the same feature of a three-bladed propeller morphology and exist as Δ - or Λ- isomers even though the ligands are achiral. We have carried out simple theoretical calculations of dispersion energy to rationalize the crystal packing of active and racemic crystal structures. The results were compared with actual packing arrangements of several complexes determined by ourselves or in the literature. Formation of optically labile metal complexes with chiral ligands was followed by CD spectroscopy and the chirality conversion in chiral/achiral solvents and in the solid state has been studied.

Theoretical Calculation of Dispersion Energy

To understand how dispersion energies influence the packing of chiral complexes in the crystal, we have carried out dispersion energy calculations for a conformationally rigid neutral model complex of D_3 symmetry.[10,11] The dispersion energy between a racemic or an active pair was calculated by the method of Coulson and Davis[18] based upon the transition monopole treatment of London[19]. The dispersion energy, E_D, and the intermolecular potential, V_E, are given by the following equations:

$$E_D = -2 \Sigma_{n(A)} \Sigma_{m(B)} [(A_0B_0 \mid V_E \mid A_nB_m)]^2 [E_{0n}{}^A + E_{0m}{}^B]^{-1}$$

$$V_E = \Sigma_{n(A)} \Sigma_{m(B)} q_\mu{}^{0n} \; q_\nu{}^{om} (1/R_{\mu\nu})$$

Even if the distance between the center of two molecules is the same, there is a discrimination between a racemic and an active pair, on account of the difference between corresponding $R_{\mu\nu}$ in the two cases (μ is an atom of molecule A and ν is an atom of molecule B and $R_{\mu\nu}$ is the interatomic distance). The calculation examined pairwise mutual orientations of the complex that maximize dispersion energies.

For each orientation, the two molecules were brought together until one of the atoms of molecule A came into van der Waals contact with an atom of molecule B, and then the dispersion energy was calculated. This type of interaction must be relevant in crystal packing analysis.

A few examples of the results obtained for the case of contact discrimination are as follows. Along the molecular C_3 axis, both the racemic and active pair can pack adequately well in the C_3 collinear mutual orientation. Along the C_2 axis, the heterochiral pair pack well, since adjacent rings are parallel to each other. In contrast, for the homochiral pair, the adjacent ring planes are not parallel but can be made so, if one of the C_3 axes is rotated by a dihedral angle that equals the tetrahedral angle or its supplement. For crystals, we have to consider not only the pairwise interactions but also all interactions with the surrounding molecules. All the ring planes, not necessarily adjacent ones, become parallel when the C_3 axes are parallel or tilted by the tetrahedral angle.

Crystal Structure of [Cr(pd)$_3$]

The theoretical results were compared with the actual structures for racemic[20] and active[12] $[Cr(pd)_3]$ (pd = 1,2,-diaminopropane). The compound is an ideal system for study as the complex is neutral, hence excluding any complication which may arise from counter ions. No solvents of crystallization were involved in either crystal. Making allowance for the bulky methyl group of pd, there is a moderate agreement with calculation in both cases. There are two independent molecules in the asymmetric unit of active crystal. As anticipated, the C_3 axes of active pairs are either almost parallel or are tilted at a dihedral angle close to the tetrahedral angle (see TABLE Ia).

Optical Resolution by Density Difference

Our structure determination of the optically active $[Cr(pd)_3]$ has revealed that the density of 1.28 g cm^{-3}, is quite different from that of the racemic crystal (1.36 g cm^{-3}). An optical resolution exploiting the difference was attempted[12]. From *n*-hexane-benzene 4:1 solution, the racemic as well as the optically active crystals were produced and the two types were not readily distinguished morphologically under the microscope. Using a 2.5 M aqueous solution of CsCl which has a density of 1.316 g cm^{-3}, *i.e.* the intermediate density of the racemic and active crystals, the two types of crystals were nicely separated as checked by CD spectroscopy.

Crystal Structure of Λ-[Cr{(-)bdtp}$_3$]

We have studied[13] another neutral D_3 metal complex where dispersion forces must be dominant. The coordination complex, $(-)_{589}$-tris[(-)-cyclic-O,O'-1(R),2(R)-dimethylethylenedithiophosphato]chromium(III), abbreviated as (-)-[Cr{(-)bdtp}$_3$], exhibits an interesting feature from the point of chiral discrimination/recognitions and the mode of packing. As shown in Fig. 1a, it contains a four-membered chelate ring and another five-membered ring is joined to each four-membered ring at the tetrahedral geometry. Hence the two rings are expected to be almost perpendicular to each other. The results is that when the three inner rings form a right-handed propeller, the outer rings necessarily form a left-handed propeller. The space group is $P2_12_12_1$. It is clear from the *a* axis projection (Fig.1b) that the chelate rings of the four molecules in the unit cell are almost parallel to each other. TABLE Ib summarizes the dihedral angles between the C_3

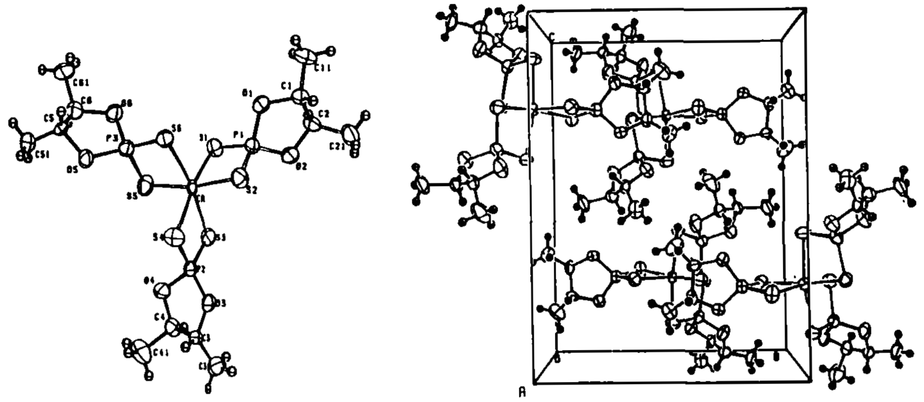

FIGURE 1 Molecular (left) and crystal (right) structure of Λ-[Cr{(-)bdtp}$_3$].

axes. The structures are made up of layers. Within a layer, C_3 axes are either exactly or near parallel to each other. Between the layers, the dihedral angles are close to the tetrahedral angle or its supplement, as predicted by our theoretical work (TABLE Ib).

Crystal Structure of K-Λ-(+)-[Ni(phen)$_3$]-Λ-(-)-[Co(ox)$_3$].2H$_2$O

The D_3 metal complex cation $[\mathrm{Ni(phen)_3}]^{3+}$ (phen = 1,10-phenanthroline) and an anion $[\mathrm{Co(ox)_3}]^{3-}$ (ox = oxalate dianion) form a homochiral crystal. The complex forms columns of alternating cations and anions with the molecular C_3 axes colinear with the column as required by the cubic space group $P2_13$. The four columns in the unit cell are mutually tilted at exactly the tetrahedral angle as also dictated by the space group (TABLE Ic). Thus, the structure can be rationalized by the model calculation, as expected from the aromatic nature of the phen ligand.

Crystal Structure of [Co(en)$_3$][Rh(ox)$_3$]

In the case of the diastereoisomeric complex $[\mathrm{Co(en)_3}][\mathrm{Rh(ox)_3}]$ (en = ethylenediamine), unlike the case involving the phen ligand, hydrogen bonding is expected to play a major stabilizing role in the crystal packing. The $[\mathrm{Co(en)_3}]^{3+}$ and $[\mathrm{Rh(ox)_3}]^{3-}$ system is attractive for study as no additional anions or cations are required for crystallization. The crystal from the homochiral cation and anion pair was more stable and was easily obtained[14]. Attempts to produce crystals of its heterochiral counterpart were

TABLE I The observed angles (deg) between the molecular C_3 axes in crystals.

---

a. Δ-$[Cr(pd)_3]$

I....Is 3.7 I.....IIs 73.0 I....II 75.3 II....IIs 74.5

I and II are independent molecules and subscript s indicates that the molecule is related by a 2_1 screw.

b. Λ-$[Cr\{(-)bdtp\}_3]$

within a layer I .... Isb 167.3

between layers I .... Isa 107.2 I .... Isc 74.3

Isa, Isb and Isc are related to I by a 2_1 screw along the *a*, *b* and *c* axes, respectively.

c. K-Λ-(+)-$[Ni(phen)_3]$-Λ-(-)-$[Co(ox)_3].2H_2O$

within a column Co....Rh 0.0

between columns Co....Co 109.5 Co....Rh 109.5 Rh....Rh 109.5

---

unsuccessful. However, we did obtain a mixed crystal from a solution containing optically pure Δ-$[Rh(ox)_3]^{3-}$ and optically impure $[Co(en)_3]^{3+}$ (60% Λ and 40% Δ)[14].

The homochiral crystal is made up of columns of alternating cations and anions in which the C_3 axes of the cations and anions are exactly colinear. There is extensive hydrogen bonding within the columns as well as between the columns. In the heterochiral mixed crystal, the crystal packing and hence the hydrogen bonding network is completely different to that seen for the homochiral crystal, however, it does share some features in common, *i.e.*, C_3 colinear cation-anion pair. The local hydrogen bonding scheme is very similar for both the homochiral and the heterochiral pairs.

We have found that there seem to be rationalizing factors which govern the crystal packing mode of D_3 metal complexes, whether they are dispersion force dominated or hydrogen-bonding dominated. They tend to discriminate the handedness of other complexes not along the C_3 axis but in the direction perpendicular to it.

Chiral Discrimination of $[Cr(bdtp)_3]$ in Solution

The formation of the $[Cr(bdtp)_3]$ complex from chiral ion (-)bdtp$^-$ and $CrCl_3.6H_2O$ was followed by CD spectroscopy[15]. Depending on the solvent employed, either Δ- (R,R) or Λ-(R,R) was preferentially formed: the Δ- (R,R) diastereoisomer in $CHCl_3$, and the Λ-

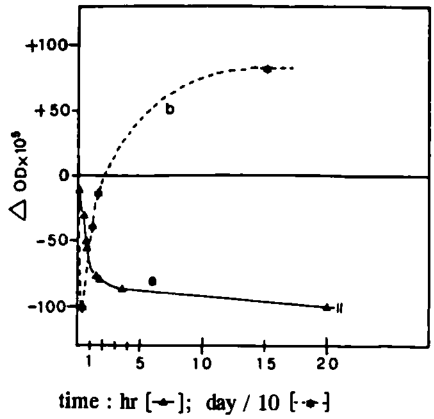

FIGURE 2. Variation of the differential optical density ΔOD of [Cr{(-)bdtp}$_3$] at 665 nm during formation in THF over 0 - 20 h (a) and 3 -150 days (b).

(R,R) form in EtOH. In THF, the reaction gave complex preferentially in the Δ- (R,R) form, exhibiting a negative peak at 665 nm, which was assigned as the transition $^4A_{2g} \rightarrow {}^4T_{2g}$. However, the peak reached a maximum negative value after 20 h, then it progressively reduced in intensity, inverted sign from negative to positive, and eventually reached an equilibrium state after 70-80 h (Fig. 2). This is due to a configuration inversion from Δ- (R,R) to Λ-(R,R). After dissolution of the isolated Λ-(R,R) diastereoisomer in CHCl$_3$, the solution CD peak changed gradually from a positive to a negative peak at 665nm.

Thus, thermodynamic stability of the complex changes with solvent. The Λ- (R,R) form is favoured in THF > CH$_3$CN > acetone > benzene and the Δ- (R,R) form is favoured in CHCl$_3$ > CH$_2$Cl$_2$ > EtOH. The last three are polar hydrogen bonding solvents and the compound is highly soluble in them. Solvent - complex molecule interactions, fitting the solvent into the blades of the complex appears to contribute to the favoured stabilization of the Δ- (R,R) diastereoisomer.

The Λ-(R,R) diastereoisomer is strongly preferred in the solid state. The Δ- (R,R) diastereoisomer is optically labile even in the solid state and after a long time inverts to the Λ-(R,R) form as is shown in Fig. 3. The nujol mull CD spectrum immediately after the

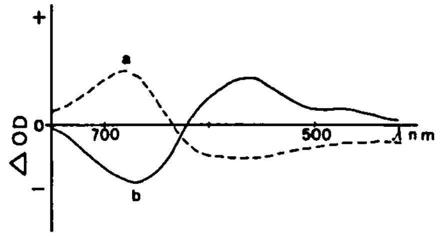

FIGURE 3. Nujol mull CD spectra of Δ- (R,R) recorded immediately after the synthesis of the solid samples (b) and aftaer a long time (a).

synthesis (full line) can be compared with the corresponding spectrum of the solid after a prolonged time (broken line). The difference between the Δ- (R,R) and the Λ-(R,R) diastereoisomers is the orientation of the alkyl groups. These adopt an equatorial position in the Λ- (R,R) form, but the axial position in the Δ- (R,R) form. The equatorial position seemed more favoured and the crystal packing was efficient as seen earlier.

Chiral Discrimination of [Cr{(+)(S)(S)Mebdtp}$_3$] in Solution

Formation of the related chromium complex, [Cr{(+)(S)(S)Mebdtp}$_3$], (Mebdtp=methylbutyldithiophosphato), was followed by absorption- and CD-

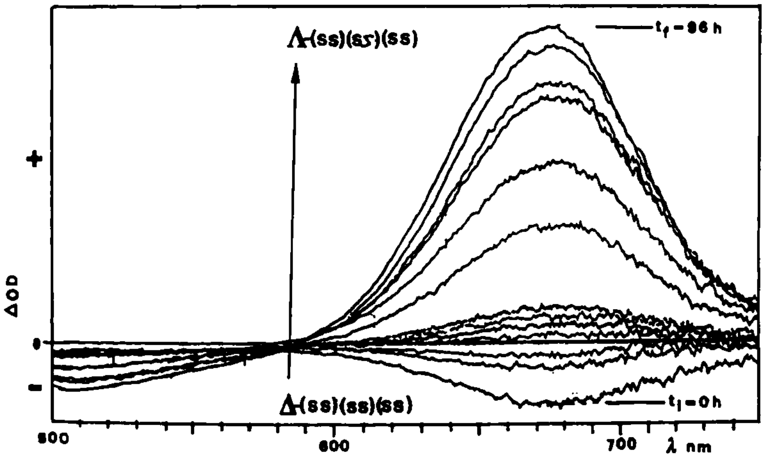

FIGURE 4. CD spectra of a chloroform solution of [Cr{(+)(S)(S)Mebdtp}$_3$]. The solution was made after the solid had been kept at 100 °C under vacuum. Spectra were measured immediately after dissolution (t = 0 h), then at intervals up to 96 h.

spectroscopy for up to 20 days of reaction.[16] Saturated OD values indicate that the formation of the complex at room temperature was complete in oneto a few days, depending on the concentration. In contrast, the chirality kept increasing for many days after the end of formation reaction. The results indicate a slight prevalence for the Λ-isomer during the formation reaction as well as in the equilibrium state. Unlike [Cr-(-)bdtp)$_3$], the Λ-diastereoisomer was favoured in all the solvents tested, including ethanol, acetonitrile, benzene, acetone, dichloromethane, and chloroform. The discriminatory ability of the title complex was much lower than in the case of [Cr{(-) - bdtp}$_3$] where the ligand is sterically more rigid.

Achiral crystals, that is a 1:1 mixture of diastereoisomers Δ and Λ-, were obtained from the solution of excess Λ. Interestingly, configurational inversion was observed even in the solid state if the solid was kept at high temperature and under vacuum. When the achiral solid complex was maintained under vacuum at 100 °C for several hours, it began to exhibit a negative Cotton effect at 670-675 nm in a nujol mull CD spectrum. No change in the CsI pellet IR spectrum or in the mp was detected. The negative peak was observed immediately after the dissolution of the solid in solvents, however, the peak decreased in intensity with time, inverted sign in a few minutes and reached an equilibrium state after 24 h with an excess of the Λ-(S,S)(S,S)(S,S) diastereoisomer (Fig. 4). Thus the chirality favoured was opposite in the solution and the high-temperature solid states.

CONCLUSION

Using theoretical analysis, CD spectroscopy and X-ray crystallography, we could provide detailed information on the molecular recognition of chiral molecules. There appear to be only a few favoured types of packing mode in the crystal structures of D_3-type metal complexes with three-bladed propeller shape. In case of optically labile complexes with chiral ligands, chirality conversion was observed in solutions and in the solid sate.

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