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Molecular Chirality Recognized by Achiral Compounds

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Three cases are described where chirality is recognized by achiral molecules, where chirality is induced into achiral compounds through interactions with chiral compounds, and lastly where induced chirality in the solid-state is utilized for an enantio-selective photoreaction. In the first instance, the thermodynamically and kinetically preferred diastereoisomer of an optically labile chromium complex depended on the nature of the achiral solvent. In the second case, for the first time 1,2-chloroethane was trapped and observed in a chiral near-eclipsed form and 1-chloropropane in the truly eclipsed form at room temperature in a 1:1 inclusion complex with an optically active host molecule. Finally, induced chirality in a prochiral compound in the solid-state was successfully employed in an enantio-selective photoreaction. In the two cases, solid-state CD provided valuable information.

Keywords: Induced Chirality, CD spectroscopy, Rotational Isomer

INTRODUCTION

Chiral recognition and discrimination are key to many biological processes involving DNA, proteins and many smaller chiral natural compounds. The chirality of a molecule is generally recognized by another chiral factor, be it another chiral molecule or an electromagnetic wave with chiral properties. However, chirality can be induced into achiral molecules through interactions with chiral compounds. We have previously reported that binding of achiral porphyrins to DNA induces measurably strong CD in the Soret band region of the porphyrin.[1] In contrast to absorption spectra, the induced CD spectra of DNA-porphyrin solutions differ greatly depending on DNA base-sequences and porphyrin-to-DNA basepair molar ratios. The two positive CD peaks that appeared in the Soret band region of the porphyrin were assigned as originating from the major and the minor groove binding modes.

We have extended this work to small inorganic and organic compounds. Here we shall discuss our results on optically labile chiral chromium complexes whose diastereoisomer preference depends critically on non-chiral solvent, and on achiral organic compounds which become chiral through interactions with chiral host molecules in inclusion crystals.

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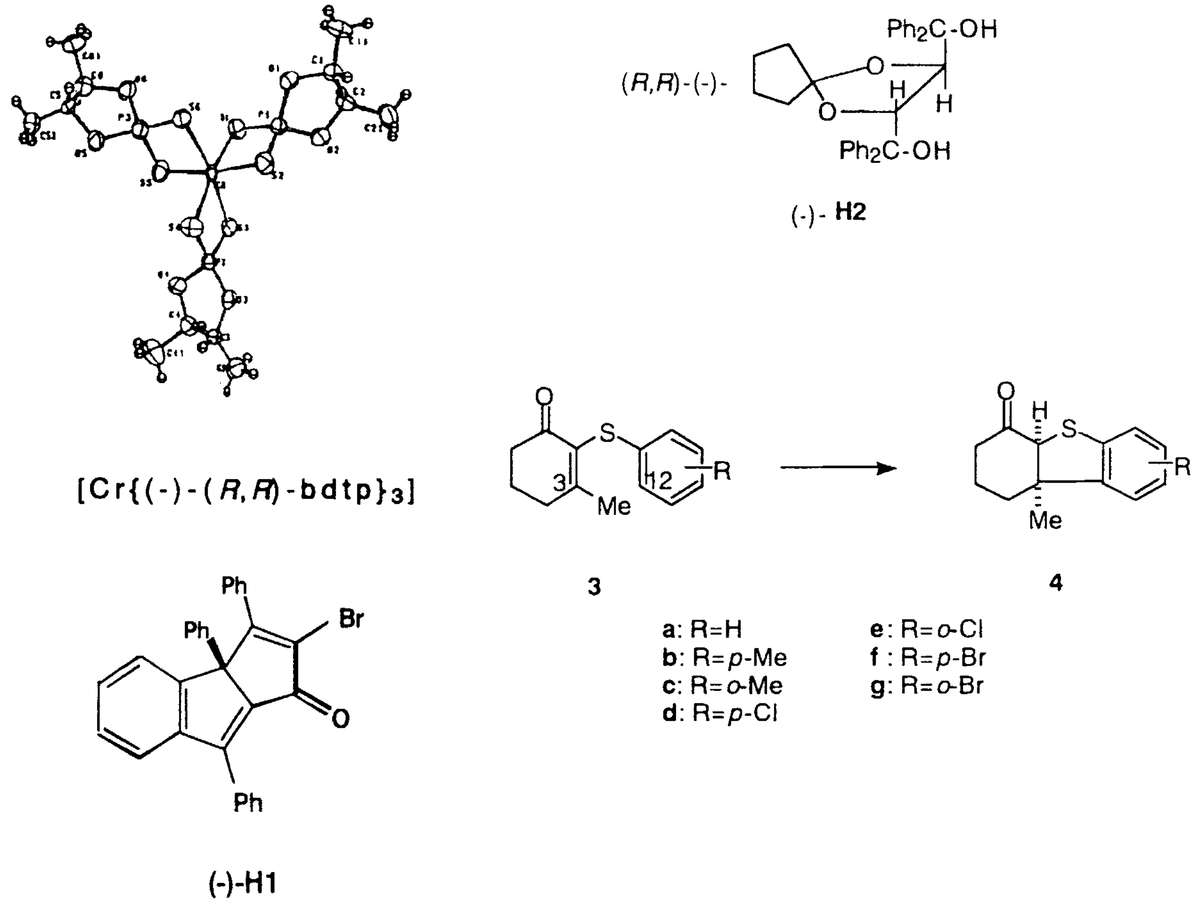


FIGURE 1 Structures of compounds studied

RESULTS AND DISCUSSION

Chiral discrimination of optical labile Cr complexes: Λ-[Cr{(-)bdtp}$_3$]

We have studied chiral discrimination of neutral metal complexes of D_3 symmetry, such as tris[(-)-cyclic-*O,O'*-1(*R*),2(*R*)-dimethylethylene dithiophosphato] chromium(III), abbreviated as [Cr{(-)bdtp}$_3$] (Fig. 1).[2,3] It has two diastereoisomers, Δ(*R,R*) and Λ(*R,R*) with respect to the metal coordination geometry. The formation of the [Cr(bdtp)$_3$] complex from chiral ligand ion (-)bdtp$^-$ and $CrCl_3.6H_2O$ was followed by observing the CD peak at 665 nm, which was assigned as the $^4A_{2g} \rightarrow {}^4T_{2g}$ transition of Cr(III). Interestingly, depending on the solvent employed, although these were not chiral, either Δ- (*R,R*) or Λ-(*R,R*) was preferentially formed: the Δ- (*R,R*) diastereoisomer in $CHCl_3$, and the Λ-(R,R) form in EtOH.

In THF, the thermodynamically and kinetically favoured diastereoisomers are different. Initially, the reaction yielded a complex preferentially of the Δ- (*R,R*) form, exhibiting a negative peak at 665 nm (Fig. 2). However, the peak reached a maximum negative value after 20 h, then it progressively reduced in intensity,

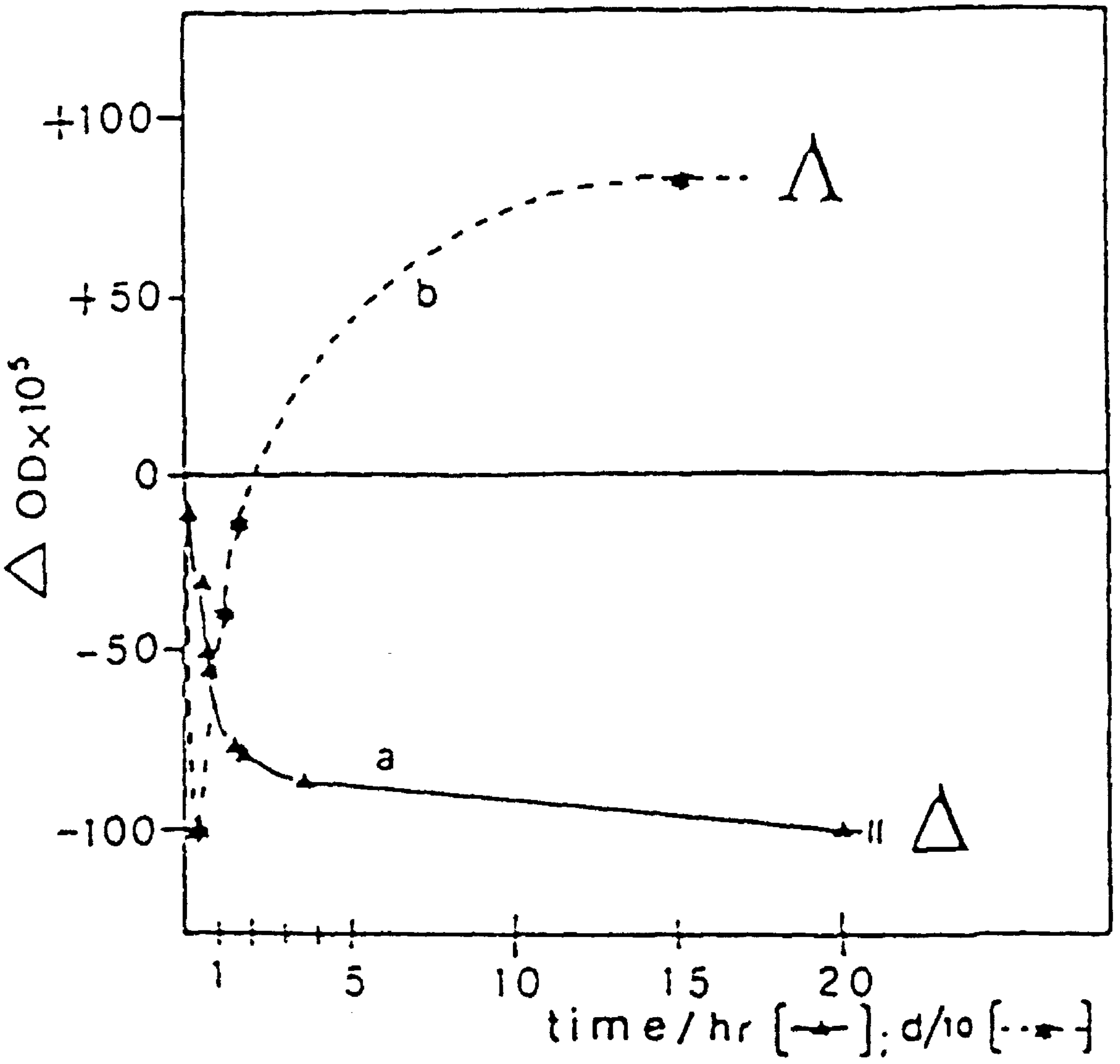
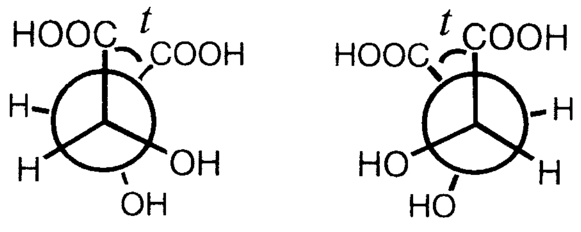


FIGURE 2 ΔOD at 665 nm during the formation of [Cr{(-)bdtp}$_3$] in THF. (a) 0 –20 h and (b) 3 – 150 days

inverted sign from negative to positive, and eventually reached an equilibrium state after many days. This is due to a configuration inversion at the metal centre from Δ- (*R,R*) to Λ-(*R,R*). This means that thermodynamic stability favours the Λ form in THF.

The thermodynamicaly preferred chirality of the complex also depends on the idendity of non-chiral solvent. For example, after dissolution of the Λ-(*R,R*) diastereoisomer (isolated from THF solution) in CHCl$_3$, the solution CD peak at 665nm changed sign gradually from positive to negative. The Λ- (*R,R*) form is favoured in THF > CH$_3$CN > acetone > benzene, whereas the Δ- (*R,R*) form is favoured in CHCl$_3$ > CH$_2$Cl$_2$ > EtOH. The last three are polar hydrogen bonding solvents in which the compound is highly soluble.

inversion mirror



$\theta = t^\circ$ $\theta = -t^\circ$

FIGURE 3 Newman projection of the meso-tartrate ion

These achiral solvents discriminate the chirality either in the reaction pathway or thermodynamic stability by way of solvent – metal complex (or solvent – reaction intermdediates) interactions. The molecule contains four-membered chelate rings and another five-membered ring is joined to each four-membered ring at the phosphorous atom in tetrahedral geometry (Fig. 1). The two rings are expected to be almost perpendicular to each other, and thus, the three inner rings and three outer-rings form a propeller of opposite chirality. The outside rings pucker and adopt either a δ or λ configuration. If the absolute configuration at the metal centre is Λ and the outside ring pucker is λ, the central C – C bond is almost parallel to the C_3 axis of the complex. This arrangement, described as the Λ(λλλ)-(*lel*) form, is the most stable conformation with the methyl groups in the equatorial position. If the absolute configuration at the metal centre changes from Λ to Δ, and if the ring conformation changes from λ to δ to keep the *lel* orientation of the ring with respect to the C_3 axis, the resulting Δ(δδδ)-(*lel*) form places the methyl groups in the less stable axial positions. The methyl groups become equatorial when the 5-membered rings take the λ configuration, oblique to the C3 axis, i.e., the Δ(λλλ)- (*ob*) form.

CD spectroscopy cannot distinguish the ring puckering mode nor the orientation of the methyl groups. Thus, it is not possible to understand what sort of solvent – metal complex interactions are involved in the chiral discrimination. X-ray diffraction work has revealed that the complex adopts the most stable Λ(λλλ)-(*lel*) form in the solid state. No solvent molecules were included in the crystal lattice and the crystal packing was highly efficient with near-parallel intermolecular ring orientations[3].

More than 25 years ago one of us (RK) started measuring solid state CD either in the Nujol mull or in KBr disc form or in single crystal to observe solid-state specific phenomena.[4,5] Application of the technique to this chromium compound is very useful as solvent interferes with the diastereoisomeric equilibrium. Solid-state CD in the Nujol mull also revealed that configuration inversion of [Cr{(-)bdtp}$_3$] and a related chromium complex, [Cr{(+)(*S*)(*S*)Mebdtp}$_3$], (Mebdtp = methylbutyldithiophosphato) occurs even in the solid state[6].

Observation of chiral rotation isomers of achiral compounds

Molecules with more than one asymmetric atom are not necessarily chiral and at the same time, those without asymmetric atoms can be chiral. For example, the meso-tartrate ion with two asymmetric carbon atoms is known to be achiral. The achirality can be explained as follows (Fig. 3). In the eclipsed conformation of the highest potential energy, the molecule has mirror symmetry and is thus achiral. When the tartrate ions adopts the most stable form of *trans*, it has an inversion centre and is thus achiral. However, the molecule can adopt other conformations as well, where the dihedral angle about the central C – C bond, θ, is neither 0 (eclipsed) nor 180° (*trans*), and in this case, the molecule is chiral. Simply because the probabilities of the molecules adopting conformations with the dihedral angle of + θ and – θ are exactly the same, a sample of meso-tartrate exhibits achirality. This analysis suggests that in principle it should be possible to trap selectively one of the chiral rotamers by using an optically active host molecule. The other goal potentially achivalbe by these means is to obtain conformations of high potential energy, i.e. The eclipsed form, which one can never observe under ordinary conditions.

TABLE I Comparison of crystal data for the two inclusion compounds

	1 *(-)-H1–1,2-dichloroethane*	2 *(-)-H1–1,2-dichloroethylene*
Formula	$C_{32}H_{23}BrCl_2O$	$C_{32}H_{21}BrCl_2O$
M	574.34	572.34
Crystal system	orthorhombic	orthorhombic
a	16.748(2) Å	16.763(2) Å
b	17.113(3)	17.033(1)
c	9.351(3)	9.318(2)
V	2680.1(9) Å^3	2660.5(6) Å^3
space group	$P2_12_12_1$	$P2_12_12_1$
Z	4	4
R, GOF	0.045, 1.53	0.045, 1.46

A chiral molecule (-)-7-bromo-1,4,8-triphenyl-2,3-benzo[3.3.0]octa-2,4,7-trien-6-one, **(-)H1** (Fig. 1) crystallizes from various solvents to form an 1:1 inclusion complex with the solvent molecule as a guest. In the case of 1,2-dichloroethylene, only the *cis* and not the *trans* isomer formed an 1:1 inclusion crystal with **(-)H1**.[7] The conformation of the solvent molecule is fixed by its double bond. The saturated form of this compound, 1,2,-dichloroethane has much smaller energy barrier hindering the rotation about the C – C bond. 1,2,-dichloroethane also formed an 1:1 inclusion compound with **(-)H1**. X-ray crystal structural analysis of the two inclusion complexes **(-)-H1–1,2-dichloroethane (1)**and **(-)-H1–1,2-dichloroethylene (2)** has shown[7]that the crystal lattice parameters of the two adducts, **1** and **2**, are surprisingly similar, with only 0.09 ~ 0.4 % difference in the same space group of $P2_12_12_1$(Table I).

As the three phenyl rings of the host molecule can rotate to some extent along their long axes, the dihedral angles between the phenyl rings as well as between the phenyl and the central fused ring can in theory take a range of values. However, all the dihedral angles are very similar in the two cases (Table II). Thus, the cavity formed by the host molecules are similar in the two inclusion compounds, indicating that the conformation of the 1,2-dichloroethane molecule must be close to *cis* rather than the most stable *trans* form. The positions of the host and the guest molecules in the unit cells were found to resemble to each other closely, as expected (Fig. 4). The conformation of the ethane derivative is close to that of cis-1,2-dichloroethylene and adopts the conformation between the *gauche* and the eclipsed form, with the dihedral angle of C*l*1-C1G-C2G-C*l*2 36(2)° (Fig. 4). It has been reported[8] that in the case of 1,2-dichloroethane the *anti* conformation is more stable than that of the *gauche* by 5.0 ± 0.4 kJ.mol^{-1}. However, the near eclipsed form, which is even more unstable than the *gauche* form, was detected for the first time in this unique environment.

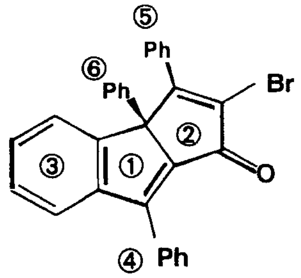
The crystal structure demonstrates the freezing of a chiral form in the chiral lattice (Fig. 4). With the opposite enantiomer of the host molecule, **(+)H1**, 1,2-dichloroethane molecule adopts the opposite chirality. In the vapour phase, the rotation energy barrier around the central ethane C – C bond is small so that a chiral form is always accompanied by its mirror image with the same population, and hence no chiral form can be isolated.

The chlorine atoms of the guest molecule appear to be the key in determining the inclusion phenomenon. The closest contacts between the guest and the host molecules are observed in the C*l*1...O1, 3.288(6) Å and C*l*2...C5 3.545(7) Å interactions in the case of the ethane derivative, and the corresponding distances are 3.247(7) and 3.541(8) Å respectively, in the case of 1,2-dichloroethylene.

In contrast to 1,2-dichloroethane, the *gauche* form of 1-chloropropane where C*l* and the methyl groups are in the *gauche* relation has been reported to be slightly more stable than the *trans* isomer.[8] With the intention of obtaining the rotamer even closer to the eclipsed state, 1-chloropropane was adopted as a guest compound.

Recrsytallization of **(+)H1** from 1-chloropropane produced a 1:1 adduct which turned out to be almost isostructural with adducts **1** and **2**. For the first time, we could observe the truly eclipsed conformation of the dihedral angle as small as 5 ± 4 ° at room temperature. The detailed work will be reported elsewhere.[9]

TABLE II Comparison of the dihedral angles between planes for the two inclusion compounds. Planes defined by numbers below are least-squared



Inclusion compound 1

	②	③	④	⑤	⑥
①	45	5	38	74	109
②		44	82	118	89
③			39	75	104
④				36	107
⑤					100

Inclusion compound 2

	②	③	④	⑤	⑥
①	45	5	39	75	108
②		43	83	118	88
③			40	76	103
④				36	106
⑤					100

Photocyclization of achiral compounds

By taking advantage of induced chirality in inclusion compounds, enantio-selective reactions can be carried out. We have been studying several enantio-selective photoreactions of prochiral compounds in the solid state either in their own crystal lattices[10,11] or as inclusion compounds with optically active host molecules.[12] We have successfully applied the inclusion method to achieve high enantioselective photocyclization of 2-thioaryloxy-3-methylcyclohexen-1-ones (3, Fig. 1) to the corresponding dihydrobenzothiophenes (4, Fig. 1).[13] For example, irradiation of the 1:1 inclusion crystals (5) with a host compound, (-)-(*R*,*R*)-(-)-*trans*-2,3-bis (hydroxydiphenylmethyl)-1,4-dioxaspiro-[4,4] nonane[14], (-)-**H2**, and **3g** (Fig. 1) in a water suspension gave the corresponding photocyclization products (+)-**4g** with an optical purity of 82 %. This outcome contrasts with the corresponding solution reaction which results in a racemic product.

X-ray crystal structural analysis of the inclusion complex **5** has been carried out.[13] The two hydroxyl groups of the host seem to play a key role in the stereo-selectivity of the photo-reaction (Fig. 5a). The molecular conformation of the host itself is dictated by the intramolecular hydrogen bonding between the two hydroxyl groups (O3---O4=2.62 Å). Additionally, one of the hydroxyl groups acts as a hydrogen donor to the carbonyl oxygen of a guest molecule (O4---O1G=2.71 Å). The average ring plane of the guest containing the carbonyl group is almost parallel to the neighboring phenyl group of another juxtaposed host molecule.

The structure of the guest in the inclusion compound is shown in Fig. 5b. The intermolecular interactions between the host and guest molecules determine the conformation of the guest molecule. The molecule is highly twisted and the dihedral angle between the two average ring planes is ca 74°. The photoreactive carbon C12 is 3.7 Å away from the target C3 on one side of the cyclohexenone ring plane, favouring the *R*-configuration at C3. Crystal structure determination of the reaction product, (+)-**4g** was also carried out,[13]which unambiguously established the absolute configuration of the *cis* isomer as 2*S*,3*R*. Thus, the conformation of the guest molecule imposed by the crystal structure explains the high enantio-selectivity of the reaction.

We have applied the Nujol mull[13] and KBr disc[15]CD technique to this system as well. Chiral host molecule (-)-**H2** did not show strong absorption nor CD peaks in the 400 – 280 nm region. In solution, the inclusion complex 5 consisting of prochiral **3g** and (-)-**H2** does not show a CD peak in the 400 – 320 nm region even at very high concentration. In contrast, the solid-state CD of the inclusion compound exhibited a rather strong CD spectrum, suggesting the spectrum mainly originates from **3g** (Fig. 6). When cocrystallized with the host of opposite enantiomer, (+)-**H2**, an almost mirror image solid-state CD spectrum was obtained. Thus, this must be the CD of the guest molecule.

Prochiral compounds exhibit chirality when frozen in a chiral conformation in a chirally shaped cavity created by chiral compounds in the solid state. This is what is anticipated from our X-ray crystal structural analysis. As expected no CD was observed for a solution of **3g**. Further work is underway to improve the quality of the solid-state CD measurements and to interpret the CD spectra based on the crystal structures.[15]

CD spectral measurement in the solid state provides an excellent means of elucidating the chiral arrangement of prochiral molecules in their own crystals or in inclusion crystals. However, substantial artefacts arising from dispersion, LD (linear dichroism) and LB (linear birefringence) have to be taken into consideration. A solid-state dedicated CD spectrophotometer or an attachment is currently being developed by Prof. Shindo of Fukui University and one of us (RK) with the help of Jasco Co. ltd. This should prove extremely useful in further studies of induced chirality.

MATERIALS AND METHODS

Spectroscopy: Absorption and CD spectra were recorded on a Shimazu UV-2200 spectrophotom-

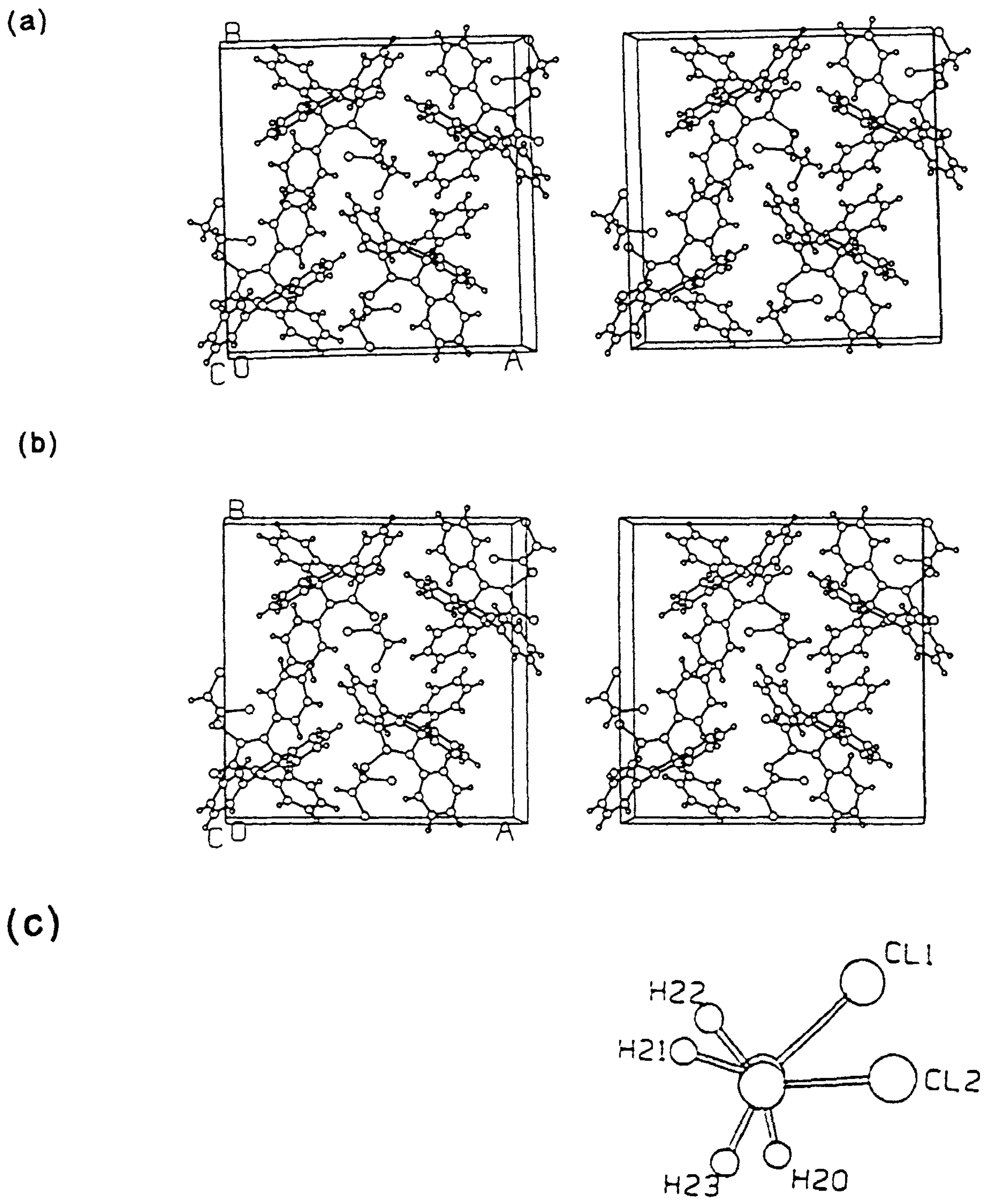


FIGURE 4 Stereoview of the unitcell of 1:1 inclusion complexes **1** (a) and **2** (b), and the Newman-type projection of the guest molecule, 1,2-dichloroethane in **1** (c)

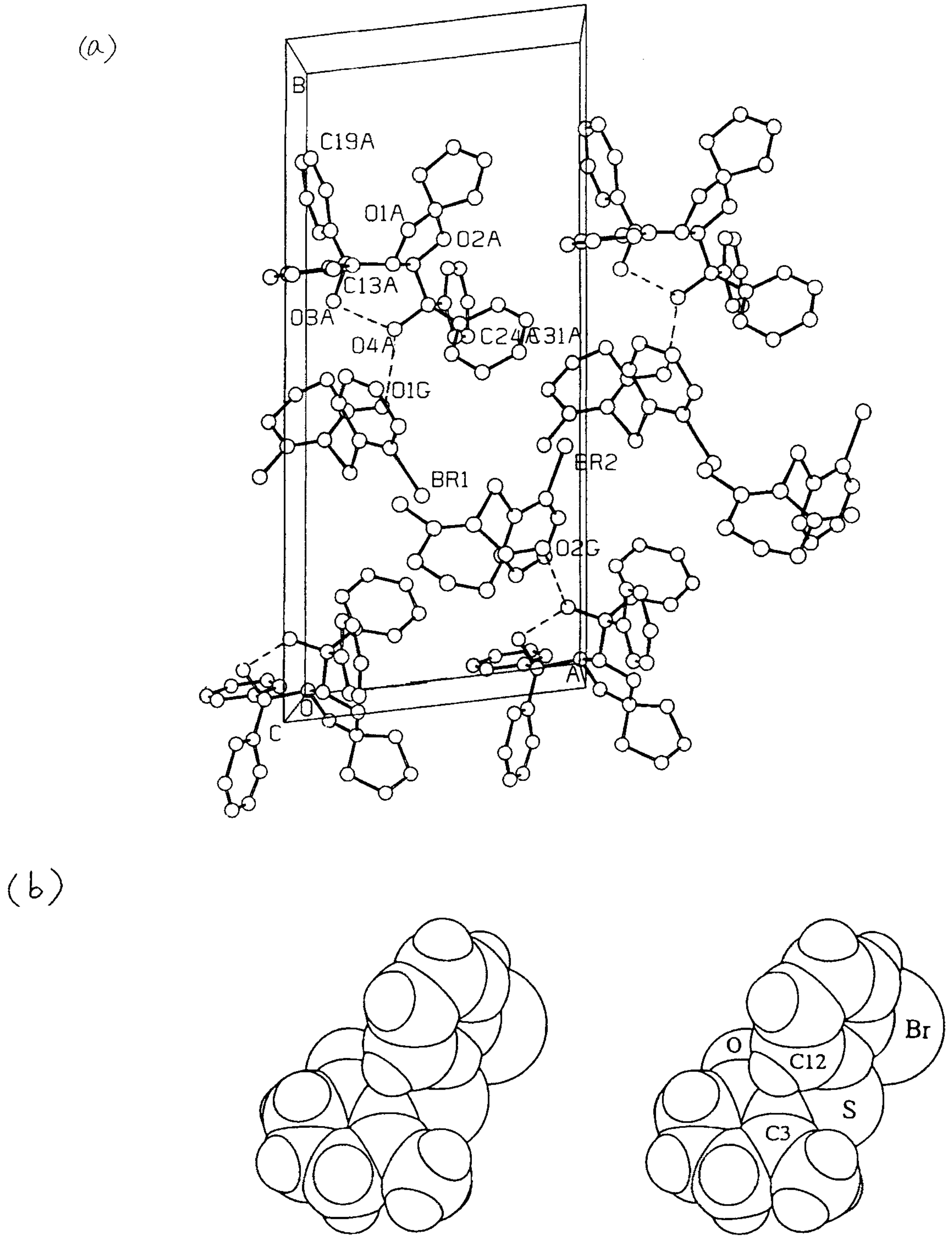


FIGURE 5 The unit cell structure of the 1:1 inclusion compound **5**, (+)-**H2**- **3g** (a), and the molecular conformation of the guest **3g** in the inclusion complex **5** indicating the reactive C13 and C12 atoms(b)

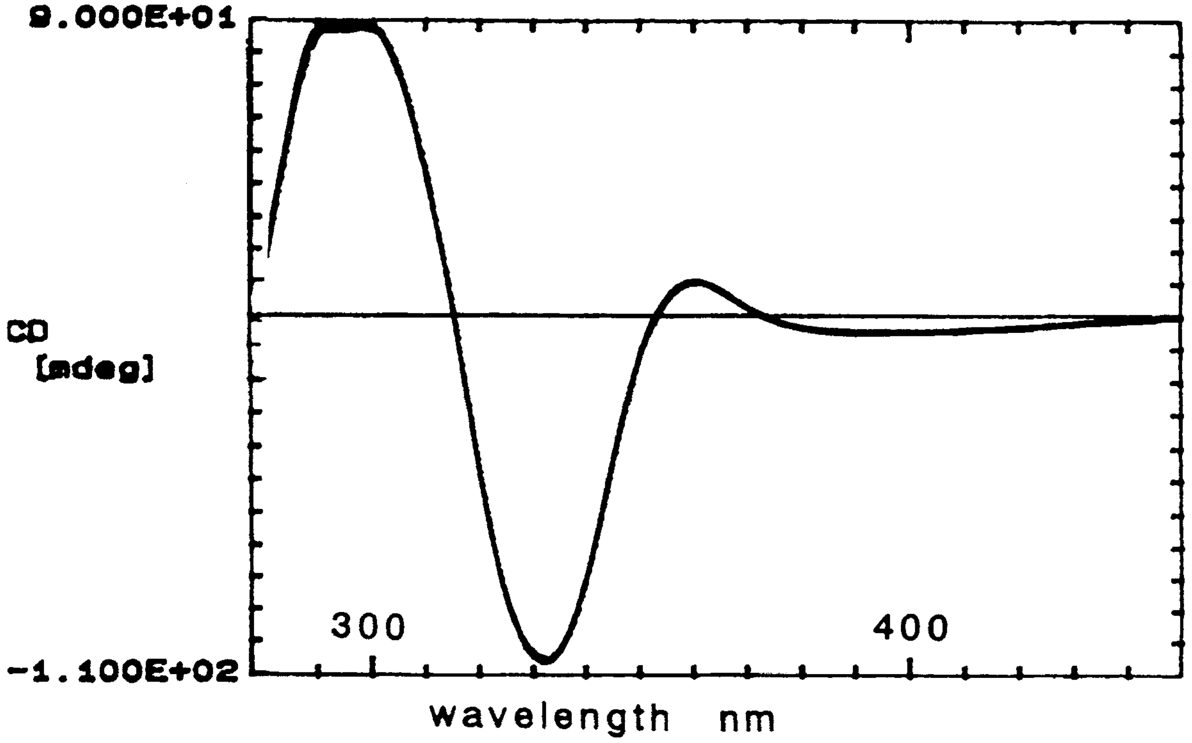


FIGURE 6 Solid-state CD spectraum of inclusion complex 5 recorded in a KBr disc

eter and a Jasco J-720 spectropolarimeter, respectively. The solution CD was measured in CH_3CN at two different concentrations.

X-ray crystallography: Reflection data were collected on a Rigaku AFC5S four-circle diffractometer and structures were solved by using TEXSAN software on a VAXstation 3200. Details of the structures can be obtained from references 7 and 13.

Crystal Data: **1**: $C_{32}H_{23}BrCl_2O$, *M* 574.34, orthorhombic, space group $P2_12_12_1$, $a = 16.748(2)$, $b = 17.113(3)$, $c = 9.351(3)$ Å, $U = 2680.1(9)$ Å^3, Mo-Kα(λ = 0.71069 Å), $Dc = 1.423$ g cm^{-3}, $Z = 4$, F(000) = 1168, pale yellow plates, crystal dimensions 0.22 × 0.20 × 0.40 mm, μ(Mo-Kα) = 17.41 cm^{-1}, 2 θ – ω scan, 3480 independent reflections ($5 < 2\,\theta < 55.0°$), The final $R = 0.045$ and GOF = 1.53 for the 1775 reflections with $I > 3\,\sigma\,(I)$. Crystal Data: **2**: $C_{32}H_{21}BrCl_2O$, *M* 572.343 orthorhombic, space group $P2_12_12_1$, $a = 16.763(2)$, $b = 17.033(1)$, $c = 9.318(1)$ Å, $U = 2660.5(6)$ Å^3, Mo-Kα (λ = 2660.5(6) Å^3, Mo-Kα(λ = 0.71069 Å), $Dc = 1.429$ g cm^{-3}, $Z = 4$, F(000) = 1160, pale yellow plates, crystal dimensions 0.35 × 0.25 × 0.50 mm, μ(Mo-Kα) = 17.53 cm^{-1}, · 2 θ – ω scan, 3456 independent reflections ($5 < 2\,\theta < 55.0°$). The final $R = 0.045$ and GOF = 1.46 for the 1579 reflections with $I > 3\,\sigma\,(I)$. Crystal Data: **5**: $C_{46}H_{45}BrSO_5$, *M* 789.82 triclinic, space group *P*1, $a = 9.812(3)$, $b = 21.721(3)$, $c = 9.477(2)$ Å, $\alpha = 91.26(1)°$, $\beta = 90.24(2)°$, $\gamma = 83.68(2)°$, $U = 2007.0(8)$ Å^3, Mo-K α(λ = 0.71069 Å), $Dc = 1.307$ g cm^{-3}, $Z = 2$, F(000) = 824, colourless columns, crystal dimensions 0.25 × 0.25 × 0.29 mm, μ(Mo-Kα) = 11.05 cm^{-1}, 2 θ – ω scan, 6821 independent reflections ($5 < 2\,\theta < 55.0°$). The final $R = 0.069$ and GOF = 2.66 for the 3006 reflections with $I > 3\,\sigma\,(I)$.

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