

Generation of Chirality in Guest Aromatic Ketones Included in the Crystals of Steroidal Bile Acids

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The strong Cotton effects (CEs) corresponding to the ketone $n-\pi^*$ electronic transition were observed in the solid-state circular dichroism (CD) spectra of the inclusion compounds of cholic acid with achiral alkyl phenyl ketones.

Deoxycholic acid (DCA), a naturally occurring bile acid, has long been known to form crystalline inclusion compounds with wide variety of organic substances.^{1,2} More recently it has been recognized that cholic acid (CA) is also a versatile host for many low molecular weight compounds and several crystal structures of its complexes have been reported.^{2,3} Their crystal lattices are composed of cumulated amphiphilic bilayers containing channel-type void spaces in which guest molecules are arranged in helicoidal columns infinitely running across the crystal. Over last several years a number of successful applications of bile acids as templates for inclusion polymerization,⁴ for organized media for highly stereospecific photochemical reactions,⁵ and for optical resolution of racemates have been described.⁶

It seems reasonable to expect that the accommodation of a symmetric and flexible molecule into the helicoidal channels of the optically active host may be possible after it assumes a chiral conformation. Therefore, it could be possible to detect the CD originating from achiral guest molecules trapped in the inclusion crystals. The easily accessible bile acids are well suited host molecules for this purpose since they do not show any absorption bands in the region above 220 nm, which could interfere with those of the guest molecules. Therefore the measurements of the CD induced by host–guest interaction in the solid state together with the X-ray crystallographic analysis, providing an unambiguous absolute configuration, could be a useful tool for studying mechanisms that govern the optical activity of many chromophores.

This is the first report on optical activity of the formally achiral guest molecules included in the crystal lattice of bile acids.⁷ Alkyl

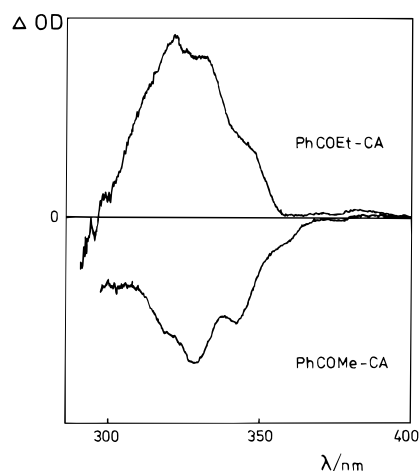
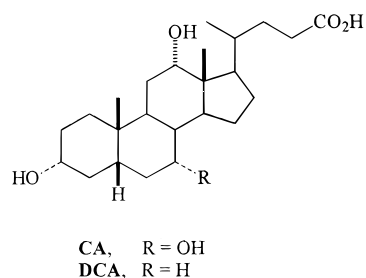


Figure 1. Solid-state CD spectra of the 1:1 inclusion compounds of cholic acid (CA) with acetophenone (1) and propiophenone (4) recorded in KBr disks.

phenyl ketones were chosen as model compounds for this study because some crystal structures of CA and DCA clathrates with aromatic ketones are known^{3,5} and since the carbonyl group conjugated with an aryl ring is an important chromophore found in many natural products such as flavonoids and steroids.⁸ The colorless needlelike crystals of the 1:1 inclusion complexes **1**·CA–**6**·CA were prepared by a crystallization of CA from the appropriate carbonyl compound. The 2:5 **1**·DCA and 1:3 **4**·DCA



- 1: PhCOMe
- 2: 4'-F-C₆H₄-COMe
- 3: 2'-Cl-C₆H₄-COMe
- 4: PhCOEt
- 5: 4'-F-C₆H₄-COEt
- 6: PhCHO

complexes were obtained by a slow evaporation of a solution of DCA with **1** or **4**, respectively, in methanol. The solid-state CD spectra of the inclusion compounds were taken in KBr disks, and the results are collected in Table 1.⁹ The CD of the acetophenone complex **1**·CA shows a negative, with a pronounced fine structure, CE in the region of the ketone $n-\pi^*$ transition (Figure 1). This spectrum is almost identical with that observed for its *p*-fluoro derivative **2**·CA. Surprisingly, the closely related propiophenone derivative **4**·CA reveals a positive CD band centered at 320 nm (Figure 1), whereas its *p*-fluoro analogue **5**·CA exhibits nearly two times stronger and oppositely signed CE. In contrast, the deoxycholic acid complexes **1**·DCA and **4**·DCA do not give any measurable CEs in this region. A twisted benzoyl group should be considered as an inherently chiral chromophore, helicity of which determines the CE sign. According to the rule, proposed

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(9) A mixture of 5 mg of the complex and 300 mg of KBr was ground and formed into a disk with a radius of 10 mm. The disk was rotated around the optical axis and the CD recordings were made for several positions in order to check a reproducibility of the spectra. For details of the experimental procedure, see also: (a) Kuroda, R.; Saito, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 433–436. (b) Rasmussen, K.; Hald, N. Ch. P. *Acta Chem. Scand.* **1982**, *A36*, 549–554.

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(1) (a) Herndon, W. C. *J. Chem. Educ.* **1967**, *44*, 724–728. (b) Giglio, E. In *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Academic Press: London, 1984; Vol. 2A, pp 207–229.

(2) Miyata, M.; Sada, K. In *Comprehensive Supramolecular Chemistry*; MacNicol, D. D., Toda, F., Bishop, R., Eds.; Pergamon: Oxford, 1996; Vol. 6, pp 147–176.

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(6) Miyata, M.; Shibakami, M.; Takemoto, K. *J. Chem. Soc., Chem. Commun.* **1988**, 655–656.

(7) Recently Toda et al. measured the solid-state CD spectra of some inclusion complexes in Nujol mulls: (a) Toda, F.; Miyamoto, H.; Kanemoto, K. *J. Org. Chem.* **1996**, *61*, 6490–6491. (b) Toda, F.; Miyamoto, H.; Kikuchi, S.; Kuroda, R.; Nagami, F. *J. Am. Chem. Soc.* **1996**, *118*, 11315–11316.

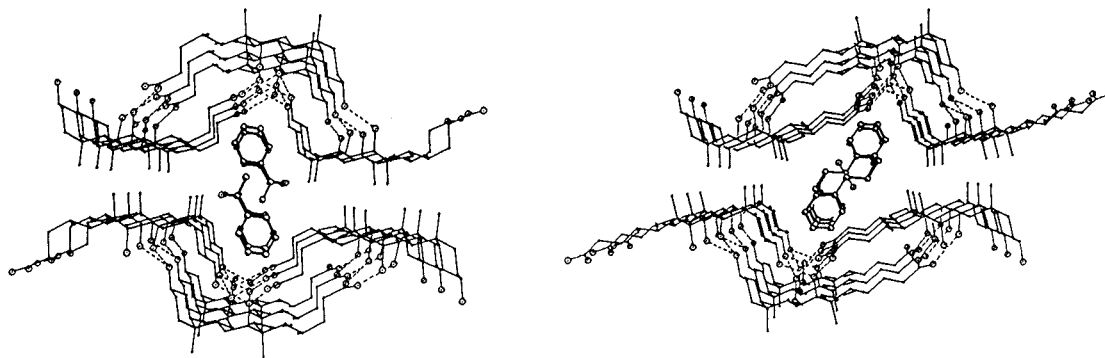


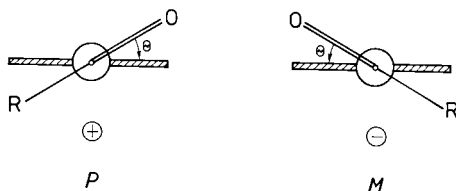
Figure 2. Comparison of crystal packing in (a, left) **1-CA** and (b, right) **4-CA** showing differences in the guest arrangement in the two different channel types formed between the CA bilayers.

Table 1. Solid-State CD Data of the CA Inclusion Compounds

compd	CD λ , nm ($[\theta]$) ^a	structure type	$\phi(\text{O}=\text{C}-\text{C}=\text{C})$, deg
1-CA	329 (−560)	α	−3.2, ^b −4.1(7) ^c
2-CA	328 (−580)	α	−6.4 ^d
3-CA	305 (670)	β	52.9 ^d
4-CA	324 (750)	β	15.7
5-CA	321 (−1460)	β	−20.0
6-CA	348 (−360)	α	(−)

^a The approximate value determined from a w/w concentration using a KBr density of 2.75 g cm^{−3}. ^b From ref 3a. ^c This paper. ^d From ref 3b.

by Snatzke,¹⁰ the *P* helicity of the skewed benzoyl group should lead to the positive $n-\pi^*$ CD sign, whereas the *M* helicity to the negative one.¹¹ This rule has already been tested on several



optically active 1-tetralones and 1-indanones; however, their conformation in solution is by no means clear due to extreme flexibility of these systems,^{10,12} and therefore, model systems with a better defined geometry would be desirable for this purpose.

In the reported crystal structures of **1-CA** and **2-CA** the guest molecules exhibit small twisting of the benzoyl group in the *M* sense ($\text{O}=\text{C}-\text{C}=\text{C}$ torsion angles are of -3.2° and -6.4° , respectively).³ Our X-ray diffraction study on the single crystals of **4-CA** and **5-CA** revealed much stronger deviations of the chromophore from planarity; its helicity is of the *P* sense in the first compound and *M* in the second one [$\text{O}=\text{C}-\text{C}=\text{C}$ torsion angles are of $15.2(7)^\circ$ and $-19.9(8)^\circ$, respectively].¹³ In effect of the guest disorder in the **6-CA** crystal, the chirality of the twisted benzaldehyde molecule cannot be assigned unequivocally from the X-ray analysis.^{13d} However, the data in Table 1 show a very good correlation between the observed $n-\pi^*$ CE sign and the helicity of the benzoyl moieties and therefore a weak negative CE detected at 348 nm for **6-CA** indicates that the *M* chirality of the benzaldehyde molecule prevails.

The variation of the magnitude and sense of twisting of the benzoyl chromophores exhibited by the guest molecules in **1-CA**–**6-CA** results from differences in the crystal packing of these

(10) Snatzke, G.; Snatzke, F. In *Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism*; Ciardelli, F., Salvadori, P., Eds.; Heyden: London, 1973; pp 109–125 and references therein.

(11) If the turn from the carbonyl group to the *cisoid* side of the benzene ring is clockwise, the helicity is *P*, if counterclockwise *M*.

(12) Luche, M. J.; Marquet, A.; Snatzke, G. *Tetrahedron* **1972**, *28*, 1677–1695.

inclusion compounds. In **3-CA**, **4-CA**, and **5-CA** the guest molecules are accommodated in the β -type channels² formed between the bilayers of the CA molecules, adopting the trans conformation of their side chains, whereas in **1-CA**, **2-CA**, and **6-CA** the guest molecules are enclathrated into the α -type channels² of the CA molecules assuming the gauche conformation of the side chain (Figure 2). All guest molecules included in the α -type channels are only slightly twisted in the *M* sense, whereas those contained in the β -type channels show much stronger twisting either in *P* (e.g., **3** and **4**) or *M* sense (e.g., **5**).

The host–guest interactions in the DCA inclusion compounds are very different from those in the related CA complexes.^{2,3a} The crystal structures and the lattice energy calculations for the 2:5 **1-DCA** and 1:3 **4-DCA** complexes, described by Lahav, Leiserowitz, and co-workers,⁵ suggest a planar arrangement of the phenyl and acetyl or propionyl moieties in the guest molecules **1** and **4**, respectively, which accounts for the lack of the detectable CEs in their CD spectra.

The present results demonstrate extreme sensitivity of the CD spectroscopy to even a very small distortion of the benzoyl chromophore from planarity; it could lead, as in the case of **5-CA**, to the relatively strong CEs. They also unequivocally proved that the Snatzke's helicity rule¹⁰ correctly predicts the $n-\pi^*$ CE sign of aromatic ketones.

The induction of chirality by the crystal lattices of bile acids in several other chromophores is currently under investigation.

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Supporting Information Available: Supporting Information Available: X-ray structural data for **4-CA** and **5-CA** including ORTEP drawings, crystal packing diagrams, a summary of crystallographic parameters, atomic coordinates, bond distances and angles, and anisotropic thermal parameters (14 pages, print/PDF). An X-ray crystallographic file, in CIF format, is available through the Internet only. See any current masthead page for ordering information and Web access instructions.

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(13) (a) The $\text{O}=\text{C}-\text{C}=\text{C}$ torsional angle found from the crystal structure of **1-CA** solved at 100 K was of $-4.1(7)^\circ$, i.e., the value very similar to that reported in ref 3a. (b) The crystal structure of **4-CA** has been recently published (see ref 3c); however, the propiophenone molecule has been refined isotropically and the carbonyl oxygen, due to supposed disorder, has been resolved into two positions. Such a treatment of the guest unit has led to the structure with a pyramidal character of the carbonyl carbon. Therefore, we report a revised structure of this complex. Crystal data for **4-CA**: $\text{C}_{24}\text{H}_{40}\text{O}_5 \cdot \text{C}_9\text{H}_{10}\text{O}$, $F_w = 542.73$, $T = 293$ K, monoclinic, space group $P2_1$, $a = 16.752(3)$ Å, $b = 7.910(2)$ Å, $c = 12.222(2)$ Å, $\beta = 114.28(3)^\circ$, $V = 1476.3(5)$ Å³, $Z = 2$, $D_x = 1.221$ g cm^{−3}. The structure was refined with SHELXL-93 on F^2 to $R_1 = 0.052$, $wR_2 = 0.111$, GOF = 1.057 for all 3125 independent reflections collected up to $2\theta_{\text{max}} = 52^\circ$ (Mo K α radiation). (c) Crystal data for **5-CA**: $\text{C}_{24}\text{H}_{40}\text{O}_5 \cdot \text{C}_9\text{H}_9\text{OF}$, $F_w = 560.72$, $T = 293$ K, monoclinic, space group $P2_1$, $a = 16.668(3)$ Å, $b = 8.150(4)$ Å, $c = 12.064(2)$ Å, $\beta = 113.24(2)^\circ$, $V = 1505.8(8)$ Å³, $Z = 2$, $D_x = 1.237$ g cm^{−3}. The structure was refined with SHELXL-93 on 2065 reflections with positive values of F^2 : $R_1 = 0.046$, $wR_2 = 0.102$, GOF = 1.05 for 1685 reflections with $F > 4\sigma(F)$ [$R_1 = 0.121$, $wR_2 = 0.136$, GOF = 1.11 for all 2577 independent reflections]. Data were collected up to $2\theta_{\text{max}} = 48^\circ$ (Mo K α radiation). (d) Gdaniec, M. unpublished results.