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Absolute sense of twist of the benzil molecule in its enantiomorphous crystals and inclusion complexes with optically active hosts

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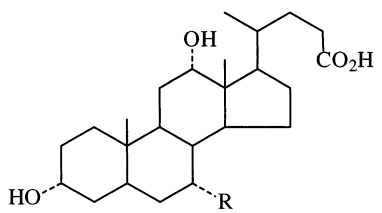
Abstract—The solid-state CD spectra were measured for optically active trigonal crystals of benzil (dibenzoyl) and its crystalline inclusion complexes with cholic and deoxycholic acids. The observed negative Cotton effect corresponding to the lowest energy n–π^* transition was correlated with the P helicity of the strongly twisted α-diketone moiety. The absolute configuration of the enclathrated guest molecule in the 1:2 inclusion complex between benzil and cholic acid was also determined by X-ray crystal analysis.

1. Introduction

Transformation of symmetrical, optically inactive species into optically active ones without use of chiral reagents is one of the most challenging and fascinating aspects of stereochemistry.[1,2] The majority of achiral compounds can assume chiral conformations due to, for example, molecular torsion. Their configurational stability depends on the energy barrier to internal rotation. Since molecular motions and internal rotations are severely restricted in the crystal state, in certain cases, the crystals of formally achiral molecules become optically active.[3] This is possible when the molecules in the crystal lattice are fixed into a chiral conformation or arranged in a chiral manner. Typical examples of achiral compounds that form optically active crystals are sodium chlorate,[4] glycine[5] and benzophenone.[6]

Spontaneous generation of chirality occurs when, during crystallization, the racemic mixture forms a conglomerate, i.e. a mechanical mixture of homochiral crystals.[3,7] Generally, undisturbed crystallization gives rise to an equimolar mixture of enantiomorphous crystals, however, an excess of one enantiomer can be prepared by recrystallization of the sample upon seeding with the desired form. Sometimes, when enantiomers are in equilibrium, the complete conversion into a single enantiomer is possible (complete asymmetric transformation), as illustrated in the crystallization of 1,1-binaphthyl.[8] The chiral crystals formed by achiral compounds can be useful as starting materials in 'absolute' asymmetric synthesis performed in the solid-state.[1,2] This type of process may also be responsible for the prebiotic origin of chirality.[9]

One of the earliest recognized examples of the compound that gains optical activity in the crystal state is benzil **1**, which crystallizes at room temperature in the trigonal enantiomorphous space groups $P3_121$ and $P3_221$. The molecule of **1** is located at a special position and assumes a skewed conformation of the C_2 symmetry.[10] The circular dichroism (CD) spectra of the oriented single crystals, as well as the anisotropic sample of **1**, have been reported on several occasions. However, no attempts have been made to correlate the observed Cotton effect sign with the absolute configuration of the molecule.[11] Though multiple-beam X-ray



PhCOCOPh
1

CA, R = OH
DCA, R = H

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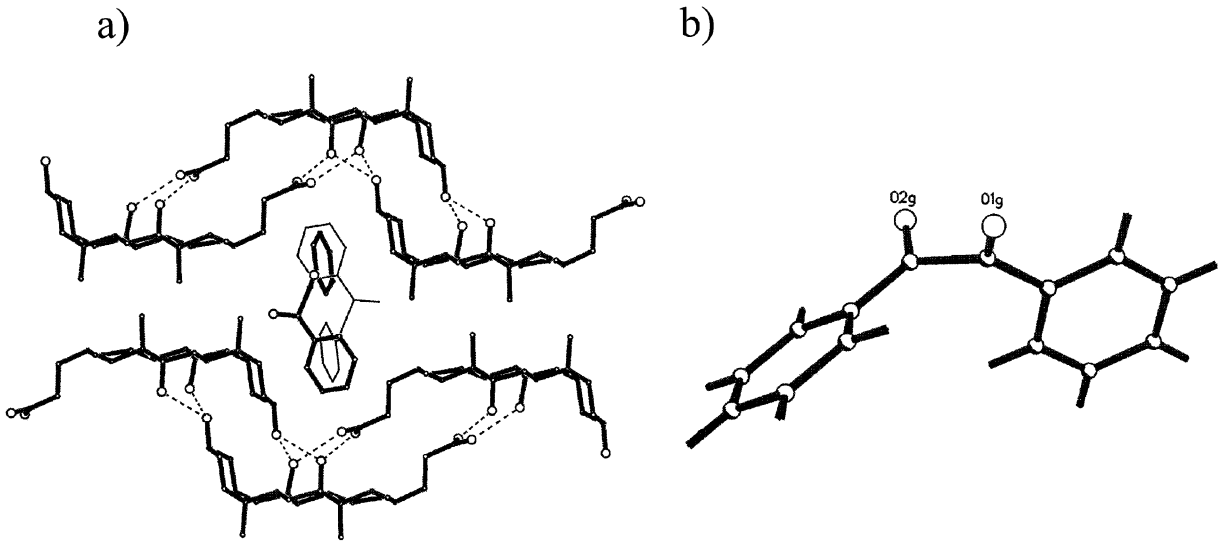

Figure 1. The crystal structure of the inclusion complex **1·CA**: (a) crystal packing viewed along the *y* axis indicating the guest disorder; (b) view of the guest **1** molecule showing its absolute configuration.

diffraction has been used for distinguishing between the enantiomorphs of **1**, there are serious limitations to this experimental method.[12] Herein, we propose a simple method for the determination of the absolute configuration of the benzil molecule in the crystalline form.

Recently, we have developed a related simple method for the generation of chirality in symmetric molecules by inclusion complexation with optically active hosts.[13,14] Easily accessible naturally occurring cholic (**CA**) and deoxycholic acid (**DCA**) are particularly well suited for this purpose.[13a] The guest molecule trapped in the crystal matrices of these bile acids are frozen in chiral conformations that makes detection of their CD in the solid-state possible. Since the configurations of **CA** and **DCA** are well established, the X-ray crystallographic analysis of single crystals of the inclusion complexes allows unequivocal assignment of the absolute configuration of the guest molecules. Therefore a combination of the X-ray and the solid-state CD measurements (KBr disk) on the complexed and uncomplexed **1** provide a means of establishing the absolute configuration of the enantiomorphous crystals of **1**.

2. Results and discussion

The pale yellow needle-like crystals of the 1:2 complex **1·CA** were prepared by co-crystallization of the components from a small amount of butan-2-ol. Similarly, **1·DCA** crystals (1:4 molar ratio according to ^{1}H NMR) were obtained by recrystallization of **1** and **DCA** from methanol. The long rods of the hexagonal form of **1** were grown by slow evaporation of a saturated methanolic solution.

The crystal structure of **1·CA** depicted in Fig. 1 shows features typical of the **CA** clathrates.[15] The hydrogen bonded host molecules are arranged into amphiphilic corrugated bilayers with hydrophilic interior and hydrophobic outer surfaces. The guest molecules are located inside the helicoidal channels formed between the neighboring bilayers running in the *y* direction. Accommodation of two host molecules and one guest molecule in the unit cell of the $P2_1$ symmetry is only possible if the space group symmetry is violated by the guest disorder. The α-diketone unit of **1** is strongly twisted in the *P* sense [O=C–C=O torsion angle is 111.8(7)°] and the two benzoyl moieties are also twisted: one in the *P* and the second in the *M* sense [O=C–C=C torsion angles are 15.7(8) and −29.1(7)°, respectively]. The geometry of the uncomplexed **1** in the crystal state is slightly different since the α-diketone moiety is also twisted (O=C–C=O torsion angle is 108.8°) but the benzoyl groups are nearly planar (O=C–C=C torsion angles are −4.0° in both cases).[10] Unfortu-

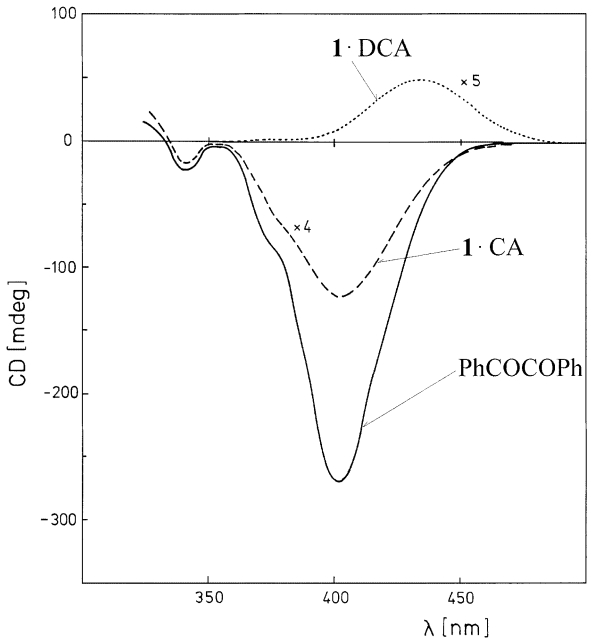

Figure 2. Solid-state CD spectra of **1** (trigonal crystal), **1·CA** and **1·DCA** taken in KBr disks.

nately, the crystal structure of **1·DCA** could not be solved.

The CD spectra of **1**, **1·CA** and **1·DCA**, taken in KBr disks, are shown in Fig. 2. The CD of the crystalline diketone **1** exhibits an intense Cotton effect near 400 nm with a shoulder at 375 nm and a much weaker band of the same sign at 340 nm. The CD of **1·CA** is characterized by two negative Cotton effects: one of moderate intensity, observed as a diffuse band at 404 nm and the second weak band at 338 nm. On the other hand, **1·DCA** shows only a weak positive CD band at 426 nm.

The chiroptical properties of α-diketones have been a subject of numerous theoretical and experimental studies.[16] The through-bond and through-space interaction between two carbonyl groups generates bonding (+) and antibonding (–) combinations of their n, π and π* orbitals. The energy separation between the highest occupied molecular orbitals n_+ and n_- is of 2 eV and does not depend significantly on chromophore twisting.[17] In consequence, two n–π* electronic transitions are observed in the visible and near UV region. The lowest energy transition can be assigned as the n_+–π_+^* excitation and the next one as an admixture of the n_-–π_+^* and n_+–π_-^* states.[17] Thus the Cotton effects near 400 nm detected in the CD spectra of **1**, **1·CA** and **1·DCA** are undoubtedly due to the first n–π* transition. The shoulder detected at slightly lower wavelengths in the spectrum of **1** corresponds to the vibronic band since a pronounced vibronic structure is clearly visible in the solution spectra of **1**.[18] Semi-empirical MO calculations for α-diketones by Richardson and Čaliga[19] have attributed to the negative Cotton effect corresponding to the long-wavelength transition to the *P* helicity of the twisted chromophore. These results were confirmed by our own INDO/S-CI calculations[20,21] performed for **1** using the geometry observed in the optically active crystals as well as that found in the **1·CA** complex. Thus the *P* chirality should be assigned to the twisted benzil **1** molecules forming the trigonal crystals in the space group $P3_121$ and showing the negative Cotton effect near 400 nm. This assignment was confirmed by the CD spectrum of the **1·CA** complex. Assuming that the contributions from the oppositely twisted benzoyl units cancel each other, the contribution from the twisted dicarbonyl moiety in the guest molecule should determine the CD sign. The observed negative Cotton effect sign of **1 CA** remains in agreement with the X-ray structure revealing the *P* helicity of the chromophore. A much weaker positive CD observed in the spectrum of **1·DCA** points to the *M* chirality of the guest **1**, though this molecule is probably twisted less than that in the **1·CA** complex as indicated by weak magnitude of the Cotton effect and its bathochromic shift caused by chromophore flattening.[22]

The origin of the weak Cotton effect observed at 340 nm in **1** and **1·CA** is less clear. According to Chaudhuri and El-Sayed it belongs to the second n–π* transition. However, bearing in mind that the half-width of this band (1100 cm^{-1}) is much lower than that of the lowest energy transition (2700 cm^{-1}) and that the opposite CD sign is expected for the second n–π* excitation,[16] this assignment is probably wrong. More likely this band can be attributed to the ^1L_b transition in the benzoyl moiety.

In conclusion, the helicity of the benzil **1** molecule in its optically active trigonal crystals can be determined from the Cotton effect sign corresponding to the lowest energy n–π* transition. The chirality of **1** can be also generated by inclusion complexation with the steroidal bile acids and the sense of twisting of the enclathrated molecules can be determined either by X-ray crystallography or the solid-state CD spectra.

3. Experimental

The solid-state CD spectra were obtained with freshly prepared KBr disks and recorded with a Jasco J-715 dichrograph. A mixture of 2–5 mg of the sample and 250 mg of dried KBr was ground and formed into a disk 0.5 mm thick and with radius of 15 mm. The disk was rotated around the optical axis and CD recordings were made for several positions in order to check a reproducibility of the spectra.

3.1. X-Ray structure analysis

Diffraction data were obtained on a Kuma KM-4CCD diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The structure of **1·CA** was solved by direct methods with the program SHELXS-86.[23] Full-matrix least-squares refinement was carried out with SHELXL-97.[24] The guest molecules were refined with occupancy factors of 0.5 for all atoms and with all 1–2 and 1–3 distances restrained to the expected values. Restraints were also imposed on the planarity of the phenyl rings and carbonyl groups. Because the benzil molecule has three conformational internal degrees of freedom the torsions around the three central formally single bonds were not restricted. Atoms of the guest molecules were refined with one common isotropic displacement parameter.

Crystal data for $C_{24}H_{40}O_5 \cdot 0.5C_{14}H_{10}O_2$ **1·CA**: monoclinic, $P2_1$, $a = 13.392(1)$, $b = 8.019(1)$, $c = 14.002(1)$ Å, $\beta = 112.809(9)$, $V = 1386.1(2)$ Å^3, $Z = 2$, $D_{calcd} = 1.231$ g cm^{-3}, $T = 130(2)$ K, $R_1 = 0.0670$, $wR_2 = 0.1615$ for 2189 reflections with $I > 2(I)$.

The atomic coordinates for the reported crystal structures are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK. Any request should be accompanied by a full literature citation.

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21. The rotatory strength [*R*] values, corresponding to the first n–π^* transition, calculated for the geometry of **1** observed in the trigonal crystals and that found in **1·CA**, are −0.425 and −0.485 ($D\mu_B$ units), respectively. The standard INDO parameters with the interaction scaling factors $f_\sigma = 1.267$ and $f_\pi = 0.585$ were used. The CI calculations were restricted to 4 singly excited configurations. A quantum electronic structure program ARGUS 1.1 was kindly provided by Dr. Mark A. Thompson (Pacific Northwest Lab., Richland, WA, USA).
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