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Inclusion Compounds of Nitrosobenzenes with Cholic Acid and Deoxycholic Acid *

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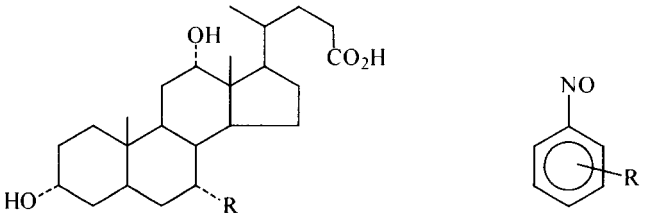
Abstract

The crystalline inclusion compounds of cholic acid (**CA**) and deoxycholic acid (**DCA**) with several nitrosobenzenes were prepared. The IR spectra and crystal structures of these compounds confirmed inclusion of the monomeric form of the C-nitroso compounds. The **DCA** compounds have 2 : 1 host:guest stoichiometry and $P2_1$ symmetry. Guest molecules are enclosed in channels and disordered. In the **CA**-nitrobenzene inclusion compound (**1**· **CA**) the host:guest stoichiometry is 1 : 1. The host molecules form typical **CA** bilayer aggregates and guest molecules are accommodated in helicoidal channels. The guest nitroso group is not coplanar with the phenyl ring; the torsion angle on the C–N bond is 8.6(8)°. The solid-state circular dichroism spectrum of **1**·**CA** shows the negative Cotton effect at 780 nm corresponding to the n–π^* electronic transition that can be associated with the *P* helicity of the guest molecule. The extremely weak magnitude of the Cotton effects exhibited by the **DCA** complexes points to a nearly planar arrangement of the NO group and the phenyl ring in the guest molecules.

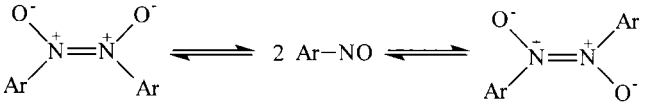
Introduction

Crystalline inclusion complexes attract increasing attention from the viewpoint of their potential applications for separation of isomers or stereoisomers, protection of labile species and development of new solid materials [1]. Chiral host compounds are suitable for the resolution of racemates [2], performing enantioselective reactions [3] and more recently for generation of chirality in symmetric molecules [4,5]. Among various chiral host compounds, naturally occurring steroidal bile acids have found particularly widespread application. Their crystal lattices are composed of amphiphilic bilayers formed by the hydrogen bonded molecules and contain channel-like empty spaces that can be filled with low molecular weight guest compounds [6]. Continuing our interest in the structure and spectroscopic properties of the inclusion complexes of cholic acid (**CA**) and deoxycholic acid (**DCA**) with different types of chromophoric substances [5, 7, 8], we directed our attention towards nitrosobenzenes as potential guest molecules. Aromatic C-nitroso compounds are known to exist in solution as equilibrium mixtures of the monomer and one or two dimeric forms (Scheme) [9, 10].



CA, R = OH
DCA, R = H

1 R = H
2 R = *o*-Me
3 R = *m*-Me
4 R = *p*-Me



(*Z*) - dimer monomer (I) (*E*) - dimer

Generally, their solutions are coloured green or blue, indicating contribution of the monomer, whereas most crystals are colourless and contain dimers assuming either the *E* or *Z* configuration. The affinity of the bile acid crystal lattices to medium sized guest molecules makes possible a selective enclathration of the monomeric nitrosobenzenes from the equilibrium mixture in solution. It opens an opportunity for studying the structural and spectroscopic properties of these species in the solid state. Furthermore, the conformationally

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flexible molecules embedded in a chiral crystal environment may assume a chiral conformation that makes possible measurement of their circular dichroism (CD) spectra.

This paper presents results of the crystallographic studies on the inclusion complexes of the bile acids with nitrosobenzene (**1**) and nitrosotoluenes **2–3**. In addition the solid state IR and CD spectra of the monomeric **1–4** trapped in the crystal host lattices are presented.

Experimental

The C-nitroso compounds **1–4** were prepared by reduction of the corresponding nitro compounds according to the literature procedures [9]. The greenish 1 : 1 inclusion crystals of **1·CA** suitable for X-ray structural analysis were prepared by evaporation of a solution of the components in 2-butanol at reduced pressure. The blue or emerald crystals of **DCA** with **1–4** were prepared by co-crystallization of the acid with an excess of the corresponding nitroso compound from methanol. CD spectra were recorded on a JASCO J-715 dichrograph. A mixture of 5 mg of the complex and 300 mg of KBr was ground and formed into a disk with 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 for reproducibility of the spectra [4, 5]. FT-IR absorptions were recorded with a Bruker IFS66 spectrometer in KBr disks.

The reported crystal structures have been solved by direct methods with SHELXS-97 [11], refined by full-matrix-least squares procedure against F^2 with SHELXL-97 [12]. Crystal data for **1·CA**: $C_{24}H_{40}O_5{\cdot}C_6H_5NO$, crystal size 0.5 × 0.5 × 0.15 mm, T = 100 K, monoclinic, $P2_1$, a = 13.426(3) Å, b = 8.045(2) Å, c = 13.970(4) Å, β = 115.32(2)°, V = 1364.0(6) Å^3, Z = 2, D_x = 1.256 g cm^{-3}, μ = 0.086 mm^{-1}, Mo Kα radiation (λ = 0.71073 Å). Data were collected up to 2θ = 50° with a Kuma KM-4 diffractometer. The structure was refined on 2578 reflections; 334 refined parameters; R_1 = 0.0407, wR_2 = 0.1042, GOF = 1.059 for 2114 reflections with $F > 4\sigma(F)$ [R_1 = 0.0679, wR_2 = 0.1105 for all 2376 independent reflections].

Crystal data for **2·DCA**: $2C_{24}H_{40}O4{\cdot}C_7H_7NO$, crystal size 0.6 × 0.2 × 0.15 mm, T = 130 K, monoclinic, $P2_1$, a = 7.2819(7) Å, b = 26.0730(14) Å, c = 13.4580(7) Å, β = 90.081(6)°, V = 2555.1(3) Å^3, Z = 2, D_x = 1.178 g cm^{-3}, μ = 0.078 mm^{-1}, Mo Kα radiation (λ = 0.71073 Å). Data were collected up to 2θ = 52.7° on a Kuma CCD diffractometer. The structure was refined on 5286 reflections; 573 refined parameters; R_1 = 0.0544, wR_2 = 0.1448, GOF = 1.070 for 4336 reflections with $F > 4\sigma(F)$ [R_1 = 0.0666, wR_2 = 0.1585 for all independent reflections]. The guest molecule was initially located on a difference Fourier synthesis in one orientation but the shape of the displacement ellipsoids of the guest as well as two residual electron density peaks in the guest region on the ΔF map pointed to possible guest disorder. The model of the guest molecule in a second orientation was built and in the refinement process constraints were imposed on the 1–2 bonding and 1–3 interatomic distances and on the planarity of the phenyl ring. Values of the constraint parameters were calculated from the geometry of 1 in **1·CA**. The sum of the occupancy factors for the two guest positions was kept equal to 1.00 with individual occupancy factors refined to 0.57(1) (guest G) and 0.43(1), (guest H). The guest molecules have been refined isotropically.

Crystal data for **3·DCA**: $2C_{24}H_{40}O4{\cdot}C_7H_7NO$, crystal size 0.5 × 0.5 × 0.08 mm, T = 130 K, monoclinic, $P2_1$, a = 7.2780(10) Å, b = 26.196(3) Å, c = 13.409(2) Å, β = 90.51(1)°, V = 2556.4(6) Å^3, Z = 2, D_x = 1.177 g cm^{-3}, μ = 0.078 mm^{-1}, Mo Kα radiation (λ = 0.71073 Å). Data were collected up to 2θ = 50° on a Kuma CCD diffractometer. The structure was refined on 4563 reflections; 573 refined parameters; R_1 = 0.0681, wR_2 = 0.1565, GOF = 1.070 for 3336 reflections with $F > 4\sigma(F)$ [R_1 = 0.0923, wR_2 = 0.1693 for all independent reflections]. The guest molecule is disordered over two positions and it has been refined as described above. Individual occupancy factors refined to 0.65(1) (guest G) and 0.35(1) (guest H).

The guest molecules in **1·CA**, **2·DCA** and **3·DCA** are shown in Figure 1.

Results and discussion

CA easily gives 1 : 1 co-crystals with nitrosobenzene (**1**) but attempts to prepare analogous complexes with nitrosotoluenes **2–4** failed. On the other hand, all the compounds **1–4** smoothly form inclusion compounds with **DCA**. IR spectroscopy is a useful tool for distinguishing between the monomeric and dimeric form of C- nitroso compounds. Due to a greater degree of double bond character of the NO linkage, the monomer is expected to exhibit the higher NO stretching frequency compared to the dimer forms. It has been shown that the monomer exhibits a strong band in the 1480–1590 cm^{-1} region, whereas the presence of one band in the 1250–1299 cm^{-1} region or two bands in the 1350–1400 cm^{-1} region is characteristic of the *E* or *Z* dimer, respectively [13]. The FT-IR spectra of **1·CA**, **1· DCA**, **2· DCA**, **3· DCA**, and **4· DCA** showed a sharp absorption band at 1504, 1505, 1498, 1502 and 1511 cm^{-1}, respectively, clearly indicating that the inclusion of the monomeric form of the nitrosobenzene molecule occurs. This observation has been confirmed by X-ray crystallography of inclusion complexes **1·CA**, **2·DCA** and **3·DCA**. Only monomeric forms of the guest molecules have been found in the hydrophobic channels formed in the host matrices of **CA** and **DCA**. In the studied complexes the interactions between nitrosobenzenes and bile acid molecules are purely of the van der Waals nature.

The crystal packing of **1·CA** is shown in Figure 2. The molecules of 1 are helicoidally arranged along the channel with the dihedral angle between the mean planes of the nearest aromatic molecules equal to 76° (Figure 2b). The nitroso groups are directed to the center of the channel with the nitroso N atom located very close to the 2_1 axis. The closest distance between the N atoms in the channel is 4.023 (1) Å. The nitroso group is not co-planar with the phenyl ring and the torsion angle around the C–N bond is 8.6(8)°.

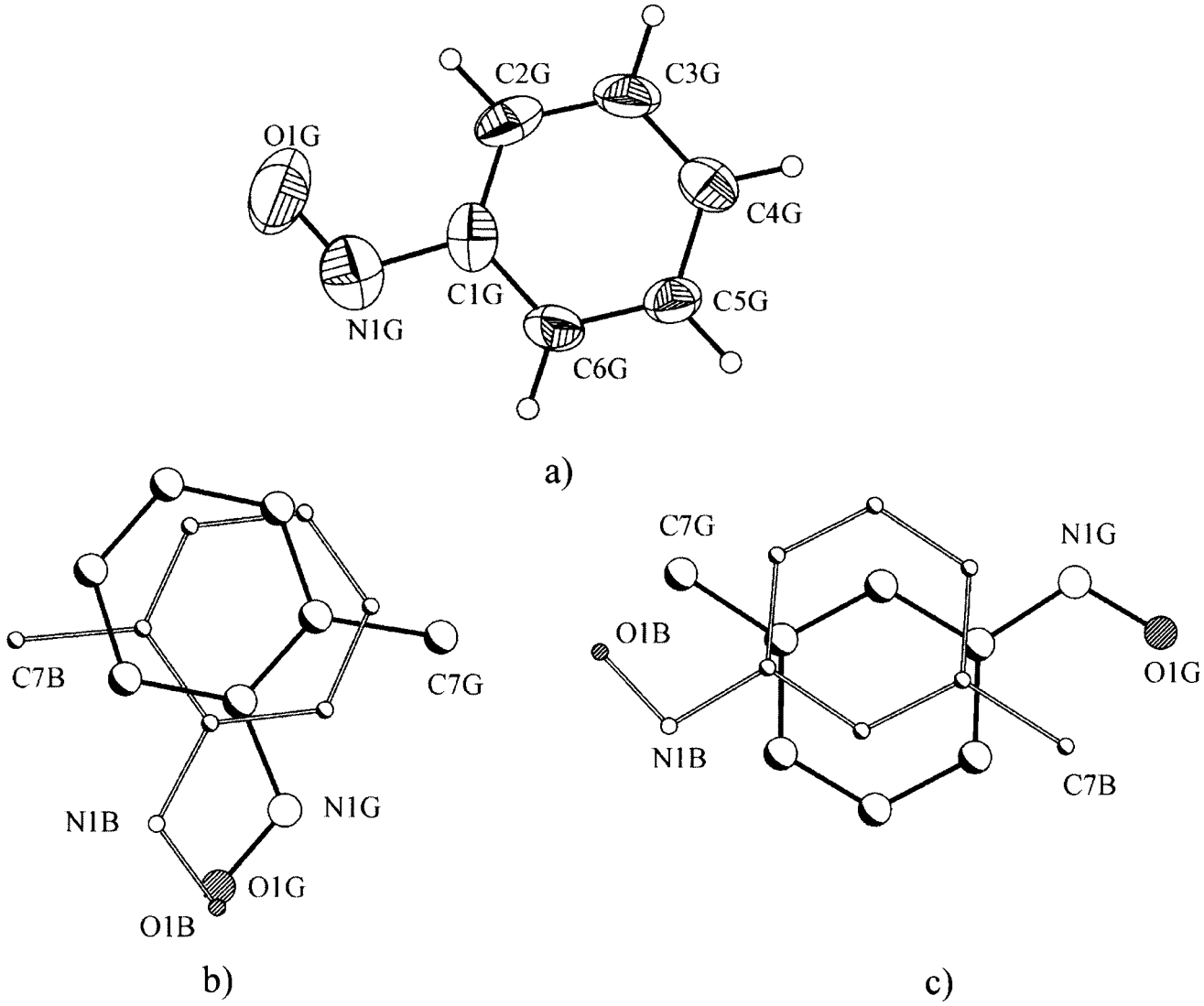

Figure 1. Ortep drawing of nitrosobenzene in **1·CA** (a) and disordered nitrosotoluene guests in **2·DCA** (b) and **3·DCA** (c).

The planar arrangement of the phenyl ring and the NO group would lead to a very short distance between the nitroso O atom and the hydrogen atom at C-6 of the two neighboring guests in the channel. The observed torsion around the C–N bond lengthens this distance up to 2.58 Å.

Whereas **DCA** inclusion compounds usually form orthorhombic crystals with guest molecules enclosed in hydrophobic channels located between the host bilayers the nitrosotoluenes **2–3** co-crystallize with **DCA** in the monoclinic space group $P2_1$ (Figures 2a and 3a). Only one monoclinic inclusion compound of **DCA** has been reported so far [14]. It has been shown that in this monoclinic complex with *o*-xylene the **DCA** host matrix shows only minor deviations from $P2_12_12_1$ symmetry characteristic of the α-type orthorhombic crystals. The unit-cell parameters are also very similar to the α-type but in the monoclinic form the screw symmetry is retained only along the longest cell axis. For $P2_12_12_1$ symmetry, a 2 : 1 host:guest ratio and a unit cell comprising four host and two guest molecules, the disorder of the guest has to be assumed a priori. When the crystal symmetry is reduced to $P2_1$ disorder of the guest molecules, while still possible, is no longer invoked by space-group symmetry violation. In the **DCA**/*o*-xylene complex, studied at room temperature, only one position of the guest, but with large atomic displacement parameters, has been identified.

Our interest in the crystal structure of the **DCA** compounds was mainly focused on the geometry of the guest molecules and the $P2_1$ symmetry of these complexes seemed to promote ordered-guest structures. However, in **2·DCA** and **3·DCA**, two overlapping positions of the guest were found (Figures 1, 3b and 4b) and no precise information about the rotation of the nitroso group around the C–N bond could be obtained.

The monomeric C-nitroso compounds are characterized by a long-wavelength absorption near 750 nm, corresponding to the n–π^* electronic transition [15], which is responsible for the blue or green colour of their solutions. In contrast, the analogous transition in the corresponding dimers occurs at much shorter wavelengths and therefore these compounds are colourless. A bright colouring of the complexes studied confirms the monomeric structure of the guest molecules trapped in the crystal matrices. Inclusion of

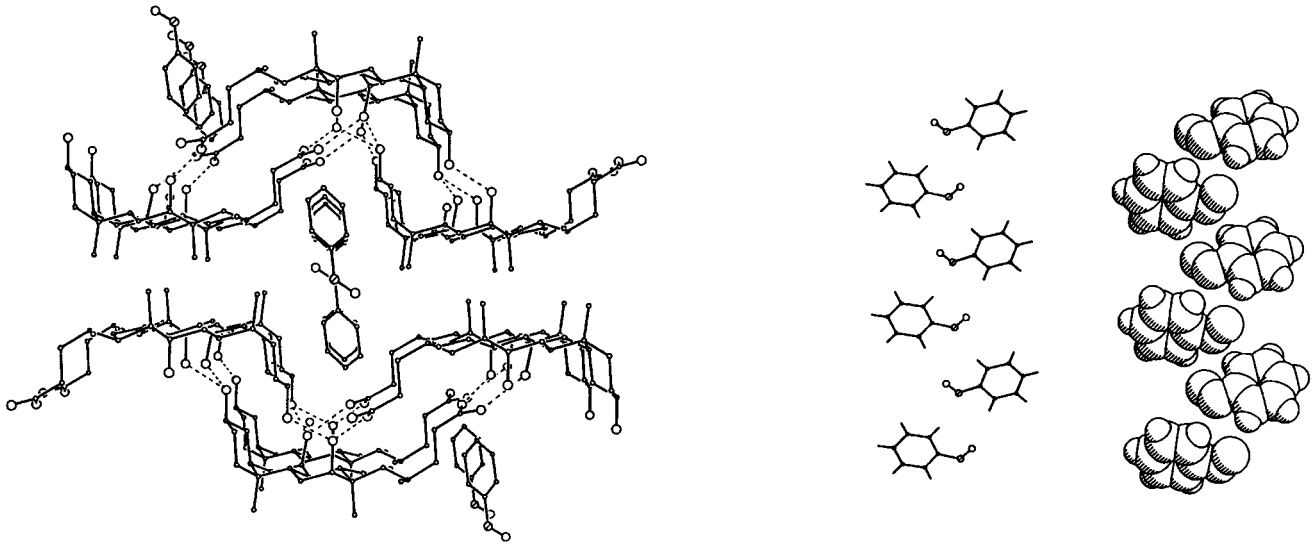

Figure 2. Crystal packing of **1**·**CA** viewed along *y* and arrangement of the guest molecules in the channel.

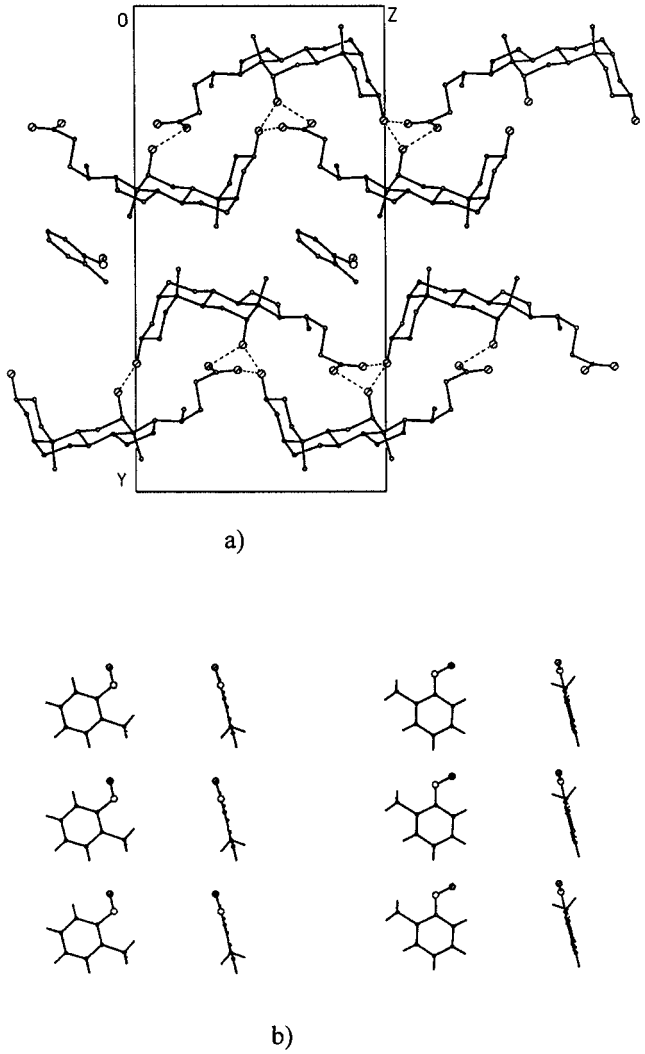

Figure 3. Crystal packing in **2**·**DCA** viewed along *x* (only one position of the guest is shown) and arrangement of the guest molecules in the channel (separate view for the two disordered guest positions).

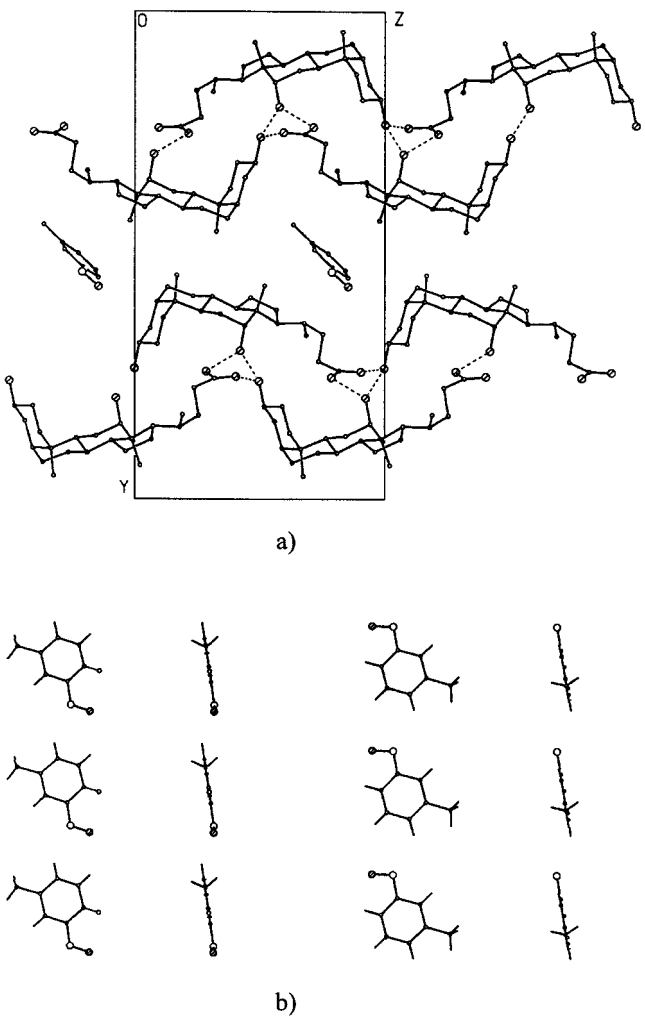

Figure 4. Crystal packing in **3**·**DCA** viewed along *x* (only one position of the guest is hown) and arrangement of the guest molecules in the channel (separate view for the two disordered guest positions).

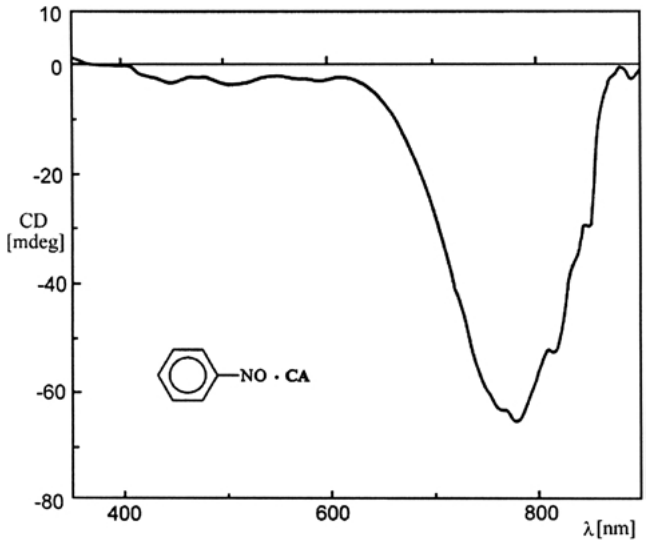

Figure 5. Solid state CD spectrum of **1·CA** taken in a KBr disk.

Table 1. Circular Dichroism (CD) data

Compd.	CD λ, nm ([Ω])[a]
1·CA	778 ((550)[b]
1·DCA	0
2·DCA	780 (+)[c]
3·DCA	800 (−)[c]
4·DCA	760 (+)[c]

[a]Molecular ellipticity in deg cm^2 $dmol^{-1}$.
[b]Approximate value determined by considering the weight concentration (KBr density 2.75 g cm^{-3}).
[c]Only the CD sign can be determined.

nitrosobenzenes in the helical channels of the bile acid host matrix may lead to generation of chirality in these molecules that makes possible CD measurements in the solid state [5]. A slight twisting of the NO group from the phenyl ring plane results in formation of the inherently chiral chromophore, the helicity of which determines the observed Cotton effect sign. Thus the CD of **1·CA** measured in a KBr disk shows a negative CD band with marked vibronic structure at 780 nm (Figure 5) which can be associated with the *P* chirality of the guest nitrosobenzene (the observed C=C–N=O angle is 8.6°). However, the CD spectra of the **DCA** complexes show only very weak Cotton effects or, as in the case of **1·DCA**, no measurable CD in the region of the n–π^* transition was detected (Table 1). This may be an indication of a nearly planar arrangement of the NO group and the phenyl ring in the guest molecules.

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References

1. J. L. Atwood, J. E. D. Davies, and D. D. MacNicol (eds.): *Inclusion Compounds*, Vol. 4, Oxford University Press, Oxford (1991) and refs therein.
2. F. Toda: *Top. Curr. Chem.* **140**, 43 (1987); F. Toda in G. W. Gokel (ed.), *Advances in Supramolecular Chemistry*, Vol. 2, pp. 141–191, JAI Press, London (1992); F. Toda in J. L. Atwood, J. E. D. Davies, and D. D. MacNicol (eds.), *Inclusion Compounds*, Vol. 4, pp. 126–187, Oxford University Press, Oxford (1991); G. Kaupp: *Angew. Chem. Int. Ed. Engl.* **33**, 728 (1994).
3. Y. Ito: *Synthesis* 1 (1998); K. Tanaka and F. Toda: *Chem. Rev.* **100**, 1025 (2000); K. Tanaka, E. Mochizuki, N. Yasui, Y. Kai, I. Miyahara, K. Hirotsu, and F. Toda: *Tetrahedron* **56**, 6853 (2000).
4. R. Kuroda and T. Honma: *Chirality* **12**, 269 (2000).
5. M. Gdaniec and T. Połoński: *J. Am. Chem. Soc.* **120**, 7353 (1998).
6. M. Miyata and K. Sada in D. D. MacNicol, F. Toda, and R. Bishop (eds.), *Comprehensive Supramolecular Chemistry*, Vol. 6, pp 147–176, Pergamon, Oxford (1996).
7. M. Gdaniec, M. J. Milewska, and T. Połoński: *Angew. Chem. Int. Ed. Engl.* **38**, 392 (1999).
8. E. Nowak, M. Gdaniec, and T. Połoński: *J. Incl. Phenom.* **37**, 155 (2000).
9. D. A. Fletcher, B. G. Gowenlock, and K. G. Orrell: *J. Chem. Soc., Perkin Trans 2*, 2201 (1997).
10. D. A. Fletcher, B. G. Gowenlock, and K. G. Orrell: *J. Chem. Soc., Perkin Trans 2*, 797 (1998); D. A. Fletcher, B. G. Gowenlock, K. G. Orrell, D. C. Apperley, M. B. Hursthouse, and K. M. A. Malik: *J. Chem. Res. (S)* 202 (1999).
11. G.M. Sheldrick: *Acta Crystallogr.* **A46**, 467 (1990)
12. G.M. Sheldrick: *SHELXL-97*. Program for Crystal Structures Refinement from Diffraction Data, University of Göttingen (1997).
13. W. Lüttke: *Z. Elektrochem.* **61**, 976 (1957); D. A. Dieterich, I. C. Paul, and D. Y. Curtin: *J. Am. Chem. Soc.* **96**, 6372 (1974); D. A. Fletcher, B. G. Gowenlock, K. G. Orrell, V. Sik, D. E. Hibbs, M. B. Hursthouse, and K. M. A. Malik: *J. Chem. Soc., Perkin Trans 2* 191 (1996).
14. S. Cerrini, G. Pochetti, F. Gallese, and E. Possagno: *Acta Crystallogr.* **C49**, 1087 (1993)
15. E. S. Stern and C. J. Timmons: *Electronic Absorption Spectroscopy in Organic Chemistry*, Chapters 4 and 6, E. Arnold Ltd., London (1970).