

Optical activity of benzophenone and thiobenzophenone generated by spontaneous crystallization and inclusion complexation with cholic acid

Monika Szyszyng,^a Elżbieta Nowak,^{b,†} Maria Gdaniec,^b Maria J. Milewska^a
and Tadeusz Połowski^{a,*}

^aDepartment of Chemistry, Technical University of Gdańsk, 80-952 Gdańsk, Poland

^bFaculty of Chemistry, A. Mickiewicz University, 60-780 Poznań, Poland

Received 3 September 2003; accepted 21 October 2003

Abstract—The solid state CD spectra were measured for enantiomorphous crystals of benzophenone **1** and 4,4'-dimethylbenzophenone **2**. The helicity of the constituent molecules was determined from the sign of the Cotton effect corresponding to the ketone $n-\pi^*$ transition. In addition the crystalline 1:2 inclusion complexes of the ketone **1** and thiobenzophenone **4** with cholic acid were prepared and their CD spectra were measured. The observed negative Cotton effect sign of **1**·CA and positive one for **4**·CA corresponding to the lowest energy $n-\pi^*$ transitions were correlated with the *M* and *P* helicity of the enclathrated guest molecules, respectively. The helicity of the guest molecules was confirmed by X-ray crystal structure analyses.
© 2003 Elsevier Ltd. All rights reserved.

1. Introduction

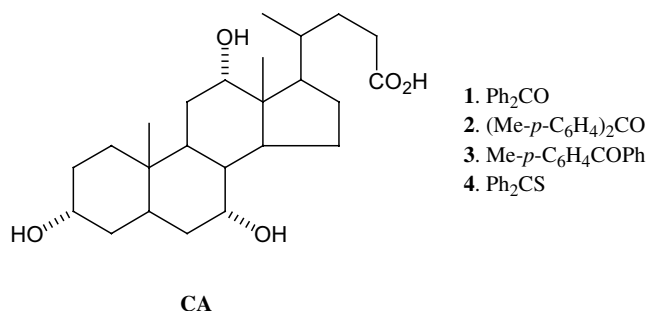
Generation of chirality in achiral compounds is considered one of the most intriguing topics in organic solid state chemistry.¹ Molecules devoid of stereogenic centers can adopt chiral conformations caused by internal torsion. Usually such compounds are conformationally labile in solution due to a rapid interconversion between the enantiomers. However, they may occasionally form optically active crystals with the component molecules frozen in a chiral conformation. Spontaneous generation of chirality is a relatively rare phenomenon that occurs when the racemic mixture crystallizes as a conglomerate, that is, an equimolar mixture of enantiomorphous crystals from which a suitable single crystal can be selected.² It can be illustrated by the asymmetric crystallization of glycine,³ benzil,^{4,5} 1,1-binaphthyl⁶ or more recently 1,2-bis(*N*-benzoyl-*N*-methylamino)benzene and *N*-(4-chlorophenyl)-*N'*-cyanoguanidine.⁷

Sometimes seeding the sample of the equilibrating enantiomers with the desired form may lead to a conversion of the whole quantity of the racemate into a single enantiomer (complete asymmetric transformation).^{2b,6}

Chiral crystals formed of achiral compounds have attracted growing attention as starting materials or catalysts in asymmetric synthesis.^{1,8} They may also be responsible for the origin of homochirality in biomolecules.⁹ Unfortunately, the asymmetric crystallization of achiral compounds without external chiral influence is a rare and highly unpredictable phenomenon. A different approach to generate optical activity in symmetric molecules offers inclusion complexation with chiral hosts.^{5,10,11} Recently we have shown that naturally occurring cholic acid (CA) is particularly well suited for this purpose.^{5,10} The guest molecules embedded in the crystal lattice of CA are forced to assume a chiral conformation that can be detected by solid state circular dichroism (CD) measurements. Since the configuration of CA is well established, the X-ray crystallographic analysis of single crystals of the inclusion compounds makes possible unequivocal assignment of the absolute configuration of the guest molecules.

* Corresponding author. E-mail: tadpol@chem.pg.gda.pl

† Present address: EMBL, Hamburg, Germany.



An important example of the symmetric organic compound crystallizing in a chiral space group ($P2_12_12_1$) is benzophenone **1**, the molecules of which adopt a helical propeller conformation.¹² 4,4'-Dimethylbenzophenone **2**¹³ and the metastable trigonal form of 4-methylbenzophenone **3** behave similarly.¹⁴ Surprisingly the optical activity of these crystals have not received much attention. On the other hand, the induced CD of **1** in solution has been the subject of intense experimental and theoretical investigations.¹⁵ Herein we report the solid state CD spectra of the chiral crystals of **1** and **2** taken in KBr disks. In order to correlate the observed Cotton effect signs with the molecular chirality (absolute sense of twist) of the benzophenone molecules we prepared the inclusion complex of **1** with CA and combined its CD spectrum with the X-ray crystallographic structure. For comparison we also performed a similar study for thiobenzophenone **4**. A substitution of sulfur for oxygen in the carbonyl group shifts the $n\text{--}\pi^*$ absorption to much longer wavelengths and causes better separation of the overlapping bands facilitating the spectroscopic measurements.¹⁶ Since **4** itself does not form optically active crystals, we measured its CD induced by the complexation with CA.

2. Results and discussion

The long rods of **1** and **2** were obtained by crystallization from methanol. The needle-like crystals of the 1:2 inclusion complex of **1**-CA were prepared by co-crystallization of CA with an excess of **1** in the presence of a small amount of diethyl ether. Deep blue crystals of the 1:2 inclusion compound **4**-CA were obtained from freshly prepared thiobenzophenone **4**¹⁷ by co-crystallization with CA from a small amount of 2-butanol, which does not form inclusion complexes with CA.¹⁸ It is noteworthy that **4** is a very sensitive substance and its enclathration in the crystal matrix of CA leads to its stabilization that allows it to be stored almost indefinitely at room temperature.

The CD spectra of **1** and **2** taken in KBr disks are presented in Figure 1. Both compounds exhibit relatively strong Cotton effects centered at 360 nm with a distinct vibronic fine structure. They can unequivocally be assigned to the forbidden $n\text{--}\pi^*$ transition of the ketone chromophore.

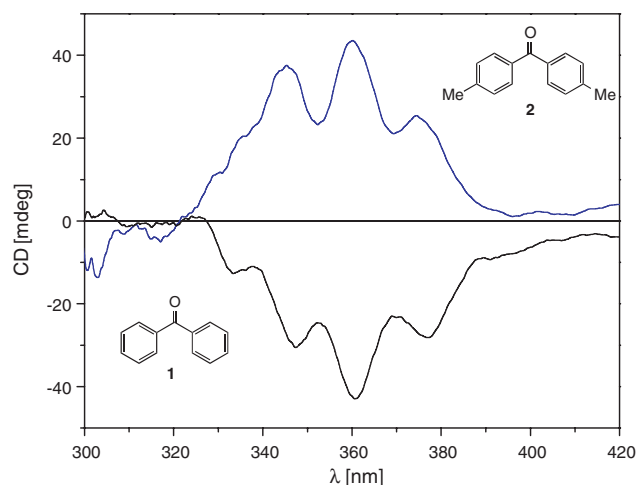
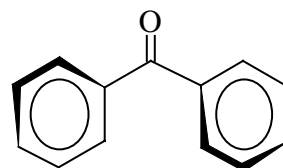
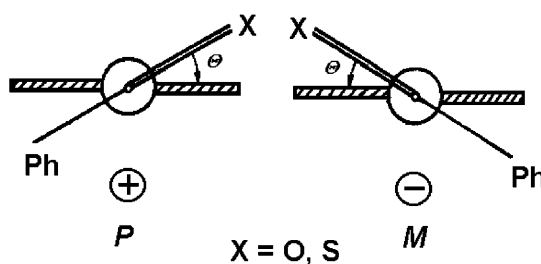


Figure 1. Solid state CD spectra of the chiral crystals of **1** and **2** taken in KBr disks.

For steric reasons, a molecule of **1** cannot assume a planar conformation and is intrinsically chiral. Various theoretical calculations (molecular mechanics, semi-empirical, and ab initio methods) have shown that the minimum energy conformer assumes a helical geometry (the phenyl rings are twisted out of the central carbonyl plane in opposite directions by the same torsion angle about 30°).¹⁹ A very similar molecular geometry was also



observed in the crystal structures of **1** and **2**. According to the Snatzke's helicity rule, the *P* helicity of the skewed benzoyl chromophore should lead to the positive $n\text{--}\pi^*$ Cotton effect sign, whereas the *M* helicity to the negative one.^{10a,20} Thus the observed negative CD for the crystals of **1** suggests the *M,M*-helicity of the constituent molecules and the positive one for **2** the *P,P* helicity of the ketone molecules. These assignments were further confirmed by the chiroptical spectra of the CA inclusion complexes. The solid state CD spectrum of **1**-CA taken in the KBr pellet is shown in Figure 2. It exhibits negative Cotton effect in the region of the $n\text{--}\pi^*$ transition



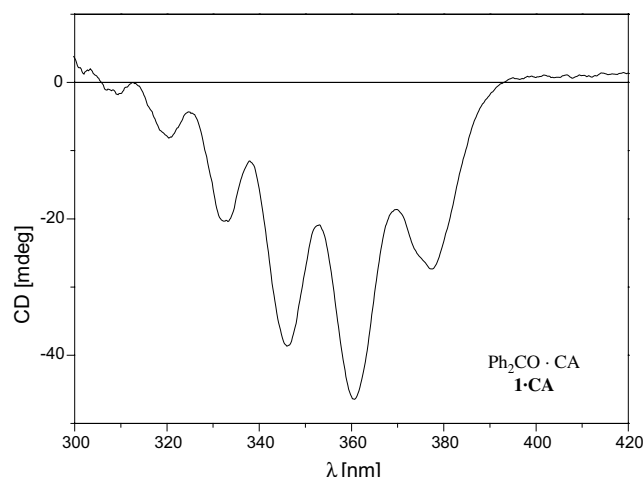


Figure 2. Solid state CD spectrum of the inclusion complex **1-CA** taken in KBr disk.

very similar to that exhibited by the enantiomorphous crystals of **1**. The crystal structures of **1-CA** and **4-CA** resemble those found in many of the **CA** tubulate inclusion compounds.²¹ The hydrogen-bonded host molecules are arranged in corrugated amphiphilic bilayers with the helical channels formed between them. The reported earlier room temperature X-ray structure of **1-CA** (Fig. 3) revealed two types of channels in the host matrix with the disordered guest molecules trapped inside and assuming four different conformations.²² To obtain a more reliable geometry of the included guest molecules, the X-ray analysis of **1-CA** was repeated at 100 K. This revealed three different conformations of the guest units. The molecules trapped in channel I show *M,M* helicity whereas channel II is occupied by the *P,M* and *M,M* conformers (30% and 70%, respectively). However, the carbonyl group in the minor *P,M* con-

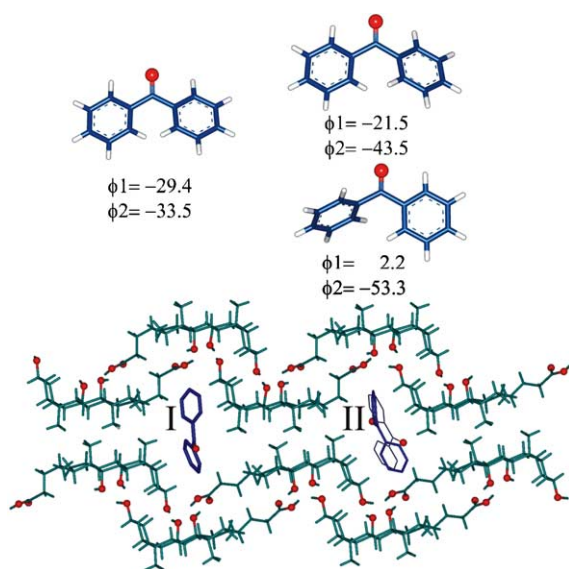


Figure 3. The crystal structure of the inclusion complex **1-CA** viewed along the *y* axis and the geometries of three conformers of **1** included in the host lattice; ϕ_1 and ϕ_2 denote the two torsion angles $C=C-C=O$ characterizing the helicity of **1**.

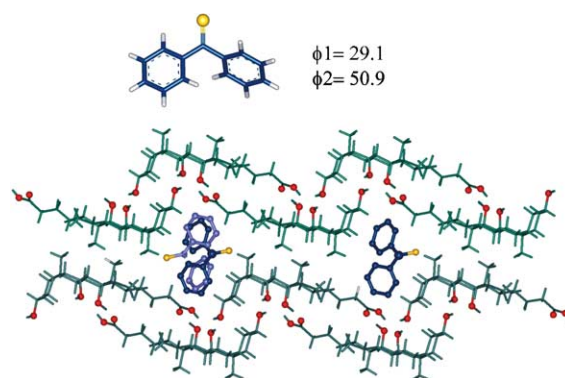


Figure 4. The crystal structure of the inclusion complex **4-CA** viewed along the *y* axis and the geometry of the guest molecule included in the host lattice; ϕ_1 and ϕ_2 denote the two torsion angles $C=C-C=S$ characterizing the helicity of **4**. The channels are disordered (see Experimental).

former is approximately co-planar with one of the phenyl rings [the corresponding $C=C-C=O$ torsion angle is of $2(1)^\circ$]; the second one is strongly twisted in the *M* sense [the $C=C-C=O$ torsion angle is $-53(1)^\circ$]. Thus all three conformers should contribute to the negative Cotton effect observed in the CD spectrum of **1-CA**.

In contrast, the X-ray structure of **4-CA** (Fig. 4) revealed that despite the channel disorder the host lattice of the complex contained only one type of the guest molecules. They assume the *P,P* conformation [the $C=C-C=S$ torsion angles are of $29.1(7)^\circ$ and $50.9(7)^\circ$], which is similar to that found in the crystals of pure **4** (the corresponding torsion angles are of 31.9° and 42.7°).²³

The weak long-wavelength absorption of aliphatic and aromatic thioketones has been widely described as corresponding to the electronic $n-\pi^*$ transition.^{16,24} It is similar in nature to the analogous ketone excitation but occurs at substantially lower energies. Thus a very strong positive CD band near 600 nm in the solid state CD spectrum of **4-CA** (Fig. 5) should be assigned to the

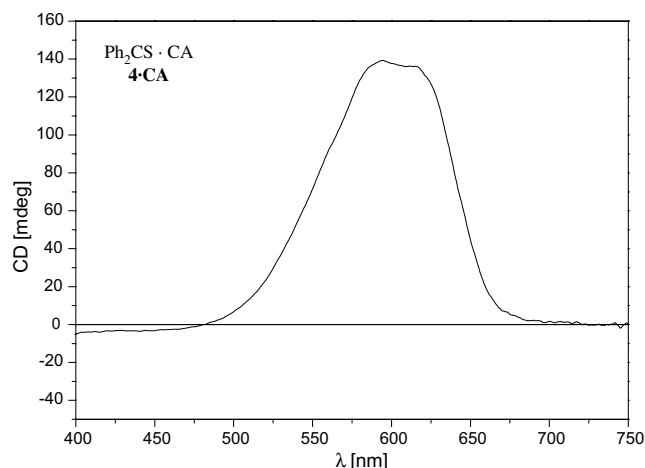


Figure 5. Solid state CD spectrum of the inclusion complex **4-CA** taken in KBr disk.

thioketone $n-\pi^*$ excitation with the P,P helicity of the guest molecule accounting for the observed positive sign of the Cotton effect of the complex.

In conclusion, the optical activity of the chiral crystals of **1** and **2** was detected with solid state CD spectra. The constituent molecules are not planar and their helicity can be determined from the sign of the Cotton effect corresponding to the ketone $n-\pi^*$ transition. The chirality of **1** and **4** was also generated by enclathration of these compounds in the crystal matrices of **CA**. The helicity of the guest molecules can be assigned either by X-ray crystallography or deduced from the solid state CD measurements of the complexes.

3. Experimental

Thioketone **4** was obtained according to the literature method.¹⁷ The solid state CD spectra were taken 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 a radius of 15 mm. The disk was rotated around the optical axis and the CD recordings were made for several positions in order to check the reproducibility of the spectra.

3.1. X-ray structure analysis

Diffraction data were collected at 100 K using a Kuma CCD diffractometer with graphite monochromated Mo K α radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods with the program SHELXS-97.²⁵ Full matrix least-squares refinement was carried out with SHELXL-97.²⁶

Crystal data for $2C_{24}H_{40}O_5 \cdot C_{13}H_{10}O$ (**1-CA**): monoclinic, $P2_1$, $a = 25.256(1)$, $b = 7.8602(4)$, $c = 28.131(1)$ Å, $\beta = 101.551(4)^\circ$, $V = 5471.4(4)$ Å³, $Z = 4$, $D_{\text{calcd}} = 1.200$ g cm⁻³, $T = 100(2)$ K, $R_1 = 0.0583$, $wR2 = 0.1020$ for 4143 reflections with $I > 2\sigma(I)$. There are two symmetry independent channels in the host matrix. Whereas the guest molecules trapped in channel I are ordered, those in channel II are disordered. The sum of occupancy factors of the guest molecules in channel II was fixed to 1.0 but the individual occupancies were allowed to refine; the ratio of the two overlapping conformers of **1** in this channel is 70:30. For these molecules restraints were imposed on all 1–2 and 1–3 distances as well as the planarity of the phenyl rings and the carbonyl group. The non-hydrogen atoms of the disordered guests were refined with isotropic displacement parameters.

Crystal data for $2C_{24}H_{40}O_5 \cdot C_{13}H_{10}S$ (**4-CA**): monoclinic, $P2_1$, $a = 13.156(1)$, $b = 8.042(2)$, $c = 14.104(3)$ Å, $\beta = 105.810(9)^\circ$, $V = 1384.5(2)$ Å³, $Z = 1$, $D_{\text{calcd}} = 1.218$ g cm⁻³, $T = 100(2)$ K, $R_1 = 0.0589$, $wR2 = 0.1489$ for 2691 reflections with $I > 2\sigma(I)$. The nearest guest

molecules in the channel are not related by the crystallographic 2_1 axis directed along the channel but are transformed by the unit translation along the y direction. As a result, the superposition of two guests images (each with occupancy 0.5) related by the 2_1 axis is observed on electron density maps. The guest molecule was refined with an occupancy factor 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 the thiocarbonyl group. Due to the molecule of **4** having two conformational internal degrees of freedom the torsions around the two central formally single bonds were not restricted. Atoms of the guest molecules were refined with isotropic displacement parameters.

Crystallographic data (excluding structure factors) for the structures herein have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 218521–218522. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

We are indebted to Dr. J. Frelek (IChO PAN, Warsaw) for CD measurements for the use of her JASCO J-715 instrument and Mrs. A. Sokół for her assistance in the preparation of KBr disks. The financial support from the Committee of Scientific Research (project no 3 T09A 097 22) is also gratefully acknowledged.

References and Notes

- (a) Green, B. S.; Lahav, M.; Rabinovich, D. *Acc. Chem. Res.* **1979**, *12*, 191; (b) Sakamoto, M. *Chem. Eur. J.* **1997**, *3*, 684; (c) Ito, Y. *Synthesis* **1998**, *1*; (d) Tanakam, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025.
- (a) Jacques, J.; Collet, A.; Wilen, S. M. *Enantiomers, Racemates, and Resolutions*; Wiley: New York, 1981; (b) Eliel, E.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; Chapter 7.2.
- (a) Iitaka, Y. *Acta Cryst.* **1958**, *11*, 225; (b) Shimon, L. J. W.; Lahav, M.; Leiserowitz, L. *New J. Chem.* **1986**, *10*, 723.
- (a) Brown, C. J.; Sadanaga, R. *Acta Cryst.* **1965**, *18*, 158; (b) More, M.; Odou, G.; Lefebvre, J. *Acta Cryst.* **1987**, *B43*, 398.
- Połośński, T.; Szyrzyng, M.; Gdaniec, M.; Nowak, E.; Herman, A. *Tetrahedron: Asymmetry* **2001**, *12*, 797.
- (a) Wilson, K. R.; Pincock, R. E. *J. Am. Chem. Soc.* **1975**, *97*, 1474; (b) Kondepundi, D. K.; Laudadio, J.; Asakura, K. *J. Am. Chem. Soc.* **1999**, *121*, 1448.
- Cunningham, I. D.; Coles, S. J.; Hursthouse, M. B. *Chem. Commun.* **2000**, 61.
- Feringa, B. L.; van Delden, R. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3419.
- (a) Addadi, L.; Lahav, M. In *Origins of Optical Activity in Nature*; Walker, D. C., Ed.; Elsevier: Amsterdam, 1979;

- Chapter 14; (b) Buschmann, H.; Thede, R.; Heller, D. *Angew. Chem., Int. Ed.* **2000**, 39, 4033.
10. (a) Gdaniec, M.; Połoński, T. *J. Am. Chem. Soc.* **1998**, 120, 7353; (b) Gdaniec, M.; Milewska, M. J.; Połoński, T. *Angew. Chem., Int. Ed.* **1999**, 38, 392; (c) Szyszyng, M.; Nowak, E.; Gdaniec, M.; Milewska, M. J.; Herman, A.; Połoński, T. *J. Org. Chem.* **2001**, 66, 7380.
11. (a) Olszewska, T.; Milewska, M. J.; Gdaniec, M.; Połoński, T. *Chem. Commun.* **1999**, 1385; (b) Olszewska, T.; Milewska, M. J.; Gdaniec, M.; Małuszyńska, H.; Połoński, T. *J. Org. Chem.* **2001**, 66, 501.
12. Fleisher, E. B.; Sung, N.; Hawkinson, S. *J. Phys. Chem.* **1968**, 72, 4311.
13. (a) Ito, Y.; Matsuura, T.; Tabata, K.; Ii-bun, M.; Fukuyama, K.; Sasaki, M.; Okada, S. *Tetrahedron* **1987**, 43, 1307; (b) Kojic-Prodic, B.; Bresciani-Pahor, N.; Horvatic, D. *Acta Crystallogr.* **1990**, C46, 430.
14. Kutzke, H.; Al-Mansour, M.; Klapper, H. *J. Mol. Struct.* **1996**, 374, 129.
15. (a) Bosnich, B. *J. Am. Chem. Soc.* **1967**, 89, 6143; (b) Matsuura, N.; Takenaka, S.; Tokura, N. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1419; (c) Schipper, P. E.; O'Brien, J. M.; Ridley, D. D. *J. Phys. Chem.* **1985**, 89, 5805.
16. Maciejewski, A.; Steer, R. P. *Chem. Rev.* **1993**, 93, 67.
17. Scheeren, J. W.; Ooms, P. H. J.; Nivard, R. J. F. *Synthesis* **1973**, 149.
18. Nakano, K.; Sada, K.; Miyata, M. *Chem. Lett.* **1994**, 137.
19. (a) Abraham, R. J.; Haworth, I. S. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1429; (b) Rappoport, Z.; Biali, S. E.; Kaftory, M. *J. Am. Chem. Soc.* **1990**, 112, 7742.
20. 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; Chapter 3.2 and references cited therein.
21. Miyata, M.; Sada, K. In *Comprehensive Supramolecular Chemistry*; MacNicol, D. D., Toda, F., Bishop, R., Eds.; Pergamon: Oxford, 1996; Vol. 6, Chapter 6.
22. Nowak, E.; Gdaniec, M.; Połoński, T. *J. Incl. Phenom.* **2000**, 37, 155.
23. Rindorf, G.; Carlsen, L. *Acta Crystallogr.* **1979**, B35, 1179.
24. (a) Emeis, C. A.; Oosterhoff, L. J. *J. Chem. Phys.* **1971**, 54, 4809; (b) Engelbrecht, J. P.; Anderson, G. D.; Linder, R. E.; Barth, G.; Bunnenberg, E.; Djerassi, C.; Seamans, L.; Moscovitz, A. *Spectrochim. Acta* **1975**, A31, 507; (c) Szymanski, M.; Maciejewski, A.; Steer, R. P. *J. Phys. Chem.* **1988**, 92, 2485; (d) Lightner, D. A.; Bouman, T. D.; Wijekoon, W. M. D.; Hansen, A. E. *J. Am. Chem. Soc.* **1990**, 112, 7742.
25. Sheldrick, G. M. *Acta Crystallogr.* **1990**, A46, 467.
26. Sheldrick, G. M. SHELXL-97, Program for Crystal Structures Refinement from Diffraction Data, University of Göttingen, Germany, 1997.