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Structure Reactivity Correlation in Inclusion Complexes: Deoxycholic Acid–Thiocamphenilone

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Abstract. The 2 : 1 inclusion complex formed between deoxycholic acid ($C_{24}H_{40}O_4$, M_r = 392.58) and thiocamphenilone ($C_9H_{14}S$, M_r = 154.28) crystallizes in the space group $P2_12_12$ with a = 13.738(2), b = 27.203(4), c = 7.189(1) Å and Z = 4. The structure was refined to R = 0.158 and R_w = 0.195 for 1649 observed reflections with $|F_o| \geqslant 3.0\sigma|F_o|$. The crystal structure is characterized by an assembly of anti-parallel pleated bilayers, formed by molecules of deoxycholic acid held together through hydrogen bonds. The guest thiocamphenilone occupies the crystallographic two-fold axis and is disordered. The orientation of the guest molecule obtained from crystallographic data is consistent with the results obtained from the potential energy calculations.

Key words: Deoxycholic acid, thiocamphenilone, crystal structure, potential energy calculations.

Supplementary Data relating to this article are deposited with the British Library as Supplementary Publication No. SUP 82042 (23 pages).

1. Introduction

3α,12α-Dihydroxy-5β-cholan-24-oic acid (deoxycholic acid, DCA (Figure 1a)) forms many stoichiometric crystalline inclusion complexes, termed choleic acids, of the channel type with a wide variety of organic molecules [1–4]. The majority of the choleic acids crystallize in the orthorhombic system and a few in tetragonal and hexagonal space groups [5–7]. In the orthorhombic system, the space group observed so far is $P2_12_12_1$, except for the complexes (+)-camphor-choleic acid [8], di-*tert*-butyl thioketone-choleic acid [9] and the structure reported here, all belonging to $P2_12_12$.

In the orthorhombic choleic acids, one observes a two-dimensional bilayer motif with axial dimensions b = 13.6 and c = 7.2 Å. The molecules form chains by translation along the 13.6 Å axis interlinked front-to-end by O(hydroxyl)-H···O (carbonyl) hydrogen bonds. These molecules are further joined by hydrogen bonds about the 2_1-axes which are parallel to the

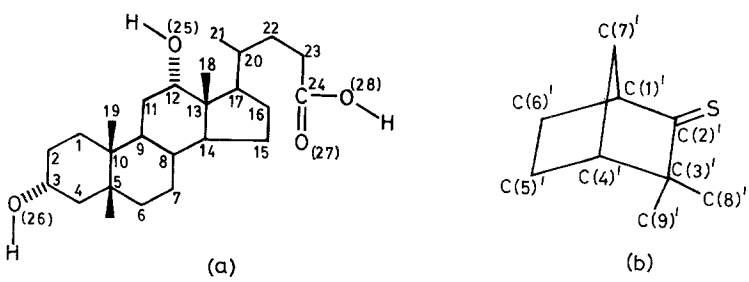

Fig. 1. (a) Atomic numbering of DCA. (b) Atomic numbering of thiocamphenilone.

13.6 Å axis and spaced along the c-axis by 7.2 Å, thus generating the bilayer. These bilayers contain grooves parallel to the c-axis which allow DCA to form channel inclusion complexes.

Interesting studies on the solid state photochemistry of molecular complexes of DCA with ketones [5, 7, 10, 11] and peroxides [12] have been reported by Lahav, Leiserowitz and co-workers. The photoexcited carbonyl chromophore was shown to abstract hydrogen from the steroid channel wall.

In this context we undertook a study of thioketone complexes of DCA to establish the behaviour of thioketones in the channels of DCA. Also, the photochemical behaviour of thioketones has been fairly well explored both in solution [13, 14] and in the solid state [15]. Earlier we have reported the X-ray structure-photochemical reactivity correlation of the DCA complex with di-*tert*-butyl thioketone [9]. This paper presents an extension of this investigation on the DCA-thiocamphenilone complex (Figure 1b).

2. Experimental

Single crystals of the inclusion complex between DCA and thiocamphenilone were grown by slow evaporation of methanol from an ice-cold solution containing a 2 : 1 molar ratio of DCA and the thioketone. The crystals possessed the light red colour of the thioketone and did not show a sharp melting point (m.p. 135–155 °C). Formation of the inclusion complex was confirmed by its IR and ^{13}C spectral characteristics in the solid state.

2.1. PHOTOLYSIS

Powdered single crystals of the complex were irradiated using a low pressure mercury arc lamp (254 nm) in a petridish. The progress of the reaction was monitored by the variation in m.p., ^{1}H-NMR and IR spectra. Although the thione colour disappeared, no 1 : 1 products resulting from the reaction of the guest thione with the DCA were obtained. Polymeric products obtained could not be characterized owing to the difficulty encountered in their separation.

2.2. X-RAY STRUCTURAL ANALYSIS

Preliminary oscillation and Weissenberg photographs indicated that the crystals belong to the orthorhombic space group $P2_12_12$. All the reported orthorhombic choleic acids have cell constants $a \sim 26°$ Å and $b \sim 13$ Å. It may be mentioned that there is an interchange of a and b axes in the complex reported here from those of the orthorhombic DCA complexes reported earlier [4].

The unit cell parameters were obtained from a least-squares analysis of diffractometer-angle measurements for 25 centered reflections in the θ range $30° < \theta < 45°$.

A crystal with dimensions 0.53 × 0.25 × 0.04 mm was chosen to collect intensities up to $\theta \leqslant 65°$ on an EnrafNonius CAD-4 diffractometer with graphite monochromatized CuKα radiation (λ = 1.5418 Å) using the $\omega/2\theta$ mode and a scan speed of 1°/min. Three standard reflections 211, 571, and 340 measured every 2000 sec of data collection were quite stable and showed only statistical fluctuations until the end of data collection. A total of 2830 reflections were measured in the hkl range h : 0 to 16, k : 0 to 32 and l : 0 to 8. Of these, 1649 were considered significant with $|F_o| \geqslant 3.0\sigma|F_o|$, where $\sigma(|F_o|)$. $|F_o|$ was evaluated using counting statistics [16]. The data were corrected for Lorentz and polarization effects but not for absorption.

3. Structure Determination and Refinement

The structure was solved using the direct methods program MULTAN-80 [17]. The E-map computed using the default number of largest E-values (282) did not yield any part of the structure. Therefore, the number of largest E-values were increased to 400. The E-map corresponding to the phase set with the best figures of merit revealed 26 out of the 28 nonhydrogen atoms of DCA. The remaining two atoms were fixed from a Karle recycling [18] operation with these 26 atoms.

It must be mentioned that there are only two molecules of the guest in the unit cell. Since the guest molecule is devoid of a molecular two-fold symmetry axis, it is expected to be disordered about the crystallographic two-fold axis.

Isotropic refinement of the 28 nonhydrogen atoms of DCA converged to $R = 0.24$. The difference Fourier map showed seven peaks having electron density in the range 1-2 e $Å^{-3}$ around the crystallographic two fold axis. The biggest peak which was off the two-fold axis, was chosen as the sulphur atom of the guest molecule. This was connected to another peak (C(2)′) (for numbering scheme see Figure 1b) which lies on the two-fold axis and at a distance of about 1.65 Å, a value close to the C=S bond length. The model for the guest molecule proposed from these seven peaks had the two-fold axis passing through atom C(2)′ and the mid point of C(3)′ and C(4)′. Using these coordinates, the standard geometry of the guest molecule was generated, and this model was introduced in the refinement as a rigid group with an occupancy value of 0.5 and a temperature factor (B) of 16 $Å^2$ for all the atoms. The rigid part in the structure, namely DCA had a temperature factor of ~ 9 $Å^2$ for the side chain atoms. Thus this value of 16 $Å^2$ was thought to be reasonable for the disordered guest molecule.

Isotropic refinement of DCA and the rigid geometry of the guest molecule converged to $R = 0.19$. The R-value reduced to 0.17 when the DCA atoms were treated anisotropically. All the hydrogen atoms of DCA were fixed at stereochemically reasonable positions, and included in the refinement process. These were assigned temperature factors of the corre-

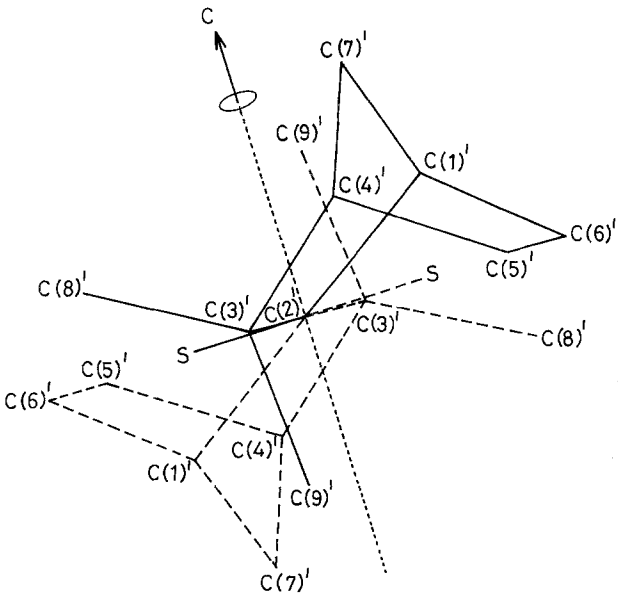

Fig. 2. Projection on the XYO plane showing the two positions of the disordered guest thioketone (related by a two-fold axis).

sponding nonhydrogen atoms to which they are attached and were not allowed to refine. Refinement using the full-matrix least-squares program SHELX-76 [19] converged to $R = 0.158$ and $R_w = 0.195$, the weighting function being $w = 3.1274/(\sigma^2|F| + 0.002|F|^2)$. R and R_w, are $\Sigma\,||F_o| - |F_o||/\Sigma\,|F_o|$ and $(\Sigma_w(|F_o| - |F_c|)^2/\Sigma\, w|F_o|^2)^{1/2}$, respectively. The function minimized in the refinement was $\Sigma\, w(|F_o| - |F_c|)^2$. Maximum Δ/σ for nonhydrogens was 0.011. Final difference Fourier map showed the maximum peak height of 1 e Å^{-3}. However, this peak was not chemically sensible as far as the disordered guest molecule is concerned. Figure 2 illustrates the nature of the disorder of the guest molecule about the crystallographic two-fold axis. The final atomic coordinates of DCA are reported in Table I and those of the guest molecule in Table II.

Table I. Fractional atomic coordinates ($\times 10^4$) and equivalent isotropic temperature factors ($\times 10^3$) for nonhydrogen atoms of the host molecule of complex: -Deoxycholic acid-Thiocamphenilone. E.s.d.'s are given in parentheses. The temperature factor is of the form: $U_{eq} = \frac{1}{3}\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \vec{a}_i \cdot \vec{a}_j$.

Atom	x	y	z	U_{eq}(Å^2)	Atom	x	y	z	U_{eq}(Å^2)
C(1)	6678(9)	1337(5)	3723(21)	39(5)	C(15)	3245(13)	949(9)	9743(28)	86(8)
C(2)	7035(11)	1846(6)	4380(25)	52(6)	C(16)	2222(12)	1215(7)	9531(25)	66(7)
C(3)	7749(11)	1765(5)	6021(27)	53(6)	C(17)	2239(10)	1513(6)	7755(23)	50(6)
C(4)	7259(12)	1491(6)	7556(23)	49(5)	C(18)	2708(10)	798(5)	5731(26)	50(6)
C(5)	6892(11)	993(6)	6923(25)	54(6)	C(19)	6011(13)	507(7)	4393(28)	69(7)
C(6)	6471(12)	685(7)	8584(27)	61(6)	C(20)	1194(11)	1522(6)	6885(26)	53(6)
C(7)	5444(12)	902(8)	9222(24)	73(7)	C(21)	1095(12)	1816(7)	5089(24)	59(6)
C(8)	4761(10)	945(6)	7525(23)	46(5)	C(22)	418(9)	1730(6)	8353(26)	52(6)
C(9)	5244(11)	1263(6)	5923(22)	52(6)	C(23)	573(13)	2223(6)	8958(31)	71(7)
C(10)	6215(10)	1012(5)	5271(24)	43(5)	C(24)	−219(12)	2403(6)	10286(27)	59(7)
C(11)	4508(10)	1353(5)	4392(20)	42(5)	O(25)	3786(7)	2090(3)	5826(0)	45(3)
C(12)	3548(10)	1598(6)	5093(22)	48(5)	O(26)	8024(9)	2252(4)	6603(20)	80(5)
C(13)	3053(10)	1281(6)	6631(24)	47(5)	O(27)	−1070(9)	2374(7)	9953(21)	118(8)
C(14)	3846(12)	1185(6)	8124(21)	50(5)	O(28)	71(8)	2603(4)	11793(19)	71(5)

Table II. Positional parameters of the guest molecule.

Atom[a]	x/a	y/b	z/c
S	0.5715	0.5112	1.1518
C(1)′	0.4284	0.4548	0.9745
C(2)′	0.5000	0.5000	0.9724
C(3)′	0.5359	0.5050	0.7691
C(4)′	0.4831	0.4621	0.6574
C(5)′	0.3730	0.4795	0.6563
C(6)′	0.3371	0.4744	0.8611
C(7)′	0.4788	0.4200	0.8175
C(8)′	0.6453	0.4927	0.7649
C(9)′	0.4954	0.5534	0.6895

[a] All the atoms were assigned occupancy 0.5 and isotropic temperature factor 16 Å^2.

4. Potential Energy Calculations

A major problem encountered in solving the crystal structure of an inclusion complex is the location of the guest molecule, for the following reasons:

(1) More often, the size of the cavity is greater than that needed to accommodate the guest molecule which, therefore, can occupy more than one definite position, especially in the absence of specific host-guest interactions.
(2) The thermal motion of the guest molecule tends to be generally high.
(3) The contribution of the guest molecules to the intensity of the Bragg reflections is usually low in comparison with that from the host.

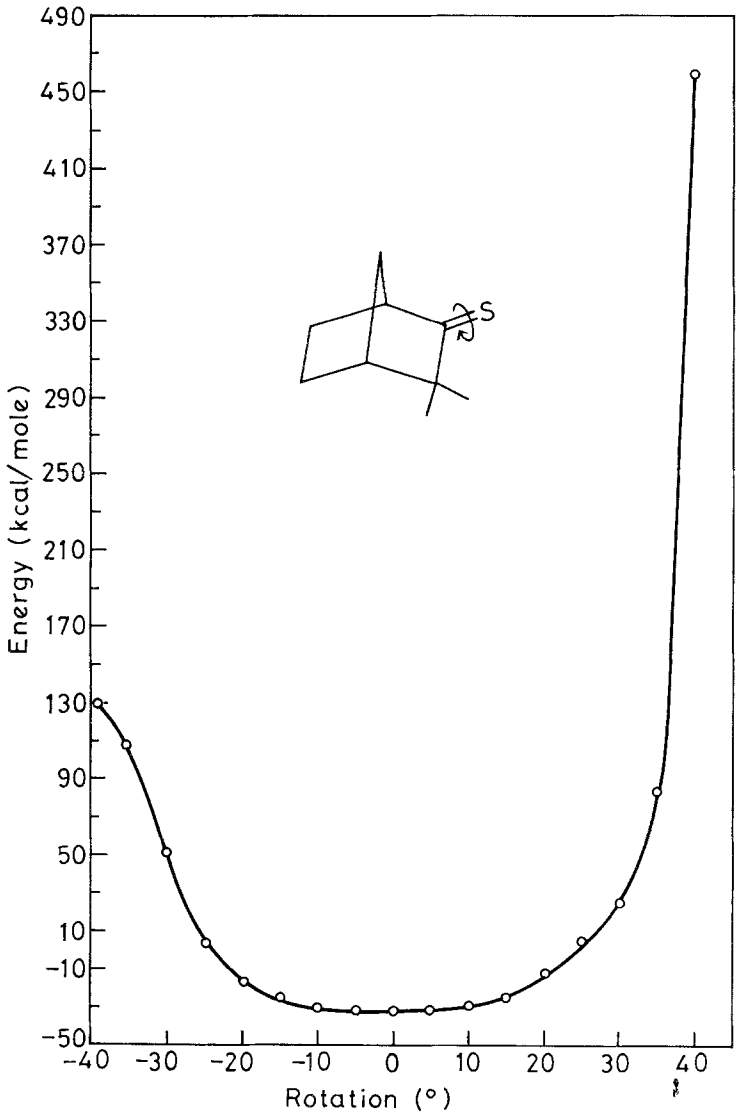

Fig. 3. Van der Waals energy of the complex as a function of rotation of the guest molecule about the C=S bond.

Under these circumstances, it would be essential to resort to potential energy calculations performed by fixing the known positions of the host molecules but allowing the guest molecule to rove in the empty space as a function of their rotational and translational degrees of freedom. This method has been applied to several DCA complexes [20–22].

In view of the complex nature of the disorder for the inclusion compound reported in this paper, it was considered essential that, in addition to the crystallographic methods used for locating the disordered atoms, an independent approach such as the potential energy considerations must be adopted to ensure that the guest molecule has been located correctly. The computer program WMIN developed by Busing [23] was used for this purpose. The energy was calculated as a pairwise potential as follows:

$$E = -\sum_{i}^{\text{one cell}} \sum_{i \neq j}^{\text{all cells}} A_i A_j / r_{ij}^6 + \sum_{i}^{\text{one cell}} \sum_{i \neq j}^{\text{all cells}} D_i D_j / r_{ij}^{12}$$

where the first and second terms represent the van der Waals attractive and repulsive contributions, respectively. The constants were derived from those proposed by Mirsky [24]. Keeping the DCA molecules fixed in their positions, the thioketone molecule was rotated about the C=S bond and the nonbonded van der Waals interaction energy was computed at intervals of 5° up to a maximum of ± 90°. The results are depicted in Figure 3. The energy remains at a shallow minimum in the angular range − 20 to + 20°. It is encouraging to note that the results of this van der Waals energy calculation essentially support the model proposed from the crystal structure. It is possible that a few orientations other than this may exist but their occurrence is expected to have much less weighting. Indeed, one of the reasons for the high R-value of this complex could be due to the fact that a few other possible orientations are not included in the structure factor calculations.

5. Discussion

5.1. STRUCTURE-REACTIVITY CORRELATIONS

Although no products resulting from the attack of the guest on the host DCA were isolated, and no polymeric products were identified, the feasibility of host-guest reactions of this complex in the crystalline state was examined in the light of the above X-ray structure.

The intermolecular contacts involving the hydrogens of DCA and sulphur of the guest are given in Table III. However, these distances are more than the van der Waals sum between S and H. But there are exceptions known in these types of intermolecular reactions. Especially in the DCA-ketone complexes studied [10] where there is abstraction in the solid state, the distance between the ketone oxygen and the steroid hydrogen range between 2.9–3.9 Å. On the basis of this, one could expect the thiocarbonyl sulphur to abstract any one of the hydrogens – 2H(15), 2H(16), 3H(18), H(20), H(5), 1H(6) (Table III). But the distance between the steroid carbon and the sp^2 carbon of the guest is too large (Table III) to allow the resulting diradicals from the hydrogen abstraction to interact and form a C—C bond. Hydrogen abstraction by the thiocarbonyl carbon from the channel walls is also improbable due to the large distance between the reactive centres (Table III). Thus, based on X-ray evidence, it appears that a 1 : 1 product between the guest thioketone and the host DCA resulting from hydrogen abstraction is not possible. However, the unidentified polymeric product may result from the geometrically allowed initial hydrogen abstraction by the thiocarbonyl sulphur from the DCA wall. The exact mechanism of this process is not understood at this stage.

Table III. Intermolecular contacts of importance (<5 Å) for reactivity between host and guest atoms.

Atom pair	Distance	Atom pair	Distance
(a) *S(thione)···H(steroid) contacts (Å):*			
S···2H(15)	3.90	S···H(5)	3.42
S···2H(16)	3.23	S···1H(6)	3.66
S···1H(18)	4.21	S···2H(6)	4.07
S···2H(18)	4.83	S···2H(16)	4.03
S···3H(18)	3.26	S···3H(18)	4.72
S···H(20)	3.83	S···1H(19)	4.84
S···1H(22)	4.42	S···H(20)	4.01
S···H(3)	4.65	S···1H(22)	4.11
S···2H(4)	4.18	S···2H(22)	4.35
(b) *C_{sp^2}(thione)···H(steroid) contacts (Å):*			
C(2)′···1H(16)	4.92	C(2)′···2H(16)	3.46
C(2)′···1H(18)	4.95	C(2)′···3H(18)	4.49
C(2)′···H(5)	4.93	C(2)′···H(20)	4.46
C(2)′···1H(6)	4.59	C(2)′···1H(22)	4.11
C(2)′···2H(15)	4.62	C(2)′···2H(22)	4.95
(c) *C_{sp^2}(thione)···C(steroid) contacts (Å):*			
C(2)′···C(16)	4.532	C(2)′···C(22)	4.938

5.2. MOLECULAR GEOMETRY AND CRYSTAL STRUCTURE

The bond lengths and angles involving the nonhydrogen atoms are given in Table IV deposited with the British Library as part of Supplementary Publication No. SUP 82042.

The conformation of the side chain of the DCA molecule is gauche and the D-ring approaches half-chair symmetry as observed in other choleic acids [6, 25–27].

The packing arrangement of the complex is illustrated in Figure 4. The crystal packing is

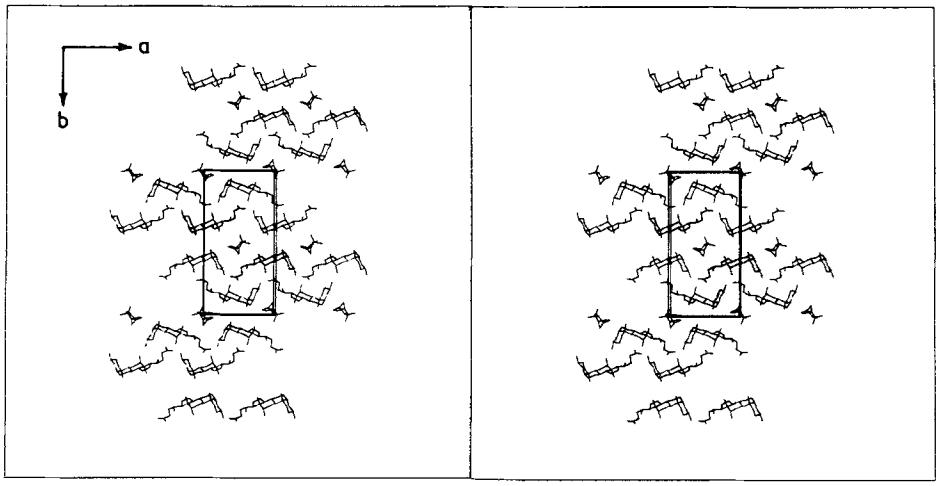

Fig. 4. Packing of the molecules down the *c*-axis.

characterized by an assembly of anti-parallel pleated bilayers formed by molecules of DCA held together by a helical system of intermolecular hydrogen bonds along the c-axis [$0(26)\cdots0(27)^a = 2.731(20)$; $0(28)\cdots0(25)^b = 2.597(14)$; $0(25)\cdots0(26)^c = 2.711(14)$ Å, $a = 1 + x,y,z$; $b = x - \frac{1}{2},\frac{1}{2} - y, 2 - z$; $c = x - \frac{1}{2},\frac{1}{2} - y, 1 - z$]. The overall packing in these crystals is the same as in the DCA-camphor complex [8] and the DCA-di-*tert*-butyl thioketone complex [9], both crystallizing in the space group $P2_12_12$. In these complexes, the DCA channel walls are directly opposite, the molecules being related by the two-fold rotation axis. Between the hydrophobic surfaces of adjacent DCA bilayers, there are channels with cross-sectional area of 4×7 Å^2 centered on the two-fold axis, and the void in the channel is sufficient to accommodate the guest thioketones. The interaction between the host and guest molecule is mainly of the van der Waals type.

6. Conclusion

While the inclusion complexes of DCA with ketones have been reported to undergo intermolecular reactions [5, 7, 10, 11], the analogous chromophore, namely thioketone, did not yield any 1 : 1 products. Both di-*tert*-butyl thioketone reported earlier [9] and thiocamphenilone presented in this paper, although giving good crystals of the complexes, did not undergo the expected reactions. The intermolecular contacts between the host and guest molecules support the observed lack of photoreactivity. However, the conclusion based on the crystallographic result is not definitive, the guest molecule being highly disordered.

Acknowledgement

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Supplementary Material (SUP 82042)

Table IV. Bond lengths and angles involving nonhydrogen atoms of DCA.
Table V. Torsion angles (°) for the side chain and *D* ring of DCA with Δ and ϕ_m.
Table VI. Anisotropic thermal parameters of nonhydrogen atoms of DCA.
Table VII. Positional parameters of hydrogen atoms of DCA.
Table VIII. Bond lengths and angles involving hydrogen atoms of DCA.
Table IX. Observed and calculated structure factors.