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Crystal Structure and van der Waals Energy Study of the 2:1 Inclusion Compound between Deoxycholic Acid and Norbornadiene

By A. D'Andrea

Istituto di Chimica Fisica, Università di Roma, 00185 *Roma, Italy*

W. Fedeli

Laboratorio di Strutturistica Chimica 'Giordano Giacomello' del CNR, Area della Ricerca, CP 10,
00016 *Monterotondo Stazione, Roma, Italy*

E. Giglio

Istituto di Chimica Fisica, Università di Roma, 00185 *Roma, Italy*

F. Mazza

Laboratorio di Strutturistica Chimica 'Giordano Giacomello' del CNR, Area della Ricerca, CP 10,
00016 *Monterotondo Stazione, Roma, Italy*

and N. V. Pavel

Laboratorio Ricerche di Base, ASSORENI, Monterotondo, Roma, Italy

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Abstract

The crystals are orthorhombic, space group $P2_12_12_1$, with $a = 27{\cdot}125$ (8), $b = 13{\cdot}456$ (4), $c = 14{\cdot}212$ (5) Å, $Z = 4$. The structure has been refined to $R = 0{\cdot}11$ and $R_w = 0{\cdot}14$ for 2451 observed reflections with $I > 3\sigma(I)$. The crystal structure is characterized by an assembly of bilayers which are slightly different from those of other orthorhombic phases studied so far. The section of the cavities in which the norbornadiene is accommodated is almost square, so that molecules or substituents of approximately spherical shape can be occluded. Van der Waals energy calculations allowed the location of the guest molecules which mainly interact with methyl groups.

Introduction

3α,12α-Dihydroxy-5β-cholan-24-oic acid (deoxycholic acid, DCA) forms an orthorhombic canal complex with bicyclo[2.2.1]hepta-2,5-diene (norbornadiene, NBD). This choleic acid (DCANBD) has been studied among others (Candeloro De Sanctis & Giglio, 1979; Coiro, D'Andrea & Giglio, 1979, 1980, and references therein) to determine its stoichiometry and the nature of the interactions between host and guest molecules. Previous investigations gave information about the crystal structures of orthorhombic choleic acids containing guest molecules, both aromatic, such as acetophenone, *p*-diiodobenzene and phenanthrene, and aliphatic, such as acetic and palmitic acids. Generally, the flat aromatic molecules are strongly anchored to methyl groups of DCA, giving rise to polarization bonding involving the π charge clouds, whereas the aliphatic molecules are engaged through weaker van der Waals interactions. Thus, the choleic acids with aromatic guest molecules exhibit higher melting points and cohesion energies and hardly release the acholic constituents from the DCA canals. Since NBD, together with molecules having double and triple bonds, is intermediate between these two classes of compounds it was considered interesting to establish the nature of its interactions with the host molecules.

Another purpose of this work is to see whether molecules bulkier than those planar and thread-like compounds so far investigated can be occluded in the DCA canals. Molecules bulkier than NBD are under study in order to test to what extent the section of the channels can be enlarged, in order to determine the limits of the inclusion ability of DCA.

Moreover, the *c* axis of ~14·2 Å (twice 7·1 Å) indicates that in the asymmetric unit there are two crystallographically independent DCA molecules and, hence, that the bilayer structure differs from that found in other orthorhombic phases.

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Experimental

DCANBD was crystallized at room temperature by evaporation from a solution of DCA in NBD and methanol. The composition of DCANBD was checked by ^{1}H NMR, gas chromatography and density measurements. The observed density (1·12 Mg m^{-3}) was obtained by flotation in cyclohexane and carbon tetrachloride and agrees with eight DCA and four NBD molecules in the unit cell. A DCA:NBD ratio of 2·1 was measured by NMR with CD$_3$OD as solvent. A similar ratio of 2·04 was found for a DCANBD solution in acetone by gas chromatography. The amount of NBD was determined with a Hewlett–Packard model 7620 A apparatus equipped with a Hewlett–Packard 3380 A integrator and a 1·8 m × 3·2 mm i.d. column packed with Chromosorb WHP (80–100 mesh) coated with 6% Dexsil 300 GC. NBD was released at 352 K. Crystal data are given in the *Abstract* and Table 1.

A colourless prism with a maximum dimension of 0·8 mm was chosen to determine the cell constants from a least-squares refinement performed on 15 reflections and to collect intensities up to $2\theta = 54°$ on a Syntex $P2_1$ automated diffractometer with graphite-monochromatized Mo $K\alpha$ radiation. The data were recorded by the ω-scan mode at a scan rate within the range 0·5 to 29·3° min^{-1}, depending on the peak intensity, with a scan width of 1·0°. Three reflections, selected for orientation control and measured every 100 reflections, remained essentially constant. Backgrounds were estimated by stationary counting for half the scan time. Lorentz and polarization corrections were applied taking into account the monochromator crystal (Azaroff, 1955) but no absorption corrections were made.

Structure determination, potential-energy calculations and refinement

The structure was solved by assuming the same atomic coordinates for DCA as those found in the phenanthrene–choleic acid complex (Candeloro De Sanctis, Giglio, Pavel & Quagliata, 1972), neglecting NBD. Since the translation period along c for the orthorhombic choleic acids studied by us is about 7·2 Å, namely $c/2$, R was computed as a function of the translational and rotational degrees of freedom of one DCA molecule for all the reflections having l even with $\sin\theta/\lambda \leq 0{\cdot}28$ Å^{-1}. However, it was soon clear that the intensities of the reflections of the layers with l odd, which were generally weaker than those with l even, cannot be accounted for considering the contribution of NBD only, so that it was apparent that the DCA molecule placed at $(x, y, \frac{1}{2} + z)$ cannot be generated by a simple translation of $c/2$. Thus, new calculations were accomplished by moving the two DCA molecules independently and by introducing NBD. The agreement was satisfactory, R being 0·14. Unfortunately, R remained nearly constant if NBD was moved along c in a narrow region around the axis at $(a/4, b/2)$ because the contribution of NBD is negligible except for the *hk*0 reflections. Therefore, we were unable to locate the NBD C atoms.

Table 1. *Crystal data of DCANBD*

Deoxycholic acid, $C_{24}H_{40}O_4$, $M_r = 392{\cdot}58$
Norbornadiene, C_7H_8, $M_r = 92{\cdot}14$
Systematic absences: *h*00, *h* odd; 0*k*0, *k* odd; 00*l*, *l* odd
$F(000) = 1928$, $V = 5187{\cdot}3$ Å^3, λ(Mo $K\alpha$) = 0·71069 Å, D_m = 1·12, D_x = 1·12 Mg m^{-3}, μ(Mo $K\alpha$) = 7·9 mm^{-1}, m.p. = 449 K (at 430 K NBD is lost)

Isotropic block-diagonal least-squares refinement was performed for the two DCA molecules with programs of Domenicano, Spagna & Vaciago (1969) and scattering factors taken from *International Tables for X-ray Crystallography* (1974), the function minimized being $\sum w(|F_o| - |F_c|)^2$ with $w = (a + |F_o| + b|F_o|^2)^{-1}$. At this stage a difference synthesis showed roughly the region where NBD lies. However, owing to the presence of several peaks more than the seven expected and the unsatisfactory geometry of the possible molecular models we were again unable to locate NBD. Thus, it was decided to undertake van der Waals energy calculations in order to see whether the models corresponding to the minima fit the zone of maximum electronic density in the difference synthesis. The geometry adopted for NBD, Fig. 1, was assumed on the basis of NMR and X-ray data (Burnell & Diehl, 1972; Declercq, Germain & Van Meerssche, 1975; Ng & Penfold, 1978). That of the DCA molecules was obtained during the refinement, R being 0·15 for all the observed reflections. The H atoms of DCA were generated at the expected positions (Candeloro De Sanctis, Coiro, Giglio, Pagliuca, Pavel & Quagliata, 1978), except those of the hydroxyl and carboxyl groups. The coefficients of the potentials concerning H, C, O and the methyl groups have been reported previously (Pavel, Quagliata & Scarcelli, 1976). The energy was computed, assuming a cut-off distance of 6 Å, as a function of three Eulerian rotation angles and three translations of NBD along a, b and c, keeping fixed 16 DCA molecules which belong to two facing monolayers of two adjacent bilayers (Fig. 4) which frame a canal in three cells along c. Angular and translational increments, decreasing from 20 to 5° and from 0·3 to 0·1 Å respectively, were used in the search for the energy minima. The second-lowest minimum gave rise to good agreement between the C atoms of the corresponding model and seven peaks of the difference synthesis. All the other minima did not satisfy the difference synthesis and, therefore, were discarded.

Table 2. *Fractional coordinates* ($\times 10^4$) *and isotropic thermal parameters* (Å^2) *with e.s.d.'s in parentheses*

	x	y	z	B
C(1)	1098 (5)	1815 (9)	−791 (9)	4·4 (3)
C(2)	600 (5)	2152 (10)	−446 (9)	5·0 (3)
C(3)	655 (5)	2876 (10)	373 (10)	5·3 (3)
C(4)	949 (4)	2429 (9)	1163 (9)	4·3 (2)
C(5)	1461 (4)	2077 (9)	809 (9)	4·2 (2)
C(6)	1767 (5)	1649 (10)	1624 (10)	5·3 (3)
C(7)	1569 (5)	629 (10)	1946 (10)	4·9 (3)
C(8)	1513 (4)	−116 (9)	1145 (9)	4·4 (3)
C(9)	1196 (4)	333 (8)	341 (8)	3·6 (2)
C(10)	1431 (4)	1340 (8)	−21 (8)	3·8 (2)
C(11)	1090 (4)	−408 (9)	−442 (9)	4·2 (2)
C(12)	865 (4)	−1409 (9)	−71 (9)	4·4 (3)
C(13)	1187 (4)	−1856 (9)	707 (8)	3·8 (2)
C(14)	1275 (4)	−1080 (9)	1473 (9)	4·2 (2)
C(15)	1511 (5)	−1664 (10)	2301 (10)	5·3 (3)
C(16)	1266 (5)	−2650 (11)	2244 (11)	6·1 (3)
C(17)	969 (4)	−2709 (9)	1312 (9)	4·3 (3)
C(18)	1679 (5)	−2211 (10)	242 (9)	4·8 (3)
C(19)	1931 (5)	1172 (10)	−462 (9)	4·7 (3)
C(20)	951 (4)	−3765 (9)	898 (9)	4·3 (2)
C(21)	682 (5)	−3840 (10)	2 (10)	5·6 (3)
C(22)	774 (5)	−4527 (10)	1653 (10)	5·6 (3)
C(23)	243 (6)	−4368 (11)	1955 (10)	6·2 (3)
C(24)	90 (5)	−5151 (11)	2656 (10)	5·3 (3)
O(25)	173 (4)	3137 (7)	689 (7)	6·4 (2)
O(26)	371 (3)	−1207 (6)	288 (6)	4·6 (2)
O(27)	79 (4)	−6071 (9)	2467 (9)	8·7 (3)
O(28)	−54 (3)	−4865 (7)	3476 (7)	6·5 (2)
C(29)	1179 (5)	1883 (10)	4330 (9)	4·8 (3)
C(30)	699 (5)	2178 (10)	4759 (9)	4·8 (3)
C(31)	785 (5)	2904 (10)	5566 (9)	4·9 (3)
C(32)	1124 (5)	2449 (9)	6295 (9)	4·6 (3)
C(33)	1614 (5)	2128 (10)	5874 (9)	4·5 (3)
C(34)	1950 (5)	1687 (10)	6636 (10)	5·2 (3)
C(35)	1790 (5)	659 (10)	6967 (9)	4·9 (3)
C(36)	1691 (4)	−53 (9)	6159 (9)	4·0 (2)
C(37)	1333 (4)	399 (8)	5424 (8)	3·9 (2)
C(38)	1537 (4)	1396 (8)	5019 (8)	3·8 (2)
C(39)	1206 (4)	−373 (9)	4654 (9)	4·0 (2)
C(40)	985 (4)	−1324 (8)	5058 (8)	3·3 (2)
C(41)	1325 (4)	−1793 (9)	5804 (8)	3·8 (2)
C(42)	1442 (4)	−1005 (9)	6537 (9)	4·0 (2)
C(43)	1711 (5)	−1588 (10)	7317 (10)	5·3 (3)
C(44)	1432 (5)	−2619 (11)	7325 (10)	5·9 (3)
C(45)	1104 (4)	−2641 (9)	6422 (8)	4·2 (2)
C(46)	1794 (5)	−2160 (10)	5254 (9)	4·7 (3)
C(47)	2043 (5)	1235 (10)	4514 (10)	5·2 (3)
C(48)	1066 (5)	−3708 (10)	6020 (9)	5·1 (3)
C(49)	781 (5)	−3787 (11)	5097 (10)	6·1 (3)
C(50)	875 (5)	−4442 (10)	6773 (10)	5·2 (3)
C(51)	335 (5)	−4253 (11)	7072 (10)	5·9 (3)
C(52)	137 (5)	−5020 (10)	7691 (9)	4·9 (3)
O(53)	303 (3)	3146 (7)	5965 (7)	6·0 (2)
O(54)	505 (3)	−1096 (6)	5485 (6)	4·9 (2)
O(55)	289 (4)	−5910 (9)	7696 (8)	7·9 (3)
O(56)	−198 (3)	−4740 (7)	8291 (7)	6·1 (2)
C(57)	2651	4870	2322	49·0 (48)
C(58)	2959	4805	3899	27·2 (19)
C(59)	2205	4565	2628	31·4 (23)
C(60)	2513	4500	4206	34·0 (29)
C(61)	2867	5534	3092	32·0 (25)
C(62)	2127	5028	3600	30·0 (23)
C(63)	2392	6019	3448	23·2 (16)

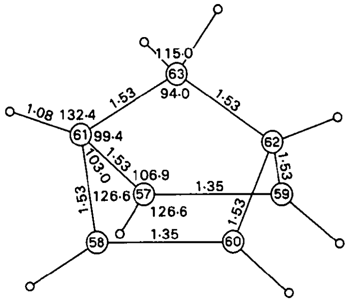

Fig. 1. Bond distances (Å) and angles (°) of the NBD model used in the calculations.

At the same time some DCANBD was irradiated by X-rays under the same operating conditions used in the collection of the intensities. Then a solution of this material in CD_3OD, investigated by proton NMR, showed a ratio DCA:NBD of 2·5, which suggests that 20% of the NBD probably changes into tetracyclo-[2.2.1.0^{2,6}.0^{3,5}]heptane (quadricyclane, Dauben & Cargill, 1961).

The refinement was resumed including NBD as found in the potential-energy calculations, except that very slight adjustments were made to the atomic coordinates of the model by using the 'molecules best fitting' program (Gavuzzo, Pagliuca, Pavel & Quagliata, 1972) to obtain the best overlap with the peaks of the difference synthesis.

The positional parameters of the two DCA molecules were treated in two distinct blocks, whereas those of NBD were kept fixed. Another block contained all the isotropic thermal parameters. In the last cycles the H atoms, generated as in the potential-energy calculations, were included, keeping their positional parameters and B values (5 Å^2) fixed. The refinement converged to a final R and R_w of 0·11 and 0·14 respectively. The final atomic coordinates are reported in Table 2.*

The bond lengths and angles of the DCA molecules are given in Fig. 2. Schematic drawings of the crystal packing and of a bilayer, viewed along c and a respectively, are shown in Figs. 3 and 4.

Discussion

The rather high R and e.s.d.'s of the atomic parameters probably occur because it was impossible to carry out an anisotropic refinement, owing to the low ratio between the number of observed reflections and the

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35666 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

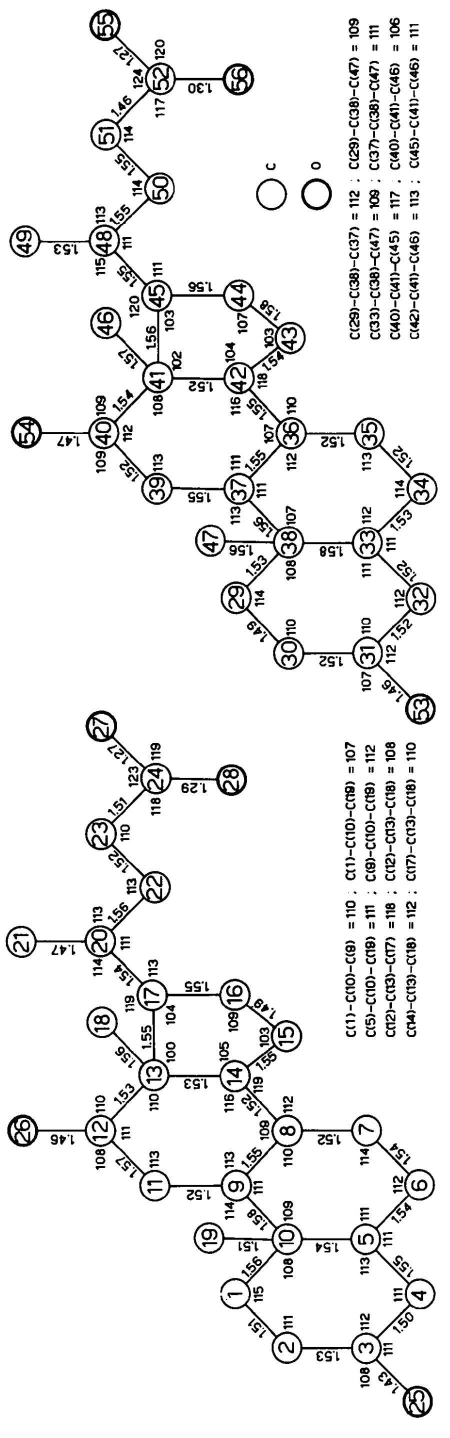

Fig. 2. Bond distances (Å) and angles (°) in the two DCA molecules of the DCANBD asymmetric unit. Average e.s.d.'s are 0·02 Å and 1·0° with maximum values of 0·02 Å and 1·3°.

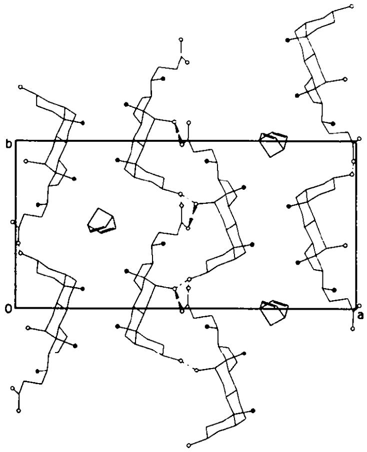

Fig. 3. A view of the DCANBD crystal structure along *c*. The filled and open circles represent methyl groups and O atoms respectively. The broken lines indicate hydrogen bonds.

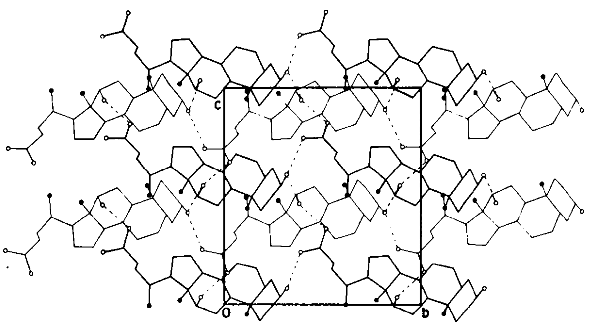

Fig. 4. Molecular packing of a DCANBD bilayer viewed along *a*. The symbols have the same meaning as in Fig. 3.

number of atomic parameters and to the approximation in locating NBD, since the guest molecule is partly converted to quadricyclane by exposure to X-rays. The very high temperature factors of the NBD atoms support this hypothesis.

The side-chain and *D*-ring conformations of the two DCA molecules are similar to each other and also to those of the other orthorhombic and tetragonal phases studied so far. The torsion angles, together with the phase angle of pseudorotation Δ and the maximum angle of torsion φ_m (Altona, Geise & Romers, 1968), are reported in Table 3 according to the convention of Klyne & Prelog (1960). The side-chain dihedral angles give rise to a *gauche* conformation coupled with the half-chair form approached by the *D* ring (Giglio & Quagliata, 1975).

The crystal packing (Fig. 3) can be described by an assembly of wavy bilayers, extended into the *bc* plane. A bilayer, composed of two monolayers, is generated from the adjacent ones by the 2_1 axis. The structure of a bilayer (Fig. 4) is mainly stabilized by an efficient scheme of hydrogen bonds, which engage hydroxyl and

Table 3. *Torsion angles (°) for the side chain and ring D of the two independent DCA molecules together with* Δ *and* φ_m

The e.s.d.'s are within the range 1·0–1·9°.

	1	2		1	2
C(13)–C(17)–C(20)–C(22)	174	176	C(13)–C(14)	44	47
C(17)–C(20)–C(22)–C(23)	66	67	C(14)–C(15)	−34	−36
C(20)–C(22)–C(23)–C(24)	178	173	C(15)–C(16)	10	12
C(13)–C(17)–C(20)–C(21)	−57	−56	C(16)–C(17)	17	16
C(16)–C(17)–C(20)–C(21)	−179	−176	C(13)–C(17)	−37	−39
C(21)–C(20)–C(22)–C(23)	−64	−63	Δ	8	5
C(22)–C(23)–C(24)–O(27)	−62	−27	φ_m	44	47
C(22)–C(23)–C(24)–O(28)	121	150			

Table 4. O$\cdots$O *distances* (Å) *in the hydrogen bonds in a bilayer*

The e.s.d.'s are within the range 0·01–0·02 Å.

$\mathrm{O(25)\cdots O(27^{i})}$	2·75	$\mathrm{O(26)\cdots O(55^{iii})}$	2·70
$\mathrm{O(25)\cdots O(56^{ii})}$	2·69	$\mathrm{O(55)\cdots O(57^{i})}$	2·77
$\mathrm{O(26)\cdots O(28^{ii})}$	2·66	$\mathrm{O(56)\cdots O(58^{iv})}$	2·65

Symmetry code

(i) $x, 1+y, z$
(ii) $-x, \frac{1}{2}+y, \frac{1}{2}-z$
(iii) $-x, -\frac{1}{2}+y, \frac{1}{2}-z$
(iv) $-x, \frac{1}{2}+y, \frac{3}{2}-z$

carboxyl groups (Table 4), and is characterized by non-polar outer surfaces with protruding methyl groups. Each monolayer is formed by rows of DCA molecules linked in each row by head-to-tail hydrogen bonds involving O(25) and O(27) or O(53) and O(54) of two consecutive molecules. In a monolayer (Fig. 4) there is an intermediate row, almost half way between the rows at $c \simeq 0$ and $c \simeq 14{\cdot}2$ Å, which cannot be reproduced by an exact translation of $c/2$ as occurs in the choleic acids with $c \simeq 7{\cdot}2$ Å (Candeloro De Sanctis & Giglio, 1979). However, the bilayers of the two groups of choleic acids with $c \simeq 7{\cdot}2$ and 14·2 Å, hereafter indicated as α and β respectively, are nearly equal, but their packing in the two types of structures is different. In fact, the rows of two facing monolayers, belonging to two adjacent bilayers, are shifted along c by ~ 3·6 Å in the α group, while they are at nearly the same height on c in the β group. These findings suggest that the bilayers can move along c as well as along b (Candeloro De Sanctis & Giglio, 1979). Moreover, the packing coefficient of the bilayer in the β structures solved so far (Tang, 1978; Candeloro De Sanctis & Giglio, 1979) is slightly higher than that of the α structures on the basis of the bilayer thickness on a and of the values of the b and c parameters.

The packing of the bilayers in the β structures gives rise to canals with sections closer to squares since the occluded molecules are or have groups of approximately spherical shape (Fig. 3). Thus, their greater bulkiness with respect to the guest molecules of the α group, which are generally flat or thread-like, causes a larger separation between two bilayers with an increase of a.

Table 5. *Shortest distances* (Å) *between NBD* C *atoms and DCA methyl groups*

$\mathrm{C(58)\cdots C(18^{i})}$	4·10	$\mathrm{C(62)\cdots C(46^{ii})}$	4·55
$\mathrm{C(58)\cdots C(21^{i})}$	4·21	$\mathrm{C(62)\cdots C(48^{ii})}$	4·52
$\mathrm{C(60)\cdots C(47)}$	4·60	$\mathrm{C(63)\cdots C(46^{ii})}$	3·90
$\mathrm{C(60)\cdots C(18^{i})}$	4·06	$\mathrm{C(63)\cdots C(19^{iii})}$	4·48

Symmetry code

(i) $\frac{1}{2}-x, -y, \frac{1}{2}+z$
(ii) $x, 1+y, z$
(iii) $\frac{1}{2}-x, 1-y, \frac{1}{2}+z$

The NBD atoms act as a lattice cement and are engaged in strong interactions mainly with the C(18) and C(46) methyl groups of DCA (Table 5). C(46) interacts with the methylene group of NBD whereas C(18) points approximately towards the centre of the double bond C(58)–C(60), causing a plausible polarization of the double bond.

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