

Side-Chain and Ring *D* Conformation in Cholanic Acids

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The conformations of some cholanic acids and related compounds are discussed. The intramolecular van der Waals energy surface of desoxycholic acid, computed as a function of four internal rotation angles of the side chain, presents several minima indicating a remarkable conformational flexibility. The agreement with the experimental conformations is satisfactory. The arrangement of the carboxyl group in the crystals mainly depends on its ability to form hydrogen bonds rather than on the intramolecular van der Waals energy. Ring *D* shows different conformations which may chiefly arise from short-range intramolecular interactions. However, anisotropic packing forces could also influence the conformation of ring *D* in the crystals.

Introduction

The molecular geometries of $3\alpha,12\alpha$ -dihydroxy- 5β -cholan-24-oic acid (desoxycholic acid, DCA), $3\alpha,7\alpha,12\alpha$ -trihydroxy- 5β -cholan-24-oic acid (cholic acid, CA) and $3\alpha,6\alpha$ -dihydroxy- 5β -cholan-24-oic acid (hydrodesoxycholic acid, HDCA) have been determined in crystals. DCA has been studied by Craven & De Titta (1972) in the acetic acid choleic acid complex (DCAA-CA) and by Candeloro De Sanctis, Giglio, Pavel & Quagliata (1972) in the phenanthrene (DCAPHE) and *p*-diiodobenzene choleic acid complexes; CA by Johnson & Schaefer (1972) in an addition compound with ethanol (CAETHA); and HDCA by Hall, Maslen & Cooper (1974). The crystal and molecular structure of the *p*-bromoanilide derivative of DCA (DCAPBA) has also been published (Schaefer & Reed, 1972).

We are attempting to provide both physicochemical information about DCA in solution and the crystal structures of the tetragonal and hexagonal modifications of DCA, as well as the helical structure of the macromolecule (Rich & Blow, 1958; Blow & Rich, 1960). Since the stereochemistry of the cholanic acids may be related to their remarkable chemical and biological behaviour we are interested in predicting the conformation of the side chain and ring *D*. Furthermore it may be useful to establish, even approximately, their conformation in order to decrease the degrees of freedom in solving the phase problem in

crystals by means of potential-energy calculations (Coiro, Giglio & Quagliata, 1972; Coiro, Giacomello & Giglio, 1971; Coiro, Giglio, Lucano & Puliti, 1973; Gavuzzo, Mazza & Giglio, 1974).

Van der Waals energy of the DCA side chain

The intramolecular van der Waals energy map of the DCA side chain has been computed. Fig. 1 shows the atomic numbering of DCA. The calculations have been performed by taking into account all the DCA atoms lying on the right-hand side of a straight line passing through the bonds C(8)–C(14) and C(11)–C(12). The hydrogen atom of the carboxyl group has been excluded, since it is a nearly free rotator and its location is strongly conditioned by the hydrogen-bonding scheme. The methyl group has been treated as one atom. The molecular geometry of DCA has been derived by adopting the bond lengths and angles of the HDCA crystal structure, which is the most reliable among those available. The hydrogen atoms and O(26) have been generated by putting C–H = 1.08 Å, H–C–C = 109.47°, C(12)–O(26) = 1.44 Å, O(26)–C(12)–C(11) = 109° and O(26)–C(12)–C(13) = 111°. The atomic coordinates of the DCA fragment, employed in the search of the energy minima, are reported in Table 1.

Semi-empirical van der Waals potential functions, previously verified (Giglio, 1970, and references quoted therein) in known crystal structures, have been used to describe non-bonded interactions involving hydrogen, carbon and oxygen atoms and methyl groups. The coefficients of the atom–atom potentials in the generalized form:

$$V(r) = a \exp(-br)/r^d - cr^{-6}$$

are listed in Table 2. Since our potentials are hard, torsional potentials have been neglected. The summation of the van der Waals energy has been accomplished by computing all the interactions in the DCA fragment except those which remain constant

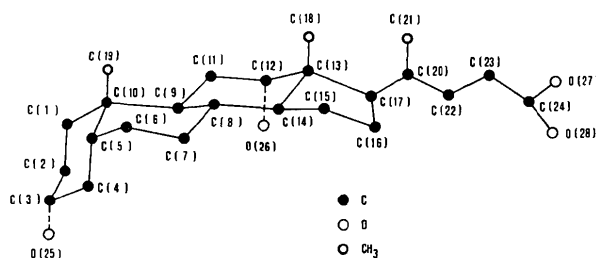


Fig. 1. Atomic numbering of DCA.

by changing the rotation angles. A cut-off distance of 6.6 Å has been assumed.

The van der Waals energy depends on four dihedral angles, C(13)–C(17)–C(20)–C(21), C(17)–C(20)–C(22)–C(23), C(20)–C(22)–C(23)–C(24) and C(22)–C(23)–

C(24)–O(28), indicated as ψ_1 , ψ_2 , ψ_3 and ψ_4 respectively. The angular values are evaluated according to the convention of Klyne & Prelog (1960). Angular increments, decreasing from 20° to 5°, are used in the search of the energy minima.

Table 1. *Orthogonal coordinates (Å) of the atoms involved in the van der Waals energy calculations*

	X	Y	Z
C(12)	-1.37764	-0.99353	2.03140
H(12)	-1.75041	-0.04712	2.39438
O(26)	-2.35919	-1.47923	1.09638
C(13)	-0.02683	-0.78048	1.34675
C(14)	0.44020	-2.17774	0.88142
C(18)	0.97047	-0.14127	2.32665
H(14)	-0.35189	-2.65455	0.32317
C(15)	1.62039	-1.89672	-0.04786
H'(15)	2.52091	-1.78485	0.53775
H''(15)	1.67695	-2.66845	-0.80128
C(16)	1.27046	-0.54883	-0.71676
H'(16)	2.08801	0.14358	-0.58045
H''(16)	1.05206	-0.71163	-1.76184
C(17)	0	0	0
H(17)	-0.87653	-0.25090	-0.57892
C(20)	0	1.53970	0
H(20)	0.88401	1.89962	0.50535
C(21)	-1.13937	2.16242	0.78566
C(22)	0	2.04147	-1.45052
H'(22)	0.85299	1.63357	-1.97246
H''(22)	-0.85299	1.63357	-1.97246
C(23)	0	3.57220	-1.58704
H'(23)	0.83425	3.98256	-1.03746
H''(23)	-0.83425	3.98256	-1.03746
C(24)	0	4.12365	-2.97984
O(27)	0	5.29622	-3.27437
O(28)	0	3.19054	-3.87780

Table 2. *The coefficients of the potential functions*
The energy is in kcal per atom pair if the interatomic distance is in Å

Interaction	$a \times 10^{-3}$	b	c	d
H—H	6.6	4.080	49.2	0
H—C	44.8	2.040	125.0	6
H—O	42.0	2.040	132.7	6
H—CH ₃	49.1	3.705	380.5	0
C—C	301.2	0.000	327.2	12
C—O	278.7	0.000	342.3	12
C—CH ₃	291.1	1.665	981.1	6
O—O	259.0	0.000	358.0	12
O—CH ₃	272.7	1.665	1026.3	6
CH ₃ —CH ₃	273.9	3.329	2942.0	0

Table 3. *Dihedral angles (°) for the side chains of some cholanic acids and related compounds*

	DCAACA*	DCAPHE	CAETHA	HDCA	DCAPBA	DICLCH	DIBRCH
C(13)–C(17)–C(20)–C(21)	-60	-59	-59	-54	-63	-57	-55
C(17)–C(20)–C(22)–C(23)	65	62	-173	-168	-171	-165	-154
C(20)–C(22)–C(23)–C(24)	178	179	-175	-99	173	176	-179
C(16)–C(17)–C(20)–C(21)	180	-175	-177	-175	177	-178	-176
C(13)–C(17)–C(20)–C(22)	173	175	179	-179	176	-179	-177
C(16)–C(17)–C(20)–C(22)	52	59	61	61	55	59	62
C(21)–C(20)–C(22)–C(23)	-62	-65	65	65	68	71	82
C(22)–C(23)–C(24)–O(27)†	-45	-56	-15	-15	-50		
C(22)–C(23)–C(24)–O(28)†	138	124	168	164			

* The atomic coordinates were kindly supplied by Craven & De Titta (1972).

† O(27) and O(28) represent the carbonyl and hydroxyl oxygen atoms respectively. Only in the case of DCAPHE are they indistinguishable since the C(24)–O(27) and C(24)–O(28) distances are equal.

Results and discussion

The observed values of the side-chain torsion angles of the above-mentioned cholanic acids together with those of two other similar compounds, 2 β ,3 α -dichloro-5 α -cholestane (DICLCH; Geise, Romers & Rutten, 1966) and 2 α ,3 β -dibromo-5 α -cholestane (DIBRCH; Geise & Romers, 1966), are reported in Table 3.

At first an energy map was computed merely as a function of ψ_1 , ψ_2 and ψ_3 , neglecting O(27) and O(28), because, reasonably, the coordinates of the oxygen atoms are mainly influenced by the possibility of forming hydrogen bonds. In this way the two cholestane derivatives can be included in the comparison of the experimental dihedral angles of the side chain with the calculated ones.

The energy map indicates that ψ_1 can vary in a very narrow range ($\sim 20^\circ$) around -55 to -60° . Therefore a section at $\psi_1 = -60^\circ$ is shown in Fig. 2 where the arrows indicate the observed points lying in three of the five lowest minima. These minima have ψ_2 values of about 60 and -170° and ψ_3 values around 50, 165 and -95° . The minima with $\psi_2 \simeq 60^\circ$ are very sharp and those with $\psi_2 \simeq -170^\circ$ rather broad. The deepest minimum has $\psi_2 \simeq -170^\circ$ and $\psi_3 \simeq 50^\circ$ and it is still the principal one if the calculations are made as a function of four rotation angles, ψ_4 being about 70° . The three minima at $\psi_3 \simeq 50$ and -95° correspond to side chains with the carboxyl group tending to fold back in such a way as to achieve contacts energetically more favoured than those, for example, of the extended side chain. However, so far only HDCA, which utilizes partially the hydrogen-bonding ability of the carboxyl group, lies in one of the three minima. Thus it seems probable that the higher van der Waals energy of the more extended conformations is largely counterbalanced by the energy gain due to the formation of more hydrogen bonds, as in DCAACA, DCAPHE and CAETHA crystals.

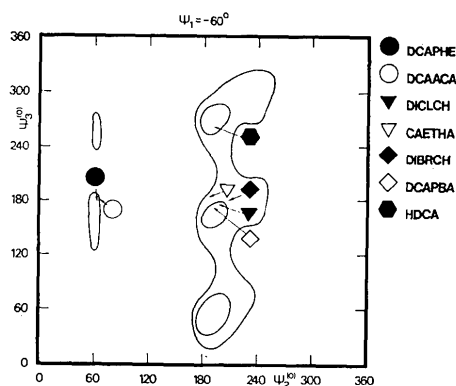


Fig. 2. Section $\psi_1 = -60^\circ$ of the van der Waals energy of DCA. Contours are drawn at 7.5 and 8.5 kcal.

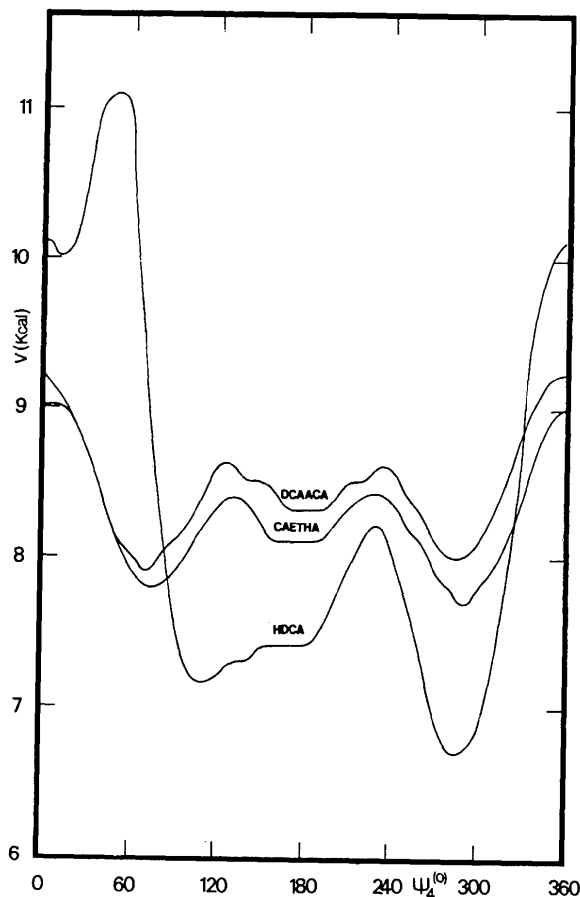


Fig. 3. Van der Waals energy *vs* ψ_4 for DCAACA, CAETHA and HDCA. ψ_1 , ψ_2 and ψ_3 are constant and assume the values of Table 3

Subsequently the four-angle analysis has been performed. The results show that O(27) and O(28) can easily rotate within large ranges of ψ_4 , the lowest minima being characterized by the same ψ_1 , ψ_2 and ψ_3 values as found in the three-angle calculations. The best allowed regions are $60 \leq \psi_4 \leq 140^\circ$ and $-120^\circ \leq \psi_4 \leq -60^\circ$. As an example the energy change *vs* ψ_4 is reported in Fig. 3 for DCAACA, CAETHA and HDCA, assuming the observed values of Table 3 for ψ_1 , ψ_2 and ψ_3 . Since O(26) is always far from the rotating O(27) and O(28), it has been kept in the HDCA analysis in order to allow a qualitative comparison among the energies of the three compounds. The DCAACA and CAETHA curves have pseudo-mirror planes at $\psi_4 = 0$ and 180° , as expected on the basis of the approximate coplanarity of C(20), C(22), C(23) and C(24), ψ_3 being nearly equal to 180° . The pseudo-mirror planes are lacking in HDCA ($\psi_3 = -99^\circ$), because C(24) is far from the plane defined by C(20), C(22) and C(23). The deepest minima are located at $\psi_4 \approx -70^\circ$ for HDCA and CAETHA and $\psi_4 \approx 70^\circ$ for DCAACA. The observed values are 138 , 164 and 168° for DCAACA, HDCA and CAETHA respectively and lie near one maximum (DCAACA), in one plateau (HDCA) and in one local minimum (CAETHA). The energy value of DCAPE is ~ 0.7 kcal greater than that of the principal minimum, so that almost all the ψ_4 values of the DCAACA and CAETHA curves may be assigned to the carboxyl group, which can be considered a nearly free rotator. The case of HDCA may be different owing to the higher energy barriers arising from the folding back of the carboxyl group.

In conclusion the side chain of the cholanic acids presents a noteworthy conformational flexibility, increasing from ψ_1 to ψ_4 , and the experimental conformations are mainly controlled by the hydrogen-bonding schemes in the crystals. Moreover the several permissible conformations allow the cholanic acids to form many hydrogen-bonding schemes.

Ring D conformation

A description of the cyclopentane ring may be given in terms of the maximum angle of torsion, φ_m , and the phase angle of pseudorotation, Δ (Altona, Geise & Romers, 1968). These parameters, together with the torsional angles about the ring D bonds, are listed in Table 4 for the above-mentioned compounds. The results from DCAPE are not very accurate and, therefore,

Table 4. Torsional angles and parameters Δ and φ_m ($^\circ$) of ring D

	DCAACA	DCAPE	CAETHA	HDCA	DCAPEBA	DICLCH	DIBRCH
C(13)–C(14)	47.5	50.1	48.1	44.5	47.3	47.0	46.8
C(14)–C(15)	–38.1	–39.3	–32.6	–32.7	–35.9	–36.1	–33.6
C(15)–C(16)	13.0	12.2	4.8	7.9	9.5	10.7	7.6
C(16)–C(17)	16.1	18.7	24.4	19.3	20.3	18.0	20.6
C(13)–C(17)	–38.3	–42.2	–43.4	–38.5	–39.8	–39.1	–40.4
Δ	2.7	7.0	23.2	14.3	11.5	8.1	15.7
φ_m	47.6	50.2	49.1	44.8	47.5	47.2	47.2

they could be shifted towards those of DCAACA. By inspection of Table 4 it can be inferred that ring *D* assumes many intermediate conformations between the half-chair and the C(13) envelope. The extreme conformations are adopted by DCAACA, which presents a nearly exact half-chair symmetry, and CAETHA, which approaches a β -envelope. DCAACA and DCAPHE show approximate C_2 symmetry, while HDCA, CAETHA and DCAPBA lie between C_2 and C_s symmetry. The ψ_2 value is $\sim 60^\circ$ for the choleic acids and $\sim -170^\circ$ for the other compounds (Δ near to 0 and to 15° respectively). If ψ_2 is $\sim -170^\circ$ the most important interactions between side chain and ring *D* are $H'(16)\cdots H'(22)$ and $H''(16)\cdots H'(22)$. The corresponding distances are practically equal, with the geometry of Table 1 and, for example, the experimental dihedral angles of CAETHA reported in Table 3. Their values, 2.25 and 2.26 Å, indicate that C(22)–H'(22) is staggered with respect to C(16)–H'(16) and C(16)–H''(16), the van der Waals energy being good enough. In this connection it is clear that ψ_2 slightly differs from 180° in order to obtain nearly equal $H'(16)\cdots H'(22)$ and $H''(16)\cdots H'(22)$ contacts, since, when ψ_2 is increased above 180° , H'(22) approaches H''(16) and moves away from H'(16). On the other hand if ψ_2 is $\sim 60^\circ$ the main interactions are $H(17)\cdots H''(23)$ and $H'(16)\cdots H''(22)$. By employing the observed DCAACA torsion angles of Table 3 the distances of the two pairs of hydrogen atoms become 2.00 and 2.23 Å. The van der Waals energy is greater than that at $\psi_2 \simeq -170^\circ$, especially because of the short $H(17)\cdots H''(23)$ distance. Thus it seems reasonable to suppose that the more frequent ring *D* conformation, characterized by $\Delta \simeq 15^\circ$, is generally coupled with a side chain where ψ_2 is $\sim -170^\circ$, this system being energetically very stable. However, when ψ_2 is $\sim 60^\circ$, so that the carboxyl group can be engaged in a more suitable hydrogen-bonding scheme, the strain energy between side chain and ring *D* increases and the cyclopentane ring approaches the half-chair symmetry. In the case of DICLCH and DIBRCH the

hydrogen bonds cannot be formed. Therefore they exhibit an intermediate conformation between C_2 and C_s symmetry.

On the basis of these arguments it is presumed that the conformation of ring *D* in the cholanolic acids is governed by the short-range intramolecular van der Waals interactions, although the influence of anisotropic packing forces in the crystals cannot be excluded.

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