

The Pseudorotation of Cycloheptane.

III.* A Re-examination of the Structures of 1-Aminocycloheptanecarboxylic Acid Hydrobromide Monohydrate and Dimethyl 1-Hydroxy-1-cycloheptanephosphonate

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(Received 13 November 1979; accepted 28 February 1980)

Abstract

The crystal structures of 1-aminocycloheptanecarboxylic acid hydrobromide monohydrate, $C_8H_{16}NO_2 \cdot Br^- \cdot H_2O$ [AHCA; Chacko, Srinivasan & Zand (1971), *J. Cryst. Mol. Struct.* **1**, 213–224] and dimethyl 1-hydroxy-1-cycloheptanephosphonate, $C_9H_{19}O_4P$ [DMPC; Birnbaum, Buchanan & Morin (1977), *J. Am. Chem. Soc.* **99**, 6652–6656] have been reinvestigated using the published diffraction data and theoretical models. The structures of AHCA and DMPC are orthorhombic and triclinic, respectively. The crystal data are $a = 25.69$ (3), $b = 6.85$ (1), $c = 6.61$ (1) Å, $Z = 4$, $P2_12_12_1$ for AHCA and $a = 8.443$ (1), $b = 11.346$ (1), $c = 6.785$ (1) Å, $\alpha = 101.30$ (2), $\beta = 111.21$ (2), $\gamma = 98.41$ (2)°, $Z = 2$, $P\bar{1}$ for DMPC. Using Waser constraints the new refinements result in $R = 0.092$ and $R_w = 0.116$ for AHCA and $R = 0.056$ and $R_w = 0.048$ for DMPC. It turns out that in both compounds *all* ring C atoms and a number of exocyclic atoms are disordered over two positions giving rise to two conformations in AHCA as well as DMPC, with occupancy ratios of 0.67 and 0.93, respectively, for the major forms. The major and minor forms are twist-chairs in both compounds, *i.e.* $TC(1)$ and $TC'(1)$ (the inverted form) in AHCA and $TC'(1)$ and $TC(5)$ in DMPC.

Introduction

The pseudorotation theory of Hendrickson (1967), Bocian, Pickett, Rounds & Strauss (1975) and Flapper & Romers (1975) (hereafter FR) gives an acceptable explanation for why cycloheptane derivatives are either liquids or highly disordered solids at room temperature; examples of such structures are 1-aminocycloheptanecarboxylic acid hydrobromide monohydrate (AHCA; Chacko, Srinivasan & Zand, 1971), calcium cycloheptanecarboxylate pentahydrate (CACC; Flapper, Verschoor, Rutten & Romers, 1977, hereafter

* Part II: Flapper, Verschoor, Rutten & Romers (1977).

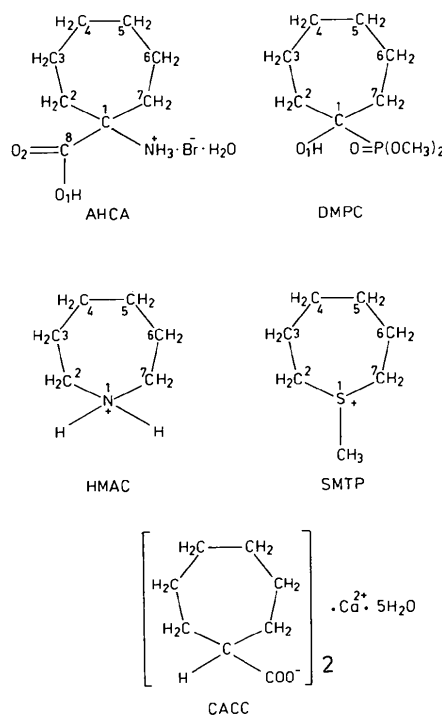


Fig. 1. Structural formulae and numbering of atoms of the seven-membered-ring compounds mentioned in the text.

FL), dimethyl 1-hydroxy-1-cycloheptanephosphonate (DMPC; Birnbaum, Buchanan & Morin, 1977), hexamethylenearmonium chloride (HMAC; Cameron & Scheeren, 1977) and *S*-methylthiepanium (SMTP; Combremont & Gerdil, 1979), see Fig. 1. An adequate interpretation of this disorder in CACC has been presented by FL; still in progress is the study of this phenomenon in SMTP, a compound containing an S atom in the seven-membered ring.

Although the investigators of the other two compounds were aware of disorder and observed alternative positions for the ring C(6) and C(7) atoms in DMPC and the C(3) and C(6) atoms in AHCA, they did not realize that the other ring atoms would have to

be disordered as well, albeit over very closely related positions (<0.5 Å). It is difficult to establish this total disorder exclusively on the basis of the diffraction data. The inadequacy of the published geometries is shown by the occurrence of unrealistic C—C single-bond distances (e.g. 1.46 and 1.70 Å) as well as by too small valency angles (104°) in the minor rings with occupancy ratios of 0.07 and 0.33, respectively. Moreover, the proposed conformations of these rings are questionable in view of the results of force-field calculations by Hendrickson (1967) and Bocian *et al.* (1975) and the empirical relationship (1) proposed by FR (see below). Such totally or predominantly disordered structures are more common than is usually assumed. Another example is the structure of *trans*-tetrachlorostilbene (Norrestam, Hovmöller, Palm, Göthe & Wachtmeister, 1977), which according to our analysis (de Kok & Romers, 1978), has a 1:1 disorder of *all* atoms.

Unfortunately, introduction of theoretical starting models into the conventional least-squares refinement is not feasible since too short atomic separations result in a severe correlation between positional and vibrational parameters. Abandoning the hope of extracting independent information concerning the bond distances of cycloheptane from the diffraction data and instead introducing theoretical models (FR) by means of 'slack constraints' (Waser, 1963), one obtains experimental

values of the pseudorotation parameters A , B and Δ , see below. The present paper is a re-examination of the diffraction data of DMPC and AHCA, in order to circumvent the disorder problem and to find additional information concerning the geometry of cycloheptane. The method applied is the same as that described by FL.

Refinement with slack constraints

In order to carry out a least-squares refinement, the following slack constraints were introduced in the matrix of normal equations: (i) seven equal C—C bond distances of 1.52 Å (see FL) and (ii) seven equal bond angles of 115° involving distances of 2.57 Å. The starting points for introduction of the minor rings were the observed alternative positions of C(6) and C(7) in DMPC and the additional sites of C(3) and C(6) in AHCA. During the first cycle the remaining atoms of the major and minor rings occupied the same positions.

The additional requirements for the carboxylic group of AHCA, *i.e.* C(1)—C(8) = 1.54, C(8)—O(1) = 1.31, C(8)—O(2) = 1.23 Å and O(1)—C(8)—O(2) = 123° , were average values taken from *Molecular Structures and Dimensions* (1972). The slack constraint C(1)—N = 1.50 Å is a compromise between the generally accepted C—N single-bond length of 1.47 Å and the value of 1.54 Å obtained by refinement without

Table 1. *Survey of observables and parameters*

The observed reflexion intensities of DMPC and AHCA are taken from Birnbaum *et al.* (1977) and Chacko *et al.* (1971), respectively. Primes indicate atoms of the minor molecules. p = occupancy ratio, x = scale factor.

	DMPC		AHCA	
	Old	New	Old	New
Reflexions	2310	2310	1095	1095
Slack constraints	—	35	—	50
Observables	2310	2345	1095	1145
C	81 (9 × 9)	81 (9 × 9)	C	32 (8 × 4)
C'	8 (2 × 4)	21 (7 × 3)	C'	8 (2 × 4)
O	36 (4 × 9)	36 (4 × 9)	O	8 (2 × 4)
O'	—	3 (1 × 3)	O'	—
H	76 (19 × 4)	—	O _w	4 (1 × 4)
P	9 (1 × 9)	9 (1 × 9)	Br	9 (1 × 9)
x	1	1	x	1
p	1	1	p	1
Parameters	212	152	Parameters	63
Observables/ parameters	10.9	15.4		11.5
R	0.045	0.056		0.092
R_w	0.051	0.048		0.116
p	0.93	0.93		0.664

$$R = \frac{\sum |F_{\text{obs}}| - |F_{\text{calc}}|}{\sum |F_{\text{obs}}|}, R_w = \left[\frac{\sum w(|F_{\text{obs}}| - |F_{\text{calc}}|)^2}{\sum w F_{\text{obs}}^2} \right]^{1/2}$$

$$\text{Anisotropic temperature factor} = \exp(-2\pi^2 \sum_{i,j} h_i h_j a_i^* a_j^* U_{ij}), i, j = 1, 2, 3.$$

constraints (see below). Furthermore, it was necessary to constrain the exocyclic angle N–C(1)–C(8). Since the corresponding endocyclic angle C(7)–C(1)–C(2) is rather large (115°), a constraint of 108° was arbitrarily adopted for N–C(1)–C(8).

The extra requirements for DMPC, *i.e.* C(1)–O(1) = 1.42 and C(1)–P = 1.825 Å in the major and minor molecules respectively, were taken from the same quoted literature. Additional constraints for the minor molecule were O(1)–C(1)–P = 103.5, C(2)–C(1)–P = 110 and C(7)–C(1)–P = 112°. Since the minor molecule only contributes ~7% to the total scattering, these values of the angles were taken from the corresponding values of Birnbaum *et al.* (1977).

We had at our disposal 1095 photographically recorded reflexions (estimated intensities, Cu K α radiation) for AHCA and 2310 diffractometer-scanned reflexions for DMPC [$I > 3\sigma(I)$, Mo K α radiation].

The assigned weights w_h in the residual $\sum w_h(F_h^{\text{obs}} - F_h^{\text{calc}})^2$ were $w_h = \{1 + [(F_h^{\text{obs}} - 150)/50]^2\}^{-1}$ for DMPC and $w_h = [1/16 + F_h^{\text{obs}} + 0.02(F_h^{\text{obs}})^2]$ for AHCA. The weights w_v in the residual $\sum w_v(r_v^{\text{obs}} - r_v^{\text{calc}})^2$ are $w_v = \sum w_h(F_h^{\text{obs}} - F_h^{\text{calc}})^2/\sigma_v^2(M - N)$, where M is the number of observations and N the number of parameters. The observed values r_v^{obs} are the required constraints, and are in general literature values. The r_v^{calc} distances are calculated from positional parameters obtained in the previous least-squares cycle. The standard errors σ_v were estimated to be 0.004 and 0.01 Å for the major and minor ring distances in DMPC and 0.005 and 0.0075 Å for the corresponding distances in AHCA.

In contrast to earlier refinements, H atoms were introduced at calculated positions, but not refined. The heavy atoms of the major molecule of DMPC were refined anisotropically, those of the minor ring and O(1) isotropically with fixed B values. The B values were equal to the Debye–Waller parameters of the corresponding major atoms during the last overall isotropic refinement. In AHCA only the Br and the ‘water atom’ Ow were refined anisotropically. The scattering factors were taken from *International Tables for X-ray Crystallography* (1974).

A survey of the number of observables and parameters in the new and old refinements is given in Table 1.* Positional parameters and B values are presented in Table 2. Our estimated standard deviations for DMPC are slightly larger than those given by Birnbaum *et al.* (1977). On the other hand, our *e.s.d.*'s for AHCA are smaller than those mentioned by Chacko *et al.* (1971). However, our *e.s.d.*'s cannot be considered to be true

standard errors. The applied constrained refinement makes their physical relevance questionable.

The occupancies of the minor molecules are the same as those found in the earlier determinations. Notwithstanding the smaller number of parameters (150 *versus* 212), our R_w value for DMPC (0.048) is lower than that in the original refinement (0.051). However, not too much weight can be attributed to this since our number of observables is larger and, moreover, the decrease in parameters is due to the fixation of the relatively unimportant H atoms. Our R value (0.056) is larger than the old value (0.045). The

Table 2. Fractional coordinates ($\times 10^4$), isotropic temperature parameters B (Å²) and occupancy ratios p for AHCA and DMPC

Estimated standard deviations are given in parentheses.

	x	y	z	B	p
AHCA					
C(1)	3555 (4)	5284 (16)	-1153 (17)	2.3 (4)	0.658 (15)
C(2)	3902 (5)	3878 (24)	-2311 (19)	2.9 (4)	0.658 (15)
C(3)	4263 (5)	2642 (18)	-1013 (30)	4.5 (6)	0.658 (15)
C(4)	4788 (5)	3563 (26)	-555 (31)	3.9 (5)	0.658 (15)
C(5)	4771 (5)	5289 (27)	889 (29)	3.6 (5)	0.658 (15)
C(6)	4376 (5)	6857 (19)	347 (28)	3.7 (5)	0.658 (15)
C(7)	3811 (4)	6283 (23)	-642 (19)	2.4 (4)	0.658 (15)
C(8)	3360 (4)	6843 (24)	-2653 (23)	3.4 (4)	0.658 (15)
O(1)	3734 (5)	7718 (24)	-3653 (26)	3.6 (4)	0.658 (15)
O(2)	2904 (4)	6822 (23)	-3237 (27)	3.0 (3)	0.658 (15)
Ow	2491 (4)	2424 (16)	-3332 (21)	3.2*	1.000
N	3086 (5)	4202 (25)	-385 (25)	2.4 (3)	0.658 (15)
Br	3347 (1)	945 (02)	3257 (03)	3.12*	1.000
C(1')	3564 (6)	5332 (25)	-1068 (21)	1.9 (6)	0.342 (15)
C(2')	3855 (8)	3603 (33)	-1964 (35)	2.8 (8)	0.342 (15)
C(3')	4435 (8)	3926 (43)	-2291 (30)	2.7 (8)	0.342 (15)
C(4')	4775 (9)	3457 (49)	-476 (41)	4.3 (11)	0.342 (15)
C(5')	4746 (8)	4913 (52)	1252 (39)	3.8 (10)	0.342 (15)
C(6')	4199 (9)	5451 (47)	1928 (24)	3.9 (11)	0.342 (15)
C(7')	3879 (9)	6578 (27)	390 (30)	1.7 (6)	0.342 (15)
C(8')	3393 (7)	6639 (30)	-2853 (25)	1.1 (5)	0.342 (15)
O(1')	3671 (9)	8245 (39)	-3011 (32)	2.4 (6)	0.342 (15)
O(2')	2966 (8)	6450 (39)	-3696 (32)	2.6 (6)	0.342 (15)
N'	3089 (8)	4561 (36)	-14 (30)	1.0 (5)	0.342 (15)
DMPC					
C(1)	4674 (2)	2699 (2)	4278 (3)	2.9 (1)	0.929 (5)
C(2)	4414 (3)	1359 (2)	4420 (3)	3.2 (1)	0.929 (5)
C(3)	2587 (3)	537 (2)	2966 (3)	3.4 (1)	0.929 (5)
C(4)	2370 (4)	-100 (2)	650 (4)	4.4 (1)	0.929 (5)
C(5)	2391 (4)	738 (3)	-834 (4)	4.7 (1)	0.929 (5)
C(6)	3892 (3)	1892 (2)	109 (4)	4.5 (1)	0.929 (5)
C(7)	3869 (3)	2668 (2)	1983 (3)	3.8 (1)	0.929 (5)
C(8)	9744 (4)	2892 (3)	5095 (7)	5.6 (1)	1.000
C(9)	7776 (6)	4121 (4)	9873 (6)	6.9 (1)	1.000
O(1)	3942 (3)	3340 (2)	5648 (3)	3.4 (1)	0.929 (5)
O(2)	7417 (2)	4770 (2)	5700 (3)	3.9 (1)	1.000
O(3)	7880 (2)	2620 (2)	4444 (4)	4.2 (1)	1.000
O(4)	7688 (3)	3243 (2)	7990 (3)	4.7 (1)	1.000
P	7010 (1)	3464 (1)	5645 (1)	2.97 (3)	1.000
C(1')	4478	2589	3860	2.9	0.071 (5)
C(2')	4551	1255	3988	3.3	0.071 (5)
C(3')	2772	402	2476	3.5	0.071 (5)
C(4')	2392	97	46	4.3	0.071 (5)
C(5')	1608	1010	-1169	4.6	0.071 (5)
C(6')	2291	2366	157	3.5	0.071 (5)
O(7')	4228	2762	1560	2.3	0.071 (5)
O(1')	3770	3049	4984	3.8	0.071 (5)

* Lists of structure factors, anisotropic temperature factors and hydrogen atom positions have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35241 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

* Isotropic B calculated from anisotropic U_{ij} .

R value for AHCA (0.092) is lower than that (0.099) obtained by Chacko *et al.* (1971), but again our number of observables is larger. The data for the two compounds were not corrected for absorption. Also, we did not consider a refinement of the H atom positions. Further uncertainties arise from the dependence of R_w on the weights given to the constraints. For these reasons the application of Hamilton's (1965) test involving R_w and R values is not justified. The main justification of our results must be the improved geometry in agreement with theoretical models.

Dihedral angles

The empirical relationship proposed by FR,

$$\begin{aligned}\omega_i &= A \sin \varphi_j + B \sin 3\varphi_j; \\ \varphi_j &= \Delta/2 + j\delta/2; \quad \delta = 4\pi/7; \\ i &= 2j + 4, \text{ mod } 7; \quad j = 0, 1, \dots, 6,\end{aligned}\quad (1)$$

allows the calculation of endocyclic torsion angles ω_i for any phase angle of pseudorotation Δ . The parameters A and B are angles which characterize the chair or boat itineraries of pseudorotation. According to Flapper (1976), these parameters are $A \sim 87^\circ$ and $B \sim 35^\circ$ in the former and $A \sim 0^\circ$ and $B = 72^\circ$ in the latter circuit. The numerical values of A and B can be obtained by means of a least-squares procedure which minimizes

$$q = \sum_i (\omega_i^{\text{obs}} - \omega_i^{\text{calc}})^2, \quad i = 0, 1, \dots, 6. \quad (2)$$

The torsion angles ω_i^{calc} , q , A , B and Δ of the major and minor rings are listed in the columns with headings b and d in Table 3. The dihedral angles ω_i^{obs} resulting from our structure determination are listed in the columns headed c .

Table 3. Observed and calculated [according to formula (1)] torsion angles ($^\circ$) in AHCA and DMPC

The values of Chacko *et al.* (1971) and Birnbaum *et al.* (1977) are given under the heading a and the corresponding calculated values under heading b . Our observed dihedral angles are to be found under heading c and the corresponding calculated values under d .

AHCA

Bond	Major ring				Minor ring			
	a	b	c	d	a	b	c	d
1-2	32.0	33.5	39.2	42.3	-32.6*	-32.1	-33.0	-35.9
2-3	-75.7	-78.6	-88.5	-86.6	69.2	71.3	87.5	85.8
3-4	71.6	72.8	70.5	70.2	-68.1	-70.4	-72.9	-72.2
4-5	-57.3	-58.7	-50.4	-51.3	63.3	62.1	49.3	50.1
5-6	73.3	70.9	70.6	70.7	-70.8	-70.4	-66.7	-67.3
6-7	-84.4	-79.9	-88.0	-86.4	74.0	71.2	89.0	87.3
7-1	37.9	39.9	37.8	41.0	-31.3	-31.7	-44.4	-47.8
q^\dagger		43.9		27.2		19.5		27.2
A^\ddagger		86.7		87.1		83.4		86.4
B^\ddagger		28.0		35.8		21.3		36.5
Δ^\ddagger		537.6		540.4		180.2		176.0
Conformation	$TC(1)$		$TC(1)$		$TC'(1)$		$TC'(1)$	

DMPC

Bond	Major ring				Minor ring			
	a	b	c	d	a	b	c	d
1-2	-42.0	-43.7	-41.7	-43.5	-65.0	-70.4	-50.6	-51.3
2-3	88.6	85.5	88.5	85.2	88.6	89.9	75.4	74.4
3-4	-69.8	-68.6	-69.4	-67.8	-69.8	-72.9	-84.0	-83.3
4-5	50.8	50.9	49.5	49.8	-1.0	-0.2	26.7	28.8
5-6	-68.6	-70.7	-67.7	-69.9	73.0	73.1	49.6	52.6
6-7	84.5	84.8	84.2	84.6	-95.0	-89.8	-88.4	-86.4
7-1	-35.7	-38.2	-35.6	-38.4	74.0	70.4	64.2	65.0
q^\dagger		25.0		29.4		81.2		20.6
A^\ddagger		86.0		85.1		97.4		86.2
B^\ddagger		35.1		35.3		31.5		35.5
Δ^\ddagger		181.9		181.8		360.1		342.5
Conformation	$TC'(1)$		$TC'(1)$		$C'(1)$		$TC(5)$	

* Erroneously stated as +32.6 by Chacko *et al.* (1971).

† Minimum value of equation (2).

‡ Calculated with formula (1).

Table 4. Bond distances (Å) and mutual separations (Å) between 'major' and 'minor' atoms in AHCA and DMPC

AHCA						
Bond	Chacko <i>et al.</i> (1971)		Our work			
	Major	Minor	Major	Minor	Mutual separation	
1-2	1.539 (23)	1.539 (23)	1.519	1.520	1-1'	0.059
2-3	1.491 (37)	1.479 (43)	1.520	1.521	2-2'	0.325
3-4	1.552 (38)	1.551 (45)	1.520	1.520	3-3'	1.297
4-5	1.457 (30)	1.457 (30)	1.520	1.518	4-4'	0.087
5-6	1.584 (37)	1.530 (56)	1.521	1.518	5-5'	0.346
6-7	1.459 (34)	1.566 (54)	1.518	1.519	6-6'	1.486
7-1	1.548 (22)	1.548 (22)	1.519	1.521	7-7'	0.314
1-8	1.492 (21)		1.541	1.545	8-8'	0.235
1-N	1.544 (20)		1.503	1.501	N-N'	0.339
8-O(1)	1.292 (20)		1.313	1.316	O(1)-O(1')	0.568
8-O(2)	1.234 (19)		1.234	1.236	O(2)-O(2')	0.466
DMPC						
Bond	Birnbaum <i>et al.</i> (1977)		Our work			
	Major	Minor	Major	Minor	Mutual separation	
1-2	1.531 (4)	1.531	1.530	1.522	1-1'	0.296
2-3	1.527 (4)	1.527	1.530	1.521	2-2'	0.335
3-4	1.509 (4)	1.509	1.527	1.528	3-3'	0.407
4-5	1.507 (4)	1.507	1.518	1.522	4-4'	0.449
5-6	1.535 (4)	1.60	1.526	1.524	5-5'	0.546
6-7	1.512 (4)	1.52	1.522	1.509	6-6'	1.418
7-1	1.529 (4)	1.72	1.521	1.528	7-7'	0.501
1-O(1)	1.433 (3)		1.435	1.421	O(1)-O(1')	0.414
1-P	1.829 (2)		1.834	1.824		

Discussion of the conformations

For the purpose of comparison, bond distances of AHCA and DMPC, together with the corresponding values obtained by earlier workers, are listed in Table 4. It must be emphasized again that the new bond lengths contain no new information and that no realistic e.s.d.'s can be given. The new ring valency angles, which vary between 115.1 and 116.0°, are omitted.

However, two bonds in AHCA, C(1)-C(8) and C(1)-N (see Table 4), require comment. In the earlier determination the length of the former [1.492 (21) Å] is too short, whereas the length of the latter [1.544 (20) Å] is too long. At the start of our refinement, these bonds showed a strong tendency to assume their normal values; this was a further reason to constrain their values to 1.54 and 1.50 Å, respectively.

Table 4 also contains the distances between corresponding major and minor atoms. With the exception of three large separations (≥ 1.3 Å), these distances vary between 0.06 and 0.6 Å and are in the range of significant overlap in a conventional least-squares refinement.

The observed and calculated dihedral angles (Table 3, columns *c* and *d*) indicate that the conformations of the major and minor rings nearly coincide with the most stable twist-chair, as predicted by Hendrickson (1967), and not with the boat favoured by Bocian *et al.*

(1975).* Interestingly, the major as well as the minor cycloheptane rings of AHCA are nearly ideal twist-chairs, *TC*, with a dyad axis running through C(1) and the midpoint of the C(4)-C(5) bond, see Fig. 2. However, the minor ring, *TC'*(1), is inverted with respect to the major ring, *TC*(1). As was pointed out by FR, exocyclic axial and equatorial bonds change their function upon inversion of the ring, with the exception of the isoclinic bonds connected to the ring C atom through which the dyad axis runs. If the fragment C(7)-C(1)-C(2) is not disturbed by inversion one would, therefore, expect no disorder for atoms C(8) and N. C(1), indeed, hardly moves [C(1)-C(1') = 0.06 Å], but C(2) and C(7) shift considerably [C(2)-C(2') = 0.32 and C(7)-C(7') = 0.31 Å]. Apparently this condition is not fulfilled and the carboxyl group C(8)OOH and the NH₃⁺ group must of necessity be disordered.

In DMPC the resulting forms are also twist-chairs. The conformation of the major ring is a nearly perfect *TC'*(1), whose phase angle Δ deviates slightly (1.8°) from the ideal value (180°). The minor ring ($\Delta = 342.5^\circ$) is intermediate between *C'*(1) ($\Delta = 360^\circ$) and *TC*(5) ($\Delta = 334^\circ$). According to the results of

* In our earlier communication (FL) ring 2*P* was observed to possess the boat conformation *B/TB*. However, according to the results of a continued constrained refinement by Verschoor (1979) only five *TC* forms are present in CACC.

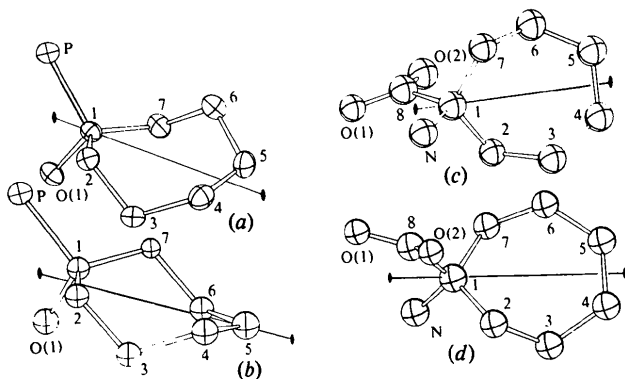


Fig. 2. ORTEP (Johnson, 1965) projections of the major and minor forms of (a) and (b) DMPC, and (c) and (d) AHCA.

Birnbaum *et al.* (1977), the minor ring would display the chair conformation $C'(1)$. In the earlier determinations (Table 4, columns *a* and *b*) the two cycloheptane rings of AHCA are too flat and display too small B values ($B_{av} = 25^\circ$ instead of 35°), whereas the minor form of DMPC is overpuckered and possesses a too large A parameter ($A = 97^\circ$ instead of 87°).

Packing

Disordered molecular structures must meet the following requirements:

(i) The packing of the alternative atoms gives rise to an alternative structure which obeys the packing rules that exist in the original structure.

(ii) The alternative atomic positions in the disturbed part must not violate the packing rules in the undisturbed part of the structure.

A part of the structure of AHCA is shown in Fig. 3 as a projection along $[001]$. The alternative molecules are drawn with thin lines, while alternative distances are given in parentheses. The NH_3^+ group donates three H atoms to form bridges to Br(i), Ow(i) and Ow(ii). The

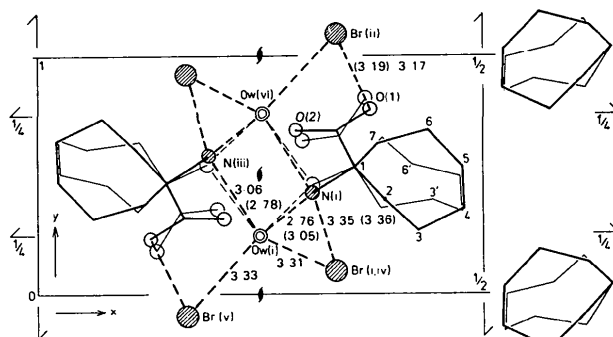


Fig. 3. Projection of a part of the structure of AHCA along $[001]$. Bold and thin lines correspond to major and minor molecules. Distances are given in Å. The numbers in parentheses refer to distances involving the minor molecules.

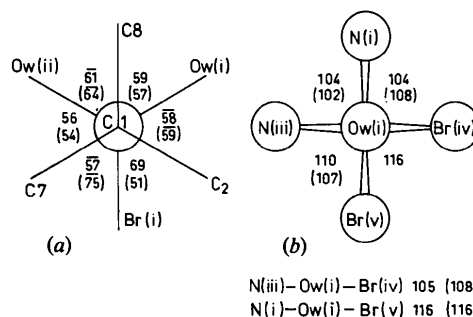


Fig. 4. (a) Newman projection along C(1)–N in AHCA and (b) coordination of water molecule Ow(i) in AHCA. (i) = x, y, z ; (ii) = $\frac{1}{2} - x, 1 - y, \frac{1}{2} + z$; (iii) = $\frac{1}{2} - x, 1 - y, -\frac{1}{2} + z$; (iv) = $x, y, -1 + z$; (v) = $\frac{1}{2} - x, -y, -\frac{1}{2} + z$.

Newman projection along C(1)–N (Fig. 4a) indicates that these hydrogen bonds are staggered with respect to the C(1)–C(2), C(1)–C(7) and C(1)–C(8) bonds. The same situation exists in the alternative structure except that the short and long N–H...O hydrogen bonds to Ow(i) and Ow(ii) have interchanged their roles. Moreover, these bonds maintain the mentioned staggered directions. We also note that the distance between Br and O(1) hardly changes if O(1) occupies a site of the minor molecule. Fig. 4(b) shows that the tetrahedral directions of the hydrogen bonds to Ow are hardly affected if minor atoms are involved.

Intermolecular van der Waals contacts involving H atoms govern the structure of the hydrophobic part of AHCA (the layers perpendicular to $[100]$ at $x = 0$ and $x = \frac{1}{2}$) by means of the screw operations $-x, \pm\frac{1}{2} + y, \pm\frac{1}{2} - z$ and $1 - x, \pm\frac{1}{2} + y, \pm\frac{1}{2} - z$. With one exception, these H...H distances between major, minor or mixed molecules are greater than 2.37 Å. The distance H(61)...H(5'1) between a major and a minor molecule is, however, too small (2.03 Å). Such a small distance may well explain why the ratio of major to minor molecules is not 1:1 and may be indicative of the existence of small domains and the absence of perfect disorder.

Two DMPC molecules are connected *via* a centre of symmetry by two O(1)–H...O(2) hydrogen bonds to give a dimeric unit. The length of these bridges (2.735 Å) is enlarged to 2.825 Å if one or two minor molecules are involved in these pairs. All other intermolecular contacts in DMPC are van der Waals interactions. With one exception, these distances between the H atoms of major, minor or mixed molecules are greater than 2.23 Å. The 'forbidden' distance, 1.96 Å for H(81)...H(6'1), involving a methyl H and an H in the minor molecule, indicates that the orientation of the C(8)H₃ group of the minor molecule has to be adapted in order to accommodate the packing. In view of the enlarged hydrogen bridge and the more disagreeable van der Waals contact, it is conceivable that the minor molecules only occur with an occupancy ratio of 0.07.

Interestingly, de Kok & Romers (1978) observed no forbidden H...H interactions in the totally disordered structure of *trans*-tetrachlorostilbene, in which the two molecules are present in a 1:1 ratio. Tentatively, we conclude that the mentioned packing rules are totally fulfilled in this compound and nearly so in AHCA and DMPC.

The authors thank Dr G. I. Birnbaum for his willingness to put at our disposal the diffraction data of dimethyl 1-hydroxy-1-cycloheptanephosphonate.

References

- BIRNBAUM, G. I., BUCHANAN, G. W. & MORIN, F. G. (1977). *J. Am. Chem. Soc.* **99**, 6652–6656.
- BOCIAN, D. F., PICKETT, H. M., ROUNDS, T. C. & STRAUSS, H. L. (1975). *J. Am. Chem. Soc.* **97**, 687–695.
- CAMERON, T. S. & SCHEEREN, H. W. (1977). *J. Chem. Soc. Chem. Commun.* pp. 939–941.
- CHACKO, K. K., SRINIVASAN, R. & ZAND, R. (1971). *J. Cryst. Mol. Struct.* **1**, 213–224.
- COMBREMONT, J. J. & GERDIL, R. (1979). 5th Eur. Crystallogr. Meet., Copenhagen, Abstr. 89-P1-5b.
- FLAPPER, W. M. J. (1976). Doctoral Thesis, Univ. of Leiden.
- FLAPPER, W. M. J. & ROMERS, C. (1975). *Tetrahedron*, **31**, 1705–1713.
- FLAPPER, W. M. J., VERSCHOOR, G. C., RUTTEN, E. W. M. & ROMERS, C. (1977). *Acta Cryst.* **B33**, 5–10.
- HAMILTON, W. C. (1965). *Acta Cryst.* **18**, 502–510.
- HENDRICKSON, J. B. (1967). *J. Am. Chem. Soc.* **89**, 7036–7046.
- International Tables for X-ray Crystallography* (1974). Vol. IV. Birmingham: Kynoch Press.
- JOHNSON, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee.
- KOK, A. J. DE & ROMERS, C. (1978). *Acta Cryst.* **B34**, 2477–2479.
- Molecular Structures and Dimensions* (1972). Utrecht: Oosthoek.
- NORRESTAM, R., HOVMÖLLER, S., PALM, T. B., GÖTHE, R. & WACHTMEISTER, C. A. (1977). *Acta Cryst.* **B33**, 370–376.
- VERSCHOOR, G. C. (1979). Personal communication.
- WASER, J. (1963). *Acta Cryst.* **16**, 1091–1094.

Acta Cryst. (1980). **B36**, 1893–1897

The Structure of Chenodeoxycholic Acid, C₂₄H₄₀O₄

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(Received 23 July 1979; accepted 28 February 1980)

Abstract

Crystals of the high-melting polymorph (m.p. 438–439 K) of chenodeoxycholic acid are monoclinic, space group *P*2₁, with *a* = 18.785 (14), *b* = 8.120 (6), *c* = 14.889 (11) Å, β = 99.10 (2)° and *Z* = 4. The structure has been refined to a residual of 0.069 for 3266 independent significant reflections measured on an automated four-circle diffractometer. The two molecules in the asymmetric unit are typical of the bile acids with *cis* *A/B* ring junctions, but are different from

each other with respect to the conformations of the 17β side chains. In the crystal all the hydroxyl and carboxyl groups are involved in a hydrogen-bonding network.

Introduction

In recent years there has been a resurgence of interest in the bile acid field. This is related to the introduction of chenodeoxycholic acid (CDCA) as a chemotherapeutic alternative to surgery in the treatment of gallstones (Dowling & Bell, 1973; Danziger, Hofmann, Thistle & Schoenfield, 1973).

Its ingestion in suitable quantity alters the composition of bile so that it becomes the dominant bile

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