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The Structure of *cis*-4-(Aminomethyl)cyclohexanecarboxylic Acid (*cis*-AMCHA) Hemihydrate

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Abstract. $NH_2CH_2C_6H_{10}COOH.\frac{1}{2}H_2O$, M_r = 166·22, monoclinic, space group $C2/c$, a = 20·2976 (14), b = 5·9325 (6), c = 15·3275 (7) Å, β = 109·192 (6)°, Z = 8, D_m = 1·262, D_c = 1·267 Mg m^{-3}, Cu $K\alpha$ radiation. The structure was solved by the direct method. Block-diagonal least-squares refinement gave R = 0·057 for 1261 independent reflections. The molecules are found to exist in the chair form with an equatorial aminomethyl group and an axial carboxyl group.

Introduction. One of the two stereoisomers of 4-(aminomethyl)cyclohexanecarboxylic acid (AMCHA), *trans*-AMCHA, shows strong antiplasmic activity, and with small doses it shows reliable hæmostatic (Shimizu, Naito, Okano & Aoyagi, 1965) and anti-inflammatory activities (Yamazaki, Tsuji & Kitamura, 1967). However, *cis*-AMCHA is almost inactive.

The crystal structures of the hydrobromide and free form of *trans*-AMCHA, and of the hydrochloride of *cis*-AMCHA have already been determined (Kadoya, Hanazaki & Iitaka, 1966). However, the crystal structure of the free form of *cis*-AMCHA was not revealed, so this study was undertaken to examine its conformation.

cis-AMCHA was synthesized according to the method of Naito *et al.* (1968).

The lattice parameters and three-dimensional intensity data were derived from the measurements using a Philips four-circle X-ray diffractometer with graphite-monochromated Cu $K\alpha$ radiation (λ = 1·5418 Å). A total of 1261 independent reflections were obtained by the θ–2θ scan method with scan speed of 4° min^{-1}. Since the size of the crystal used for measurements was approximately 0·2 × 0·2 × 0·1 mm, no absorption correction was applied. The systematic absences ($h + k$ odd in hkl and l odd in $h0l$) indicate the space group $C2/c$.

The structure was solved by the direct method with the program *MULTAN* (Germain, Main & Woolfson, 1971) using 147 normalized structure factors ($E \geq 2{\cdot}50$).

The E map gave the location of all the non-H atoms. Difference syntheses revealed all the H atoms at the expected positions. Refinement was carried out by the block-diagonal least-squares method including isotropic H atoms. The final R value was 0·057.

The atomic parameters and their estimated standard deviations are listed in Table 1.*

Discussion. The bond lengths and angles of *cis*-AMCHA are shown in Fig. 1.

Table 1. *Positional parameters* ($\times 10^4$) *and isotropic thermal parameters with e.s.d.'s in parentheses*

$B_{\rm iso}$ for the non-H atoms is calculated by the expression
$B_{\rm iso} = \frac{4}{3}\sum_i \sum_j \beta_{ij}\,(\mathbf{a}_i.\mathbf{a}_j)$.

	x	y	z	$B_{\rm iso}$ (Å^2)
O(H_2O)	0	3853 (7)	2500	5·19 (0·13)
C(1)	3891 (1)	4837 (5)	1310 (2)	2·27 (0·07)
C(2)	4555 (1)	4103 (6)	1119 (2)	2·65 (0·08)
C(3)	4434 (1)	2424 (6)	334 (2)	2·53 (0·08)
C(4)	3867 (1)	3171 (5)	−555 (2)	2·15 (0·07)
C(5)	3199 (1)	3797 (6)	−353 (2)	2·50 (0·07)
C(6)	3333 (2)	5579 (6)	397 (2)	2·73 (0·08)
C(7)	3570 (1)	3096 (5)	1784 (2)	2·04 (0·07)
C(8)	3762 (2)	1290 (6)	−1262 (2)	2·72 (0·08)
N	3217 (1)	1795 (4)	−2170 (2)	2·27 (0·06)
O(1)	3699 (1)	1054 (4)	1749 (1)	3·14 (0·06)
O(2)	3163 (1)	3859 (4)	2193 (1)	3·09 (0·06)
H(H_2O)	−26 (24)	4205 (88)	1938 (28)	10·77 (1·34)
H(C1)	4048 (18)	6154 (67)	1764 (24)	4·62 (0·88)
H1(C2)	4883 (15)	3439 (57)	1666 (20)	3·06 (0·69)
H2(C2)	4787 (17)	5577 (62)	984 (22)	3·79 (0·79)
H1(C3)	4327 (13)	1061 (51)	514 (18)	1·84 (0·58)
H2(C3)	4897 (17)	2156 (61)	181 (22)	3·53 (0·77)
H(C4)	4042 (16)	4618 (59)	−801 (21)	3·29 (0·75)
H1(C5)	2982 (15)	2442 (56)	−207 (20)	2·76 (0·68)
H2(C5)	2811 (16)	4312 (58)	−933 (21)	3·06 (0·72)
H1(C6)	2842 (18)	6089 (71)	498 (24)	4·95 (0·94)
H2(C6)	3472 (16)	6937 (57)	212 (21)	3·13 (0·73)
H1(C8)	3605 (17)	−96 (63)	−1072 (23)	4·09 (0·82)
H2(C8)	4237 (18)	957 (68)	−1363 (24)	4·63 (0·89)
H1(N)	3222 (19)	3279 (69)	−2425 (25)	5·00 (0·94)
H2(N)	2729 (18)	1807 (70)	−2152 (24)	5·12 (0·95)
H3(N)	3227 (19)	861 (71)	−2575 (25)	5·38 (0·96)

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* Lists of structure factors and anisotropic thermal parameters of non-H atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35898 (6 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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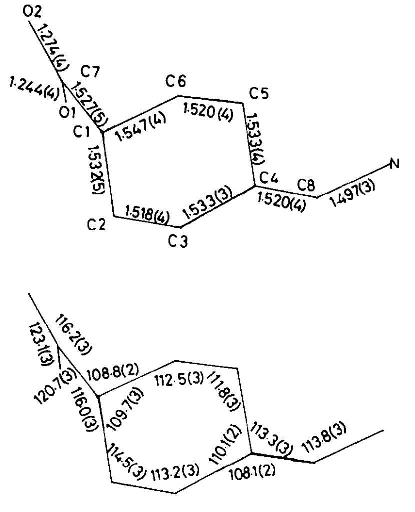


Fig. 1. Bond lengths (Å) and bond angles (°).

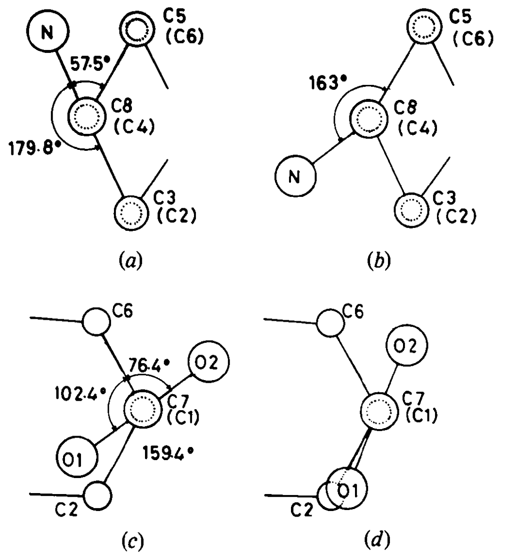
Table 2. *Internal rotation angles of the six-membered ring*

C(2)–C(1)–C(6)–C(5)	53·2 (3)°
C(3)–C(2)–C(1)–C(6)	−50·2 (3)
C(4)–C(3)–C(2)–C(1)	51·1 (4)
C(5)–C(4)–C(3)–C(2)	−51·9 (3)
C(6)–C(5)–C(4)–C(3)	55·3 (3)
C(1)–C(6)–C(5)–C(4)	−57·5 (3)

Table 3. *Deviations from the least-squares plane of the six-membered ring with e.s.d.'s in parentheses*

C(1)	−0·208 (3) Å	C(5)	−0·249 (3) Å
C(2)	0·198 (3)	C(6)	0·243 (3)
C(3)	−0·206 (3)	C(7)*	−1·693 (4)
C(4)	0·223 (3)	C(8)*	0·319 (3)

* Not included in the calculation of the plane.



(*a*) (*b*)

(*c*) (*d*)

Fig. 2. (*a*), (*b*) Projections of the aminomethyl group along the C(8)–C(4) bond showing the orientation of the aminomethyl group in (*a*) the present molecule and (*b*) its hydrochloride. (*c*), (*d*) Projections of the carboxyl group along the C(7)–C(1) bond showing the orientation of the carboxyl group in (*c*) the present molecule and (*d*) its hydrochloride.

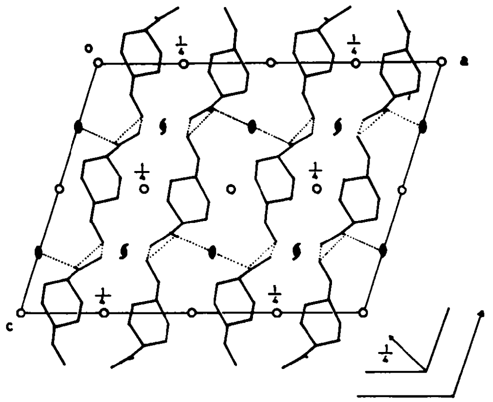


Fig. 3. Crystal structure viewed along the *b* axis.

The cyclohexane ring exists in the chair form. Table 2 shows that internal rotation angles of the cyclohexane ring are all in the *gauche* conformation.

The N atom of the aminomethyl group exists in the protonated form. Since the two C—O bond distances of the carboxyl group are nearly equal, the carboxyl group is negatively charged and resonant. Thus the molecule is in the zwitterionic form.

The carboxyl group [O(1),O(2),C(1),C(7)] is planar within the limit of experimental error. This plane is approximately perpendicular to the mean plane of the cyclohexane ring.

As seen from Table 3, the carboxyl group is axially oriented from the ring while the aminomethyl group is equatorially oriented.

Fig. 2 shows the orientation of the aminomethyl and carboxyl groups from the ring in the present molecule and its hydrochloride. The N atom of the aminomethyl group of the former is situated almost at the *trans* position to C(3). Similarly the corresponding N atom of the latter, in the protonated form, is situated nearly at the *trans* position to C(5).

In the hydrochloride, the rotation of the carboxyl group about C(1)–C(7) is such that C(2) is almost eclipsed by O(1), though O(1) rotates 21·7° around C(1)–C(7) in the present molecule. The carboxyl O does not lie at the intermediate position between C(6) and C(2).

The projection of the crystal structure along the *b* axis is shown in Fig. 3. The neighbouring molecules are connected by intermolecular hydrogen bonds between the aminomethyl group and the carboxyl group [N···O(1) 2·76 Å, N···O(2) 3·48 Å] to form chains extending along the *c* axis. Each water molecule on the twofold axis makes a bridge over two molecules through the hydrogen bonds to the carboxyl group [O(H_2O)···O(1) 2·83 Å].

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3,4-Dimethyl-5-thioformylimino-4*H*-1,2,4-thiadiazoline

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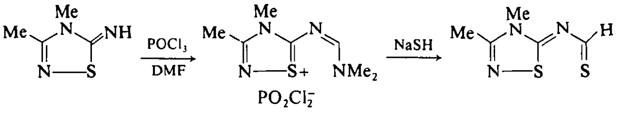
Abstract. $C_5H_7N_3S_2$, monoclinic, $P2_1/m$, $a = 7·367$ (2), $b = 6·157$ (2), $c = 8·629$ (3) Å, $\beta = 93·20$ (3)°, $U = 390·79$ Å^3, $M_r = 173·26$, $D_c = 1·472$ Mg m^{-3} for $Z = 2$, $F(000) = 180$, Mo $K\alpha$ radiation, $\lambda = 0·71069$ Å, μ(Mo $K\alpha$) = 0·544 mm^{-1}, $R = 0·0945$ for 641 reflections. The molecules of the title compound are disordered across the mirror plane with site-occupation factors of 0·5. The title compound does not contain a hypervalent S atom.

Introduction. Treatment of the imine (I) with phosphoryl chloride in dimethylformamide solution yielded the Vilsmeier salt (II), which reacted with sodium hydrogen sulphide solution to give the title compound (III) (Mitchell, 1979):



(I) (II) (III)

Crystals suitable for X-ray investigation were provided by Professor D. H. Reid and Dr J. A. Mitchell.

Data were collected using a Stoe STADI-2 two-circle automatic diffractometer with graphite-crystal-monochromatized Mo $K\alpha$ radiation for a crystal of dimensions 0·2 × 0·4 × 0·2 mm mounted about **b**. The intensities of 840 reflections in the quadrant $\pm h,+k,+l$ with $2° \leq \theta \leq 30°$, k 0–9 ($0 \leq \mu \leq 31·294°$) were measured using the ω–2θ scan mode with a step width of 0·01° in ω, a time of 1·0 s per step and 120–140 steps per scan. Backgrounds were measured at both ends of the scan for a time of (scan time/2). Standard reflections were measured every 30 reflections and showed only small random deviations from their means. Lorentz and polarization corrections were applied to the data, but no corrections for absorption were made. Systematic absences: $0k0$, $k \neq 2n$ indicated the space group to be $P2_1$ (C_2^2, No. 4) or $P2_1/m$ (C_{2h}^2, No. 11).

The E statistics strongly suggested centrosymmetry, although $P2_1$ was thought the more likely space group since $Z = 2$. The structure was solved in $P2_1$ using *SHELX* 76 (Sheldrick, 1976). The best E map gave the positions of all the non-H atoms for two molecules related by an apparent mirror plane, indicating a disordered structure: other solutions were similar. An identical structure solution was obtained by use of *MULTAN* 78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). Initial refinement was carried out, using *SHELX* 76, in $P2_1$, with the least-squares matrix blocked so that the two independent molecules refined separately in alternate cycles. A common site-occupation factor (s.o.f.) was refined for each molecule, but the sum of the two s.o.f.'s was constrained to be unity. The two s.o.f.'s refined to values, identical within experimental error, of 0·5 [0·488 (14) and 0·512 (14)]. Refinement was therefore continued in $P2_1/m$, with the s.o.f.'s of all atoms fixed at 0·5. Three cycles of full-matrix least-squares refinement with individual isotropic temperature parameters for all non-H atoms yielded an $R(= \sum\Delta/\sum F_o,\ \Delta = |F_o - |F_c||)$ of 0·1619 and an $R_G[= (\sum w\Delta^2/\sum wF_o^2)^{1/2}]$ of 0·1722 for 641 reflections with $F_o \geq 4\sigma(F_o)$. The introduction of anisotropic temperature parameters for the two S atoms in three further cycles of refinement reduced R to 0·1159 and R_G to 0·1241. Weighting

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