

Fig. 4. Relative orientation of neighboring molecules in adjacent layers: (a) for (1 α), (b) for (1 β).

phase transition of (1 α) to (1 β) are reminiscent of the transition reported for binaphthyl (Pincock & Wilson, 1971; Pincock, Perkins, Ma & Wilson, 1971). While the transformation (1 α) to (1 β) involves a conversion from a racemic space group to a chiral one, we have not been able to measure the optical purity of single crystals as had been done with binaphthyl.

It is also of interest that a thermally induced transition of a monoclinic form ($\beta \approx 90^\circ$) to an orthorhombic form of 2,3-dimethyl-1,4-naphthoquinone has been reported (Breton, Chanh & Housty, 1976) but complete structures of the two forms were not reported. It should also be noted that, whereas (4-hydroxy-3,5-dimethylphenyl)diphenylmethanol (2) and its 3,5-dibromo analog (4) are isostructural (Stora, 1971; Lewis, Curtin & Paul, 1979), there is no such relationship between any of the three forms of (1) and the two

forms of its 2,6-dibromo analog (3) that have been studied by X-ray methods (Racine-Weisbuch, 1969).

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Structure and Absolute Configuration of (*R*)-Alaproclate [2-(4-Chlorophenyl)-1,1-dimethylethyl 2-Aminopropanoate] Hydrochloride, a Selective Inhibitor of Neuronal 5-Hydroxytryptamine Uptake

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Abstract

The crystal structure and absolute configuration of (*R*)-alaproclate (pINN), 2-(4-chlorophenyl)-1,1-dimethylethyl 2-aminopropanoate hydrochloride, a compound which selectively inhibits neuronal 5-hydroxytryptamine uptake, have been determined. (*R*)-alaproclate hydrochloride hydrate, C₁₃H₁₈ClNO₂·HCl·H₂O, crystallizes in space group *P2*₁ with

$a = 15.247(7)$, $b = 7.036(2)$, $c = 7.916(3)$ Å, $\beta = 97.81(4)^\circ$ and $Z = 2$. The structure was solved using the heavy-atom method. Full-matrix least-squares refinement resulted in a final *R* value of 0.05. The absolute configuration was determined by measuring Bijvoet differences. Potential-energy maps for a free molecule have been calculated. The calculations indicate that the side chain is flexible and may exist in several conformations with minor differences in potential energy.

Introduction

(*R*)-Alaproclate hydrochloride has been found to be a potent, selective and competitive inhibitor of the accumulation of 5-hydroxytryptamine (5-HT) in brain slices and homogenates (Lindberg, Thorberg, Bengtsson, Renyi, Ross & Ögren, 1978). *In vitro* studies have shown that (*R*)-alaproclate is 250 times more selective in inhibiting the neuronal accumulation of 5-HT than that of noradrenaline. (*R*)-alaproclate is in this respect 145 times more selective as an inhibitor of 5-HT uptake than chlorimipramine, whereas its potency is one third that of chlorimipramine (Lindberg, Ross, Thorberg, Ögren, Malmros & Wägner, 1978). In a hypothalamic synaptosomal preparation from rat the (+)-enantiomer of alaproclate was three times more potent in inhibiting the accumulation of 5-HT than the (–)-form (Lindberg, Ross, Thorberg, Ögren, Malmros & Wägner, 1978). In order to elucidate the structural requirements of the molecule to compete with 5-HT in the uptake mechanism on the presynaptic side of the nerve endings, a structure determination of the (+)-enantiomer was performed. Potential-energy maps were calculated to describe the flexibility of the side chain.

Experimental

Crystals of alaproclate were supplied by Dr U. H. Lindberg, Astra Läkemedel AB, Sweden. The substance was recrystallized from a dilute solution in acetone. Accurate cell dimensions were obtained from an X-ray powder diffraction photograph, taken in a Guinier–Hägg focusing camera with strictly monochromatized Cu $K\alpha_1$ radiation ($\lambda = 1.54056 \text{ \AA}$) and KCl as an internal standard ($a = 6.2930 \text{ \AA}$). The photograph was measured by an automatic film-scanner system described by Malmros & Werner (1973). Crystal data are given in Table 1.

A crystal of approximate dimensions $0.15 \times 0.24 \times 0.075 \text{ mm}$ was mounted on a goniometer head with the φ axis approximately along the b axis. The crystal was used for data collection and measurements of Bijvoet differences. Intensity data were collected on a computer-controlled single-crystal diffractometer (Philips PW 1100) with graphite-monochromatized Cu $K\alpha$ radiation. 1473 reflections up to $2\theta = 120^\circ$

Table 1. *Crystal data*

$C_{13}H_{18}ClNO_2 \cdot HCl \cdot H_2O$, $M_r = 311.23$	$Z = 2$
Monoclinic, $P2_1$	$F(000) = 324$
$a = 15.247 (7) \text{ \AA}$	$D_m = 1.24 \text{ Mg m}^{-3}$
$b = 7.036 (2)$	$D_c = 1.22$
$c = 7.916 (3)$	$\lambda = 1.5418 \text{ \AA}$ for Cu $K\alpha$
$\beta = 97.81 (4)^\circ$	$\mu = 3.535 \text{ mm}^{-1}$
$V = 841.34 \text{ \AA}^3$	
Systematic absences:	
$0k0$ for $k = 2n + 1$	

were collected with θ – 2θ scans of 1.8° scan width at a speed of $0.02^\circ \text{ s}^{-1}$. Backgrounds were measured by stationary counts on each side of the peaks. 871 reflections having $\sigma(I)/I < 0.303$ were considered as significantly observed and were used in the subsequent calculations. Lorentz and polarization factors were applied but no corrections for absorption or extinction were made.

Structure determination and refinement

The structure was solved by the heavy-atom method. The positions of the two independent Cl atoms were determined from a three-dimensional Patterson synthesis. Successive use of Fourier and difference Fourier syntheses revealed all the non-hydrogen atomic positions. Full-matrix least-squares refinement with isotropic temperature factors gave an R value of 0.12. Anisotropic thermal parameters were then assigned and further refinement lowered the R value to 0.071. From a difference Fourier synthesis the positions of all H atoms except those belonging to the water molecule could be deduced. Since many H-atom positions could not be accurately refined they were calculated from geometrical conditions assuming a C–H and N–H distance of 1.08 \AA . The H atoms were then included in the full-matrix least-squares refinement with the C–H and N–H vectors held constant in both magnitude and direction. An overall isotropic temperature factor of 0.05 \AA^2 was assigned to the H atoms. During the final stage of the refinement a weighting scheme was introduced as $w = 1.65/[\sigma^2(F) + 0.001099F^2]$ and the function minimized was $\sum w(|F_o| - |F_c|)^2$. The final

Table 2. *Fractional coordinates ($\times 10^4$) for the non-hydrogen atoms*

Estimated standard deviations are given in parentheses.

	x	y	z
Cl(2)	9260 (2)	0	2368 (2)
Cl(1)	4144 (3)	5143 (9)	6674 (4)
C(1)	3712 (9)	4348 (19)	4657 (13)
C(2)	4216 (8)	4562 (21)	3357 (15)
C(3)	3881 (7)	3853 (20)	1754 (14)
C(4)	3073 (6)	2998 (15)	1462 (12)
C(5)	2573 (6)	2852 (15)	2817 (12)
C(6)	2891 (7)	3532 (17)	4393 (13)
C(7)	2698 (6)	2272 (16)	–280 (11)
C(8)	2892 (6)	216 (19)	–619 (10)
C(9)	2496 (6)	–395 (18)	–2417 (10)
C(10)	3861 (6)	–317 (20)	–223 (13)
C(11)	1635 (6)	–1234 (14)	601 (9)
C(12)	1441 (5)	–2777 (14)	1819 (9)
C(13)	1636 (7)	–2086 (18)	3659 (10)
O(1)	2503 (4)	–1083 (10)	596 (6)
O(2)	1077 (4)	–283 (11)	–234 (7)
O _{aq}	386 (5)	3671 (12)	3706 (7)
N	504 (5)	–3328 (11)	1433 (8)

Table 3. Fractional coordinates ($\times 10^3$) for the H atoms

Estimated standard deviations are given in parentheses.

	x	y	z
H(2)	485 (1)	526 (2)	357 (2)
H(3)	427 (1)	399 (2)	72 (1)
H(5)	193 (1)	219 (2)	261 (1)
H(6)	250 (1)	343 (2)	543 (1)
H(71)	199 (1)	245 (2)	-42 (1)
H(72)	297 (1)	313 (2)	-122 (1)
H(91)	275 (1)	50 (2)	-334 (1)
H(92)	178 (1)	-26 (2)	-256 (1)
H(93)	267 (1)	-186 (2)	-262 (1)
H(101)	424 (1)	51 (2)	-101 (1)
H(102)	394 (1)	-181 (2)	-48 (1)
H(103)	409 (1)	-4 (2)	110 (1)
H(12)	186 (1)	-399 (1)	167 (1)
H(131)	232 (1)	-169 (2)	394 (1)
H(132)	150 (1)	-321 (2)	451 (1)
H(133)	122 (1)	-87 (2)	383 (1)
N(H1)	36 (1)	-443 (1)	230 (1)
N(H2)	37 (1)	-384 (1)	14 (1)
N(H3)	9 (1)	-211 (1)	158 (1)

R values obtained were 0.051* for $R = \sum ||F_o| - |F_c|| / \sum |F_o|$ and 0.055 for $R_w = \sum w^{1/2} ||F_o| - |F_c|| / \sum w^{1/2} |F_o|$. Atomic scattering factors for the non-hydrogen atoms were taken from Cromer & Mann (1968) and for the H atoms from Stewart, Davidson & Simpson (1965). Final atomic coordinates are given in Tables 2 and 3.

Potential-energy calculations

The potential interaction energies were calculated from the sum of the Lennard-Jones (6,12) potential

$$\sum_{i>j} (B_{ij}r_{ij}^{-12} + A_{ij}r_{ij}^{-6})$$

and the electrostatic 'monopole' approximation

$$\sum_{i>j} q_i q_j \epsilon^{-1} r_{ij}^{-1},$$

where q_i is the electric charge for the i th atom and ϵ ($=1$) the dielectric constant. The A_{ij} values were derived from the Slater-Kirkwood equation (Slater & Kirkwood, 1931):

$$A_{ij} = \frac{3}{2} e h m^{-1/2} \alpha_i \alpha_j [(\alpha_i/N_i)^{1/2} + (\alpha_j/N_j)^{1/2}]^{-1}.$$

The B_{ij} values were derived from the requirement that the Lennard-Jones potentials have minima at the sum of the van der Waals distances ($R_i + R_j$). The values of

α_i (the atomic polarizabilities), N_i (the effective valence number) and R_i (the van der Waals distances) were taken from Scheraga (1968), except for the Cl atom where $R_i = 1.8 \text{ \AA}$ was used. Charges, also shown in Fig. 1, were calculated by CNDO.

Potential-energy maps were calculated by varying the torsion angles τ_1 - τ_3 two at a time along the side chain. The torsion angles are depicted in Fig. 1, and listed in Table 4. It can be seen from these calculations that the crystal structure corresponds to a minimum-energy conformation of a free molecule (*cf.* Fig. 2*a-d*). The energy minima are sharply defined for the torsion angles τ_1 - τ_3 , but more extended for the τ_4 - τ_5 map, as seen in Fig. 2(*d*). The result from the τ_4 - τ_5 map indicates that the terminal part of the side chain is allowed a certain rotational freedom and could therefore probably exist in several conformations in solution with only minor energy differences.

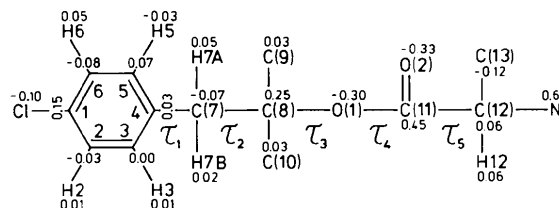


Fig. 1. The result from the CNDO calculation together with the notation of the torsion angles.

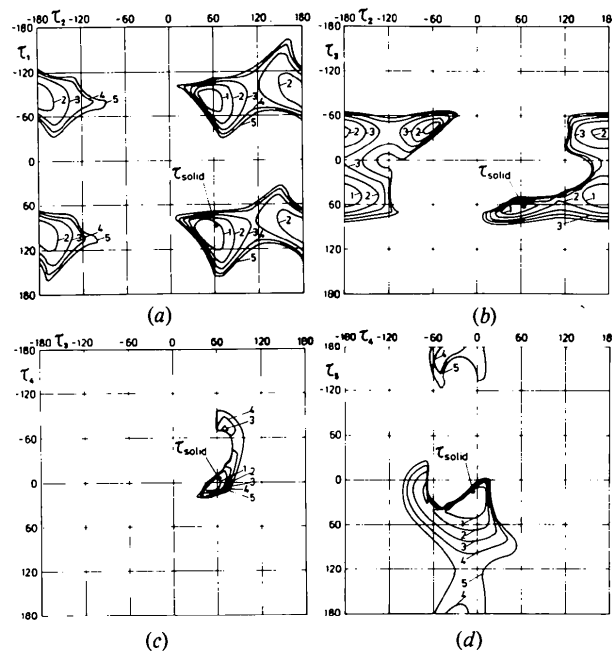


Fig. 2. Results from the potential-energy calculations in kcal mol⁻¹ (1 kcal mol⁻¹ \equiv 4.2 kJ mol⁻¹). The solid state is marked •. Torsion angles τ_i ($^\circ$) are as defined in Table 4.

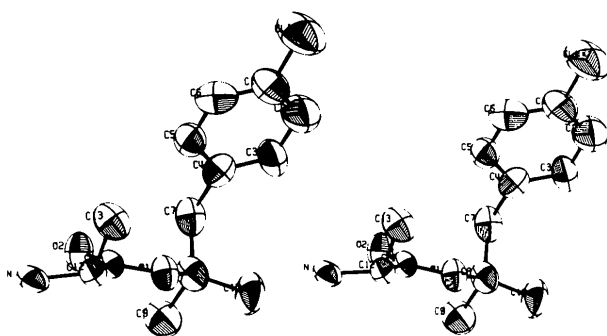
* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34693 (5 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 4. Torsion angles of the side chain

τ_1	C(3)–C(4)–C(7)–C(8)	92.5 (12)°
τ_2	C(4)–C(7)–C(8)–O(1)	61.6 (11)
τ_3	C(7)–C(8)–O(1)–C(11)	64.8 (11)
τ_4	C(8)–O(1)–C(11)–O(2)	–6.0 (13)
τ_5	O(2)–C(11)–C(12)–N	17.4 (12)

Table 5. Calculated (X_c) and observed (X_o) Bijvoet ratios ($\times 10^2$)

hkl	Cu $K\alpha$ radiation was used.			F_{obs}
	X_c	X_o	θ	
1 1 0	–57.6	–79.0	6.94	7.56
0 1 1	88.3	83.6	8.46	7.53
0 2 0	–10.0	–14.7	12.65	72.54
1 1 2	–5.1	–7.1	13.68	56.11
5 1 0	–8.6	–9.9	16.12	31.83
3 2 1	18.9	14.1	16.97	23.39
0 2 2	24.6	20.2	17.12	19.59
1 1 3	55.7	44.0	18.96	9.81
1 3 0	19.4	11.7	19.42	17.47
6 1 1	12.8	17.3	20.58	28.82
3 3 0	–19.8	–20.5	21.26	25.03
1 1 4	–27.3	–26.8	24.70	14.87

Fig. 3. Stereoview showing the absolute configuration of (*R*)-alaproclate.

Absolute configuration

The absolute configuration of (*R*)-alaproclate has been determined by measuring Bijvoet differences. The Bijvoet ratio was calculated for each Friedel pair up to $\theta = 30^\circ$ and the 12 Friedel pairs exhibiting the greatest effect of anomalous scattering by the two Cl atoms were selected for measurements. The result presented in Table 5 shows that there is a good correspondence between calculated and observed Bijvoet pairs. The absolute configuration of (*R*)-alaproclate corresponds to the coordinates in Tables 2 and 3 and to Figs. 3 and 6.

Discussion

The absolute configuration of (*R*)-alaproclate is shown in Fig. 3. Bond lengths and bond angles for the non-

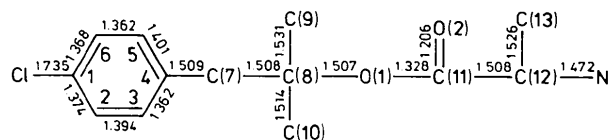


Fig. 4. Bond distances (Å). The e.s.d.'s vary from 0.009 to 0.015 Å.

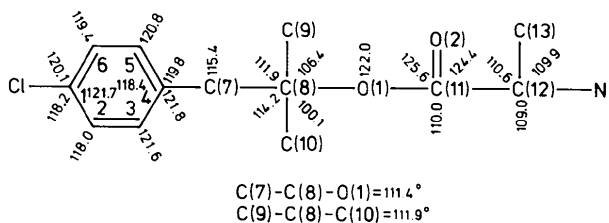


Fig. 5. Bond angles (°). The e.s.d.'s vary from 0.8 to 1.1°.

hydrogen atoms are given in Figs. 4 and 5. The N is positively charged since alaproclate is crystallized as a hydrochloride salt, and a positive charge is obtained from the CNDO calculation (*cf.* Fig. 1).

A projection of the crystal packing is shown in Fig. 6. A hydrogen-bond network, parallel with the *bc* plane, is formed by the chloride ion, the crystal water and the positively charged nitrogen. Each chloride ion is involved in four hydrogen bonds, two from H_2O molecules and two from an $-\text{NH}_3^+$ group. The $-\text{NH}_3^+$ group also forms a hydrogen bond to the crystal water. The hydrogen-bond distances are given in Table 6.

The side chain of (*R*)-alaproclate has a *gauche* conformation. Since (*R*)-alaproclate is a competitive inhibitor to 5-HT uptake it is possible that there exists a certain similarity between the structures of (*R*)-alaproclate and 5-HT. The preferred conformation for 5-HT in the solid state is not known since 5-HT itself is unstable and has so far only been crystallized as a

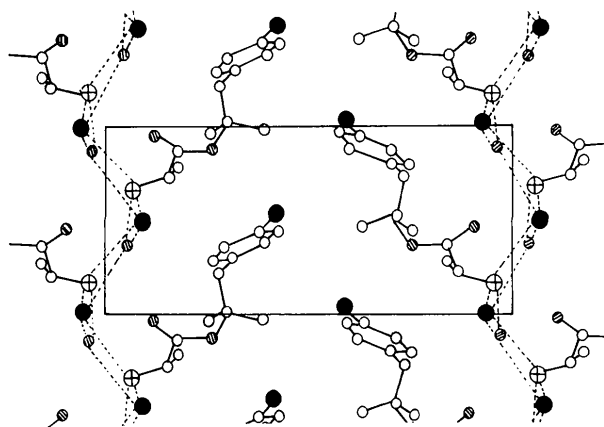
Fig. 6. Projection of the packing arrangement and hydrogen-bond system. The unit cell is oriented with the *a* axis horizontal, the *b* axis vertical and the *c* axis pointing towards the reader. ● Cl, ⊕ N, ⊙ O, ○ C.

Table 6. *Hydrogen-bond distances* (Å)

Symmetry code			
(i)	$-1 + x, y, z$	(iii)	$x, y - 1, z$
(ii)	$1 - x, y - \frac{1}{2}, -z$	(iv)	$1 - x, y + \frac{1}{2}, 1 - z$
N-Cl(2) ⁱ	3.164 (8)	O _{aq} -Cl(2) ⁱ	3.201 (8)
N-Cl(2) ⁱⁱ	3.296 (7)	O _{aq} -Cl(2) ^{iv}	3.220 (6)
N-O _{aq} ⁱⁱⁱ	2.795 (10)		

picrate salt (Thewalt & Bugg, 1970) and as a creatinine salt (Karle, Dragonette & Brenner, 1965). In the former, 5-HT has a *gauche* conformation and in the latter the side chain is fully extended. The structural and conformational requirements for (*R*)-alaproclate to compete with 5-HT in the uptake mechanism as well as stereochemical and electronic properties of a receptor model are discussed elsewhere (Lindberg, Thorberg, Bengtsson, Renyi, Ross & Ögren, 1978; Lindberg, Ross, Thorberg, Ögren, Malmros & Wägner, 1978).

The proposed mechanism for the 5-HT uptake requires that the distances between the protonated N and the centre of the benzene ring in (*R*)-alaproclate and 5-HT, respectively, are approximately equal. The distances obtained from the crystal structure determinations are 6.64 Å in (*R*)-alaproclate, 6.40 Å in the creatinine salt and 5.11 Å in the picrate salt of 5-HT. The distance obtained in (*R*)-alaproclate may well be compared to the corresponding distances of 6.55 and 6.11 Å in another antidepressant, the tricyclic compound chlorimipramine hydrochloride (Post & Horn, 1977).

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The Geometry of Small Rings.

I. Substituent-Induced Bond-Length Asymmetry in Cyclopropane

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Abstract

A subfile of numeric structural data for 299 X-ray studies of cyclopropane derivatives has been retrieved from the Cambridge Crystallographic Database. The geometries of 91 rings ($R \leq 0.10$) having electron-acceptor or electron-donor substituents have been analysed. Although individual bond-length asymmetries are quantitatively small there are consistent

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trends to support the results of MO calculations. For π -acceptor substituents the distal ring bond is *shortened* and vicinal bonds lengthened. Mean distal-bond shortenings, relative to the individual mean C–C(ring) distance, are established for C=O, C=C and C \equiv N as -0.026 (5), -0.022 (4) and -0.017 (2) Å. N=C, N=N and C=N are also implicated in effective acceptor interactions. *cis*- and *trans*-bisected conformations predominate, but for C=O, and possibly