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The Tricyclic Antidepressants: Imipramine Hydrochloride. The Crystal and Molecular Structure of 5-(3-Dimethylaminopropyl)-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine Hydrochloride

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The structure of imipramine hydrochloride, $C_{19}H_{24}N_2.HCl$, monoclinic with space group $P2_1/c$ and $a=11{\cdot}303$ (3), $b=29{\cdot}227$ (8), $c=14{\cdot}282$ (3) Å, $\beta=130{\cdot}91$ (1)°, $Z=8$, was determined by multi-solution direct methods and refined by full-matrix least-squares and conjugate gradient methods to an R of 0·057 for 2880 counter reflexions. The two molecules in the asymmetric unit have slightly different conformations of the seven-membered hetero-ring and one molecule appears to exhibit a small movement in the dimethylene bridge. Angles between benzene ring planes are 130·3 and 123·0°. The dimethylaminopropyl side chains exhibit different conformation and the amine nitrogen atoms and chloride ions form a layered arrangement in the lattice.

Introduction

Imipramine (Fig. 1) has been in use clinically since 1957 as a widely prescribed drug for treatment of depression. There is evidence that this and similar tricyclic drugs, such as desipramine and amitriptyline, act by inhibiting the process of uptake of the brain's biogenic amines, noradrenaline and 5-hydroxytryptamine, into the presynaptic nerve ending (Shaskan & Snyder, 1970; Horn, Coyle & Snyder, 1971; Horn & Trace, 1974), perhaps by effectively simulating the conformation of a biologically important region of the molecule and blocking the receptor site. The structure and possible conformation of a number of the tricyclic drugs are, therefore, under investigation by both X-ray diffraction and theoretical calculations (Horn, Kennard, Motherwell, Post & Rodgers, 1974); results for the rather atypical tricyclic drug, iprindole hydrochloride monohydrate have been reported (Rodgers, Kennard, Horn & Riva di Sanseverino).

Experimental

Powdered imipramine hydrochloride was obtained through the courtesy of Geigy Pharmaceuticals and good single crystals, which were air stable, were grown from a chloroform/xylene mixture. Attempts to grow crystals from ethanol/ethyl acetate mixtures yielded material which was slightly moisture sensitive and often twinned. A preliminary X-ray study employing a single crystal of such material, sealed in a capillary tube, suggested that over a period of 4–5 days a space-group change occurred in the solid state ($C2/c \rightarrow P2/c$ or $P2_1/c$).

Precession and Weissenberg photographic studies of the chloroform/xylene crystallized compound showed it to be monoclinic, space group $P2_1/c$ from systematic absences: $0k0$ k odd; $h0l$ l odd. Cell parameters were obtained by least-squares refinement of 2θ values of 27 general reflexions measured on a diffractometer.

Crystal data

$C_{19}H_{25}N_2Cl$	M.W. 316·86
Monoclinic	$D_c=1{\cdot}18$ g cm^{-3}
Space group $P2_1/c$	$D_m=1{\cdot}18$ (1)
$a=11{\cdot}303$ (3) Å	$Z=8$
$b=29{\cdot}227$ (8)	$F(000)=1360$
$c=14{\cdot}282$ (3)	λ(Cu $K\alpha$) = 1·54178 Å, graphite monochromated
$\beta=130{\cdot}91$ (1)°	μ(Cu $K\alpha$) = 17·72 cm^{-1}
$U=3563{\cdot}3$ Å^3	Temperature during data collection 18 (1) °C.

For data collection, a crystal (0·60 × 0·45 × 0·50 mm) was mounted on a Picker card-controlled four-circle diffractometer, with the **c*** direction parallel to the instrument φ axis. All reflexions in the range $4° \leq 2\theta \leq 120°$ were measured with a θ–2θ scan, a speed of 2° min^{-1} in 2θ, and background counts of 20 s at each

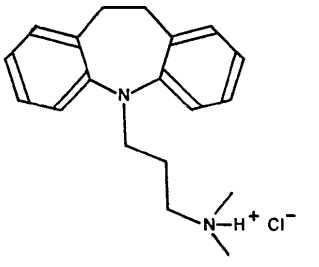

Fig. 1. Imipramine hydrochloride.

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scan limit. Four reflexions were monitored at approximately $1\frac{1}{2}$ h intervals throughout. Of 5712 observations, 2880 unique reflexions were found to have intensities $\geq 3\sigma(I)$ [where $\sigma^2(I)=S+B+(0{\cdot}054S)^2$, and S and B are scan and background counts, respectively], and these were used in the solution and refinement of the structure. Scaling, derived from monitor reflexion values, Lorentz and polarization corrections were applied to the raw data and relative structure amplitudes derived. No corrections were made for absorption or extinction.

Structure solution and refinement

The structure was solved by application of a multisolution direct-methods procedure for use with centrosymmetric space groups (Sheldrick, 1974). 378$|E|$ values $\geq 1{\cdot}2$ were employed, 12 of these with higher $|E|$ being allowed phases of either 0 or π, thus yielding 4096 (2^{12}) possible sign permutations. Each set was expanded to phase the complete list of E's, and the 'best' solutions were chosen by a small number of reliability criteria. The best E map revealed positions for 38 of the non-hydrogen atoms. A subsequent difference synthesis placed the remaining six atoms and, following four cycles of full-matrix least-squares refinement with individual isotropic thermal parameters, R was 0·143. At this stage a difference synthesis indicated that slight disorder was present in the region of C(5) and C(6) of molecule B although only two peaks could be resolved in the electron density map when C(5)B and C(6)B were excluded. No suitable disordered model could be chosen to describe the effect and refinement was, therefore, continued normally. However, the nature of the disorder in this region resulted in unreliable bond lengths and angles involving the two

Table 1. *Final fractional atomic coordinates* ($\times 10^4$) *and thermal parameters* (Å$^2 \times 10^3$) *with standard deviations in parentheses*

Thermal parameters are in the form $T=\exp\{-2\pi^2(U_{11}a^{*2}h^2+U_{22}b^{*2}k^2+U_{33}c^{*2}l^2+2U_{12}a^*b^*hk+2U_{13}a^*c^*hl+2U_{23}b^*c^*kl)\}$.

	x	y	z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)A	8018 (5)	−1345 (2)	1297 (3)	103 (2)	44 (3)	58 (2)	−1 (2)	59 (1)	3 (2)
C(2)A	7781 (6)	−1475 (2)	251 (4)	160 (3)	69 (4)	67 (2)	3 (2)	82 (1)	12 (3)
C(3)A	9008 (5)	−1654 (2)	397 (4)	165 (3)	89 (4)	88 (2)	2 (3)	102 (1)	25 (3)
C(4)A	10444 (5)	−1700 (2)	1553 (4)	157 (2)	62 (3)	119 (2)	25 (2)	121 (1)	37 (2)
C(5)A	12388 (4)	−1637 (2)	3818 (3)	87 (2)	61 (3)	115 (2)	19 (2)	86 (1)	17 (2)
C(6)A	12877 (4)	−1377 (4)	4936 (4)	48 (2)	48 (3)	122 (3)	12 (2)	57 (1)	4 (2)
C(7)A	12843 (5)	−1820 (2)	6448 (4)	56 (2)	51 (3)	56 (2)	7 (2)	26 (1)	15 (2)
C(8)A	12068 (5)	−2001 (2)	6793 (4)	80 (2)	78 (4)	50 (2)	17 (2)	39 (1)	30 (2)
C(9)A	10475 (4)	−1950 (2)	6056 (3)	84 (2)	64 (3)	61 (2)	18 (2)	56 (1)	29 (2)
C(10)A	9671 (4)	−1703 (1)	4958 (3)	56 (1)	38 (2)	51 (1)	−1 (2)	40 (1)	5 (2)
C(11)A	10453 (4)	−1509 (1)	4610 (3)	45 (1)	33 (2)	46 (1)	−2 (2)	30 (1)	2 (2)
C(12)A	12064 (4)	−1568 (1)	5366 (3)	52 (2)	37 (3)	62 (2)	−10 (2)	37 (1)	−4 (2)
C(13)A	10738 (4)	−1570 (1)	2625 (3)	100 (2)	41 (3)	87 (2)	9 (2)	81 (1)	8 (2)
C(14)A	9471 (4)	−1387 (1)	2490 (3)	77 (2)	27 (2)	63 (1)	2 (2)	57 (1)	3 (2)
C(15)A	8416 (4)	−936 (1)	3269 (3)	42 (1)	39 (3)	44 (1)	1 (2)	30 (1)	3 (2)
C(16)A	8472 (4)	−462 (1)	2833 (3)	45 (1)	30 (2)	56 (2)	3 (2)	36 (1)	3 (2)
C(17)A	7201 (3)	−162 (1)	2600 (3)	40 (1)	35 (2)	42 (1)	0 (2)	30 (1)	3 (2)
C(18)A	5886 (4)	586 (2)	1859 (4)	54 (2)	42 (3)	83 (2)	4 (2)	44 (1)	16 (2)
C(19)A	8735 (4)	557 (2)	3388 (3)	52 (2)	47 (3)	52 (2)	−14 (2)	31 (1)	−15 (2)
N(1)A	9626 (3)	−1239 (1)	3515 (2)	54 (1)	41 (2)	52 (1)	8 (1)	41 (1)	13 (1)
N(2)A	7297 (3)	322 (1)	2311 (2)	37 (1)	38 (2)	37 (1)	−4 (1)	24 (1)	0 (1)
ClA	7090 (1)	330 (1)	82 (1)	55 (1)	76 (1)	41 (1)	−9 (1)	32 (1)	−9 (1)
C(1)B	6281 (4)	6308 (2)	−510 (3)	44 (1)	75 (3)	45 (2)	6 (2)	31 (1)	−6 (2)
C(2)B	5442 (4)	6485 (2)	−1708 (3)	45 (2)	132 (5)	47 (2)	13 (2)	27 (1)	−17 (2)
C(3)B	5143 (5)	6945 (2)	−1914 (4)	48 (2)	150 (5)	73 (3)	58 (3)	15 (2)	−10 (3)
C(4)B	5619 (6)	7219 (2)	−963 (5)	65 (3)	82 (4)	86 (4)	37 (3)	9 (3)	−6 (3)
C(5)B	6709 (7)	7412 (2)	1113 (6)	106 (4)	70 (4)	123 (5)	−16 (4)	37 (3)	24 (3)
C(6)B	7563 (5)	7305 (2)	2370 (4)	140 (3)	71 (4)	100 (2)	13 (2)	90 (2)	42 (3)
C(7)B	10549 (5)	7240 (2)	3919 (4)	109 (3)	44 (3)	65 (2)	−13 (2)	54 (2)	−22 (2)
C(8)B	11914 (5)	6993 (2)	4507 (4)	83 (2)	68 (4)	61 (3)	−14 (2)	38 (2)	−28 (2)
C(9)B	11825 (5)	6538 (2)	4200 (4)	57 (2)	77 (4)	58 (2)	2 (3)	30 (1)	−2 (2)
C(10)B	10382 (4)	6341 (2)	3264 (3)	63 (2)	47 (3)	49 (2)	−6 (2)	39 (1)	−7 (2)
C(11)B	9014 (4)	6598 (1)	2637 (3)	63 (2)	33 (2)	41 (1)	1 (2)	39 (1)	−3 (2)
C(12)B	9089 (4)	7050 (1)	2994 (3)	77 (2)	37 (3)	48 (2)	−4 (2)	42 (1)	−6 (2)
C(13)B	6379 (5)	7064 (2)	220 (4)	56 (2)	50 (3)	64 (3)	15 (2)	20 (2)	7 (2)
C(14)B	6728 (4)	6594 (2)	455 (3)	37 (1)	51 (3)	44 (2)	7 (2)	23 (1)	−5 (2)
C(15)B	7339 (4)	5907 (1)	1686 (3)	73 (2)	31 (2)	44 (1)	−1 (2)	43 (1)	−10 (2)
C(16)B	7685 (4)	5749 (1)	2870 (3)	96 (2)	38 (2)	58 (2)	−9 (2)	59 (1)	−15 (2)
C(17)B	7001 (4)	5289 (1)	2723 (3)	69 (2)	44 (3)	52 (1)	−2 (2)	47 (1)	−1 (2)
C(18)B	9246 (5)	4800 (2)	3409 (4)	46 (2)	101 (4)	61 (2)	−4 (3)	29 (1)	8 (3)
C(19)B	6629 (4)	4490 (2)	2149 (4)	75 (2)	41 (3)	79 (2)	−8 (2)	51 (1)	−13 (2)
N(1)B	7512 (3)	6405 (1)	1650 (3)	51 (1)	29 (2)	52 (1)	−1 (1)	34 (1)	−7 (1)
N(2)B	7579 (3)	4900 (1)	2429 (2)	47 (1)	41 (2)	34 (1)	−2 (1)	29 (1)	−3 (1)
ClB	7276 (1)	4937 (1)	147 (1)	61 (1)	58 (1)	42 (1)	2 (1)	37 (1)	7 (1)

atoms. The structure was then refined allowing thermal anisotropy to each atom, but the number of variables required this stage to be carried out in overlapping partial cycles. After two complete cycles (six partial cycles) R was reduced to 0·072 and a difference synthesis indicated sites for many of the hydrogen atoms, the C–H distances averaging 1·06 Å. In subsequent steps all hydrogen-atom contributions were included, their placement calculated so that C–H was 1·06 Å, and their positions constrained during refinement such that the C–H vector retained its original magnitude. An overall isotropic thermal parameter was assigned to the hydrogen atoms. In order to cope with the large number of parameters (498) in the final stages, refinement by a steepest-descent (conjugate-gradient) method was employed (Sheldrick, 1974) and after 18 cycles convergence was attained at $R=0{\cdot}057$.* The weighting scheme used a modified statistical weight, sw, in the form $w^{-1}=(m+F_o+nF_o^2)/sw$ with $m=6{\cdot}975$ and $n=0{\cdot}0068$, and R_w† at convergence was 0·067. The function minimized was $\sum w\{|F_o|-|F_c|\}^2$. Tables 1 and 2 present the final atomic coordinates and thermal parameters.

* A table of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30781 (18pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1 NZ, England.

† $R_w=\{\sum w(|F_o|-|F_c|)^2/\sum wF_o\}^{1/2}$.

Table 2. *Fractional atomic coordinates* ($\times 10^3$) *for hydrogen atoms*

$U_{iso}=0{\cdot}092$ Å^2 throughout.

	A			*B*		
	x	*y*	*z*	*x*	*y*	*z*
H(1)	707	−121	119	657	596	−34
H(2)	667	−144	−65	504	626	−245
H(3)	885	−176	−39	455	708	−281
H(4)	1137	−184	164	539	758	−114
H(51)	1254	−199	404	561	754	77
H(52)	1315	−154	366	733	768	109
H(61)	1258	−103	470	783	762	286
H(62)	1410	−141	566	685	710	243
H(7)	1407	−187	702	1062	759	418
H(8)	1270	−218	764	1302	715	519
H(9)	987	−210	632	1286	634	468
H(10)	844	−166	438	1032	599	302
H(151)	730	−108	257	617	582	91
H(152)	860	−90	409	812	574	163
H(161)	828	−50	200	721	599	310
H(162)	958	−31	352	891	573	360
H(171)	733	−16	341	726	521	356
H(172)	609	−30	184	577	531	200
H(181)	487	42	109	991	510	360
H(182)	594	92	159	957	453	312
H(183)	585	61	258	946	470	422
H(191)	973	37	370	543	457	144
H(192)	871	58	411	684	439	296
H(193)	880	89	312	695	422	185
H	734	31	159	745	499	165

Table 3. *Bond lengths and angles with standard deviations in parentheses*

	Molecule *A*	Molecule *B*
C(1)—C(2)	1·387 (8) Å	1·403 (6) Å
C(1)—C(14)	1·397 (4)	1·392 (6)
C(2)—C(3)	1·365 (9)	1·369 (9)
C(3)—C(4)	1·367 (5)	1·347 (9)
C(4)—C(13)	1·391 (8)	1·377 (8)
C(13)–C(14)	1·418 (7)	1·407 (7)
C(5)—C(13)	1·503 (4)	1·474 (9)
C(5)—C(6)	1·508 (7)	1·408 (8)
C(6)—C(12)	1·508 (9)	1·521 (7)
C(12)–C(7)	1·387 (6)	1·386 (5)
C(7)—C(8)	1·361 (9)	1·382 (7)
C(8)—C(9)	1·376 (6)	1·381 (8)
C(9)—C(10)	1·393 (5) Å	1·387 (5) Å
C(10)–C(11)	1·388 (7)	1·393 (5)
C(11)–C(12)	1·392 (5)	1·396 (6)
C(11)–N(1)	1·423 (5)	1·433 (4)
C(14)–N(1)	1·422 (6)	1·421 (5)
C(15)–N(1)	1·467 (5)	1·475 (5)
C(15)–C(16)	1·534 (6)	1·536 (7)
C(16)–C(17)	1·523 (6)	1·494 (6)
C(17)–N(2)	1·496 (5)	1·501 (6)
N(2)—C(18)	1·486 (5)	1·463 (4)
N(2)—C(19)	1·485 (4)	1·478 (6)

	Molecule *A*	Molecule *B*
C(14)–C(1)—C(2)	122·2 (5)°	120·2 (5)°
C(1)—C(2)—C(3)	118·7 (4)	119·9 (5)
C(2)—C(3)—C(4)	120·5 (6)	119·0 (5)
C(3)—C(4)—C(13)	122·7 (6)	123·9 (6)
C(13)–C(5)—C(6)	117·1 (4)	121·6 (5)
C(5)—C(6)—C(12)	110·2 (4)	115·0 (6)
C(12)–C(7)—C(8)	121·3 (4)	122·0 (5)
C(7)—C(8)—C(9)	120·9 (4)	119·2 (4)
C(8)—C(9)—C(10)	118·6 (5)	120·0 (4)
C(9)—C(10)–C(11)	121·0 (4)	120·4 (4)
C(10)–C(11)–C(12)	119·3 (4)	119·8 (3)
C(10)–C(11)–N(1)	120·3 (3)	121·5 (4)
C(12)–C(11)–N(1)	120·3 (4)	118·6 (3)
C(6)—C(12)–C(7)	122·6 (4)	123·2 (4)
C(6)—C(12)–C(11)	118·4 (4)	118·4 (3)
C(7)—C(12)–C(11)	118·9 (5)	118·4 (4)
C(4)—C(13)–C(5)	115·8 (5)	115·8 (5)
C(4)—C(13)–C(14)	117·5 (3)°	117·7 (5)°
C(5)—C(13)–C(14)	126·7 (4)	126·4 (5)
C(1)—C(14)–C(13)	118·4 (5)	119·1 (4)
C(1)—C(14)–N(1)	118·8 (4)	119·5 (4)
C(13)–C(14)–N(1)	122·8 (3)	121·4 (4)
C(11)–N(1)—C(14)	120·8 (3)	115·8 (4)
C(11)–N(1)—C(15)	115·8 (4)	116·9 (2)
C(14)–N(1)—C(15)	118·1 (3)	115·6 (3)
N(1)—C(15)–C(16)	111·2 (4)	113·0 (3)
C(15)–C(16)–C(17)	108·8 (4)	112·3 (3)
C(16)–C(17)–N(2)	112·1 (4)	116·1 (4)
C(17)–N(2)—C(18)	111·1 (3)	114·0 (3)
C(17)–N(2)—C(19)	112·3 (2)	108·4 (4)
C(18)–N(2)—C(19)	110·2 (3)	110·4 (3)

Discussion

The asymmetric unit consists of two imipramine hydrochloride molecules *A* and *B*. A general view of each of these molecules together with the atom numbering scheme is shown in Fig. 2. Table 3 lists bond lengths and angles involving the non-hydrogen atoms. The tricyclic ring system of each molecule is similar in appearance, but several differences exist. Comparison between the C(5) and C(6) regions in the two molecules is not strictly valid because of the disorder in molecule *B*. However, the benzenoid parts of each molecule are, as expected, very close to being planar (Table 4) and the angles between these planes are 130·3 and 123·0° for *A* and *B*, respectively. The amount of 'twist' in the ring system is reflected in the angles between each benzene ring and the plane N(1)···C(5)···C(6); for *A* these values are 17·9 and 115·8°; for *B*, 2·3 and 125·1°. Table 5 lists the torsion angles in the seven-membered rings. The greatest differences are about N(1)–C(14) and in the dimethylene bridge, the other regions of the ring having closely similar values. The atoms N(1) are pyramidally bonded, lying 0·192 and 0·289 Å, from the C(11)···C(14)···C(15) plane, on the same side as C(6), in *A* and *B*, respectively. The conformational differences are reflected in the bond angles at N(1) (Table 3) which differ by 5·0° (σ=0·3°) and the non-bonded distances C(11)···C(14) and C(12)···C(13) which are 2·473 and 3·142 Å for *A* and 2·416 and 3·029 Å (σ=0·007 Å) for *B*. A recent n.m.r. solution study of imipramine and its hydrochloride (Abraham, Kricka & Ledwith, 1974) has shown that rapid flipping of the dimethylene bridge does occur and it is possible, therefore, in the solid state that C(5)*B* and C(6)*B* are attempting to attain a 'flip' equilibrium position from which the molecule *B* is being forced by packing constraints. This effect could manifest itself in the observed disorder and offer one possible explanation of the variation in ring parameters. It can be demonstrated from models that the remainder of the molecule can tolerate small movements in the $-CH_2-CH_2-$ moiety without appreciable disturbance of the other atomic positions.

The dimethylamino side chain exhibits a different conformation in each molecule (Table 5). The values of τ_1 correspond closely to *gauche* orientation at N(1)–C(15), but in opposite sense in each molecule, *i.e.* τ_{1A}=137·2, τ_{1B}=58·8°. For *B* this value yields well balanced intramolecular hydrogen–hydrogen approaches between the side chain and benzenoid ring *i.e.*

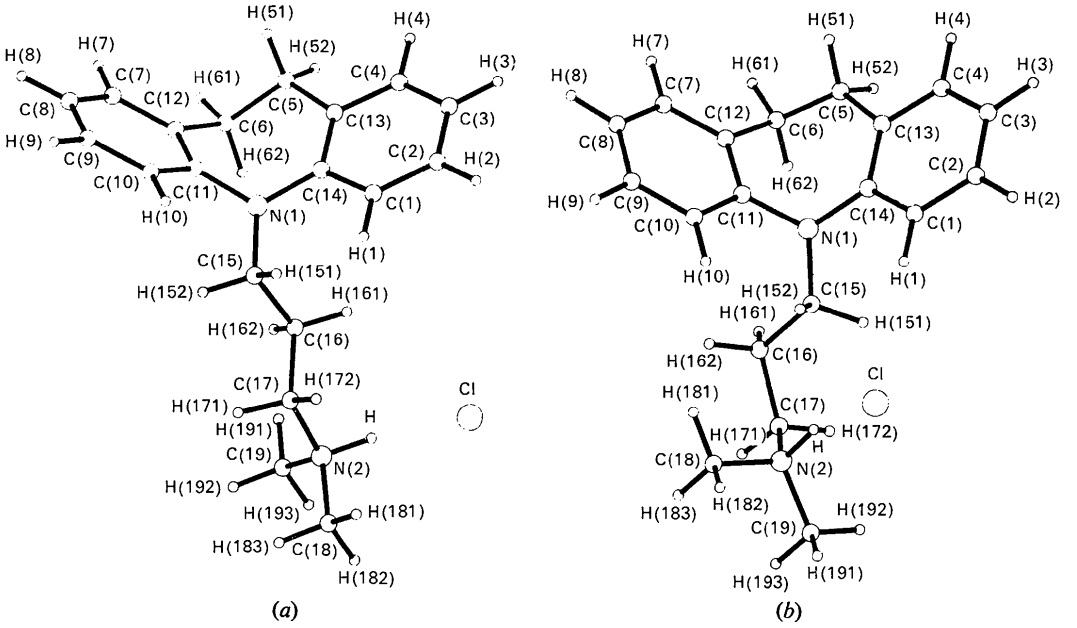

Fig. 2. Diagrams of each molecule in the asymmetric unit. (*a*) Molecule *A*, (*b*) molecule *B*.

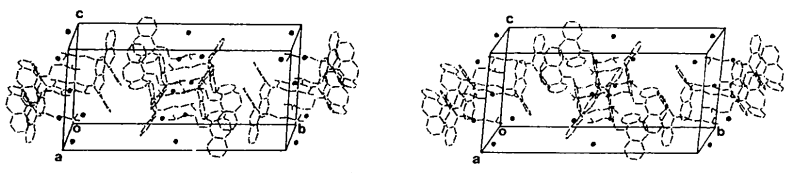

Fig. 3. Stereoscopic view of imipramine hydrochloride showing the packing arrangement. Hydrogen atoms are omitted for clarity; black circles represent Cl positions.

Table 4. *Equations of some least-squares mean planes in terms of fractional coordinates x,y,z, and deviations* (Å) *of atoms from these planes*

Plane 1

Molecule *A* $4{\cdot}391x+26{\cdot}831y-4{\cdot}396z=-0{\cdot}656$
Molecule *B* $10{\cdot}889x+4{\cdot}555y-6{\cdot}631z=10{\cdot}031$

	A	*B*
C(1)	−0·002 Å	0·019 Å
C(2)	0·004	−0·019
C(3)	−0·001	0·002
C(4)	−0·003	0·014
C(5)*	0·024	−0·087
C(6)*	0·446	−0·040
C(13)	0·005	−0·013
C(14)	−0·003	−0·004
N(1)*	0·012	−0·028

Plane 2

Molecule *A* $-2{\cdot}620x+24{\cdot}501y+7{\cdot}479z=-2{\cdot}992$
Molecule *B* $-7{\cdot}612x-8{\cdot}548y+13{\cdot}626z=-8{\cdot}883$

	A	*B*
C(5)*	−1·408 Å	−1·043 Å
C(6)*	−0·063	0·112
C(7)	−0·009	0·005
C(8)	0·007	−0·022
C(9)	0·000	0·016
C(10)	−0·005	0·008
C(11)	0·004	−0·025
C(12)	0·004	0·018
N(1)*	0·063	−0·062

* These atoms not included in the mean-plane calculation.

Table 5. *Principal torsion angles* (°)

Amine chain	Molecule *A*	Molecule *B*
C(11)–N(1)—C(15)–C(16) = τ_1	137·2	58·8
N(1)—C(15)–C(16)–C(17) = τ_2	180·0	160·5
C(15)–C(16)–C(17)–N(2) = τ_3	173·5	60·9
C(16)–C(17)–N(2)—C(18) = τ_4	164·4	64·2
C(16)–C(17)–N(2)—C(19) = $\tau_{4'}$	−66·7	−172·4
Seven-membered ring		
C(14)–C(13)–C(5)—C(6)	−17·8	5·7
C(13)–C(5)—C(6)—C(12)	70·2	49·1
C(5)—C(6)—C(12)–C(11)	−67·9	−69·2
C(6)—C(12)–C(11)–N(1)	−5·6	3·8
C(12)–C(11)–N(1)—C(14)	67·7	68·1
C(11)–N(1)—C(14)–C(13)	−44·8	−57·9
N(1)—C(14)–C(13)–C(5)	0·0	−1·9

H(151)*B*···H(1)*B* 2·15, H(152)*B*···H(10)*B* 2·05, H(152)*B*···H(1)*B* 2·22 Å, but for *A* there is a close approach of 1·85 Å between H(151)*A*···H(1)*A*. Other distances are: H(152)*A*···H(10)*A* 2·30, H(161)*A*···H(1)*A* 2·33 Å. The conformation of the chain at τ_2 and τ_3 is *trans* for molecule *A*, but *B* exhibits *gauche* orientation at τ_3. The values, τ_4 and $\tau_{4'}$, of torsion angles about C(17)–N(2) are each to chemically equivalent methyl groups at C(18) and C(19), respectively, and can, therefore, be considered internally equivalent (*i.e.* both molecules *trans* or both *gauche*). The amino nitrogen atoms of each molecule are hydrogen-bonded to the chloride ions in a direction which is very nearly parallel to **c**. The distances N(2)···Cl are 3·035 and 3·047 Å for *A* and *B*, respectively, and both are shorter by *ca* 0·08 Å than that found in iprindole hydrochloride (Rodgers, Kennard, Horn & Riva di Sanseverino, 1974). In the present compound, the position of Cl*A* is compatible with tetrahedral bonding geometry about N(2)*A* (Table 6), but the corresponding arrangement in molecule *B* is a somewhat distorted tetrahedron. The N–H···Cl angle is 170·8° in *A* and 158·7° in *B*. Some other parameters which may be of pharmacological significance (Horn, 1974) are the distances from N(2) to the geometric centres of the benzene rings; these values give a coarse measure of the amino group position in relation to the tricyclic nucleus. For *A* distances are 6·249 and 7·218 Å and for *B* they are 6·537 and 6·076 Å; in each case the first value is to the C(1)–C(4), C(13), C(14) ring. A more systematic study of these and related geometrical factors will be presented later (Horn, Post & Kennard, 1975).

Table 6. *Angles subtended at the amine nitrogen atoms* N(2) *involving* Cl

	Molecule *A*	Molecule *B*
C(17)–N(2)···Cl	109·1°	120·6°
C(18)–N(2)···Cl	108·5	101·8
C(19)–N(2)···Cl	111·2	100·8

The strong conformational dependence of drug activity, as found in many neuroleptic compounds (Post, Kennard & Horn, 1974*a*; Post, Kennard, Horn & Sheldrick, 1974) has required consideration of the possible conformations of the molecule in a non-crystalline state and a potential energy approach toward this problem is being undertaken. The method employed is a direct summation of individual neutral atom–atom interactions, with the potential energy criteria of Giglio (1969), as programmed by W.D.S. Motherwell. Preliminary results of this study (Post, Kennard & Horn, 1974*b*) indicate the possible existence, in solution, of conformations other than those found in the crystal, and a more detailed account will be reported later when the structures of related compounds are completed.

A packing diagram for imipramine hydrochloride is shown in Fig. 3. It is apparent (see also Table 1) that Cl and N(2) atoms lie very nearly in a plane perpendicular to **b** so that, for these atom types alone, a pseudo-mirror plane exists at $y=\frac{1}{4}$. In these layers of ionic interaction the environments for *A* and *B* are very similar, with three Cl···N(2) distances between 4·2–4·8 Å and one Cl···Cl distance of *ca* 4·9 Å. The propyl chain and tricyclic moiety of the structure lie back from the Cl···N(2) region and are not involved in any unusually close intermolecular contacts.

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The Crystal and Molecular Structure of the Copper(II) Chelate of L-Leucyl-L-tyrosine

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The crystal structure of the title compound, $[Cu(C_{15}H_{20}N_2O_4)(H_2O)].2H_2O.C_2H_5OH$, has been determined and refined by three-dimensional least-squares techniques. The crystals are orthorhombic, space group $P2_12_12_1$, $Z=4$, with $a=15{\cdot}545$ (1), $b=16{\cdot}121$ (2) and $c=8{\cdot}6838$ (5) Å. Diffractometer intensity data were collected for all unique reflections with $\theta<75°$, using Ni-filtered Cu $K\alpha$ radiation. The final $R=3{\cdot}5\%$ for all 2546 data. The estimated standard deviations are between 0·003 and 0·007 Å for all C, N and O atoms. The coordination of the copper(II) ion is best described as square pyrimidal. Polymer-like chains are formed in the solid state by the bridging of copper(II) ions with the terminal carboxyl groups in a direction parallel to the twofold screw axis in the **c** direction. Hydrogen bonds involving the water molecules, ethanol molecule and the peptide join the chains largely in the **a** direction.

Introduction

As part of a general study of the influence of transition metal cations on the conformation of amino acids and peptides we have determined the crystal structure of the copper(II) chelate of L-leucyl-L-tyrosine (CULT). Previously it has been reported that an interaction occurs between the Cu^{2+} ion and the activated aromatic ring of the tyrosine residue in the copper(II) chelates of both glycyl-L-leucycl-L-tyrosine (Franks & Van der Helm, 1971) and L-tyrosine (Van der Helm & Tatsch, 1972). It was, therefore, of interest to ascertain the position of the tyrosine side chain of CULT with respect to the Cu^{2+} ion. It was determined that although the conformations of the side chains were approximately the same for all three structures, a close contact was not observed in CULT. This interaction takes on added significance when one considers these molecules as possible model compounds for the active site in copper containing oxidases. Because activated aromatic rings are often substrates for these enzymes one might suggest that bonding at the active site, with subsequent electron transfer, takes place through the π-electrons of the aromatic ring.

The purpose of this communication is to present the description of the structure of CULT and to compare this structure to those in which an interaction has been observed.

Experimental

The compound CULT was prepared by reacting L-leucyl-L-tyrosine, copper sulfate and barium hydroxide in molar proportions of 1:1:1. The precipitate of barium sulfate was removed by centrifugation. The resulting solution was approximately 0·05 *M* in concentration of complex. The solution was then diluted with an equal volume of ethanol and after a few hours deep-blue needles crystallized from solution. These crystals were redissolved in water and a few drops of ethanol were added each day for several days. After three days deep-blue plates crystallized from the solution. The plate face is the (100) plane while the crystals are elongated along the *c* axis. During collection of

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