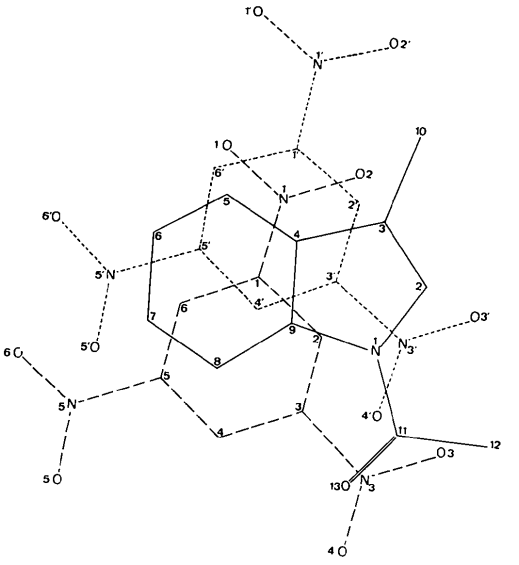

Fig. 5. Projection de deux molécules équivalentes de TNB sur la molécule d'acétyl-1 scatole intermédiaire.

Une molécule d'acétyl-1 scatole est en sandwich entre deux molécules de TNB.

La Fig. 5 représente une projection des trois molécules sur le plan moyen de l'acétyl-1 scatole.

Les distances inférieures à 3,5 Å à l'intérieur du sandwich TNB–acétyl-1 scatole–TNB′ sont indiquées dans le Tableau 2. La distance O(113)···N(203) (signalée par un astérisque) est la plus courte: $3{,}16_0$ Å.

La cohésion cristalline est assurée par des contacts de van der Waals dont un de type C–H···O est particulièrement court: C(111)–O(113)(x,y,z)··· H(112*A*)–C(112)($2-x, y-\frac{1}{2}, 1-z$) avec O(113)··· H(112*A*) $2{,}50_2$ Å, C(111)–O(113)···H(112*A*) 133°, et O(113)···H(112*A*)–C(112) 163°.

Les auteurs remercient M J. Elguero de leur avoir proposé l'étude de ce complexe et Mme R. M. Claramunt-Elguero d'avoir préparé le produit.

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X-ray Crystallographic and Nuclear Magnetic Resonance Spectroscopic Study of *p*-Chlorophenylethylamine Hydrochloride

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$(C_8H_{11}ClN)^+Cl^-$ has been examined in the solid state by X-ray crystallography and in solution by NMR spectroscopy. The crystals are monoclinic space group $P2_1/c$ with $a = 19{\cdot}89$ (2), $b = 5{\cdot}80$ (1), $c = 8{\cdot}87$ (1) Å, $\beta = 115{\cdot}6$ (1)°, $Z = 4$. The structure was refined by least squares to $R = 7{\cdot}9\%$ for 821 counter amplitudes. The ethylamine side chain is in the extended conformation, the C–C–C–N^+ torsion angle being 169°. The best plane through these atoms is inclined at 69° to the plane of the phenyl ring. In solution there is an equilibrium between the *trans* and *gauche* conformations of the ethylamine chain with a slight energetic preference for the former (of *ca* 1·8 kJ mol^{-1} at 35 °C).

Introduction

2-Phenylethylamine (PE) is present in the mammalian central nervous system (CNS) and it has been implicated in the aetiology of a number of psychiatric disease states (Martin & Baker, 1977). The *p*-chloro analogue [2-(4-chlorophenyl)ethylamine; pCPE], while not normally present in the CNS, has been identified as a metabolite of *p*-chlorophenylalanine, a drug which is frequently used to decrease the levels of 5-hydroxytryptamine (5HT) in experimental animals (Edwards & Blau, 1972). Koe & Weissman (1966) reported that the systemic administration of pCPE to rats caused a short-lasting decrease in the CNS levels of noradrenaline (NA) and 5HT, results which have been confirmed and extended indicating that this amine has no effect on the concentration of CNS dopamine (DA) (Martin & Baker, unpublished observations). In rats treated in the same manner with PE, a decrease in the CNS levels of NA and DA was found with little effect on 5HT (Jackson & Smythe, 1973). Further, *in vitro* evidence shows that pCPE has marked effects on the normal membrane transport of both NA and 5HT though little effect on DA transport (Baker, Bertollini, del Carmine, Martin & Raiteri, 1976). This is in marked contrast to the parent compound PE which in similar *in vitro* experiments exhibits marked effects on NA and DA transport and is relatively much less effective against 5HT transport (Raiteri, del Carmine, Bertollini & Levi, 1977).

The introduction of the *p*-chloro substituent into PE therefore appears to enhance the ability of the resultant compound to interact with the 5HT system while decreasing its interaction with the dopaminergic system in the mammalian CNS. We have used X-ray crystallography and NMR spectroscopy to investigate the molecular parameters which might account for these marked differences in neurochemical characteristics.

Experimental

X-ray crystallography

The crystals were in the form of thin plates. A crystal, 0·9 × 0·5 × 0·05 mm, was mounted about the direction of elongation (**b**) and cell dimensions and the intensities were measured on a Stoe two-circle computer-controlled diffractometer with graphite-monochromated Mo $K\alpha$ radiation. Reflexions were scanned within the range $0{\cdot}1 < \sin\theta/\lambda < 0{\cdot}54$ Å^{-1}. The scan rate was 0·6° min^{-1} and 30 s background counts were taken at each end of the scan. 821 reflexions [$I > 3{\cdot}5\sigma(I)$] were considered observed and were used in the analysis. The data were, however, of relatively poor quality. Reflexion occurred over a considerable range of angle so that highly accurate intensities could not be obtained.

Crystal data. $(C_8H_{11}ClN)^+Cl^-$, $M_r = 192{\cdot}1$, monoclinic, $a = 19{\cdot}89$ (2), $b = 5{\cdot}80$ (1), $c = 8{\cdot}87$ (1) Å, $\beta = 115{\cdot}6$ (1)°, $U = 923$ Å^3, $Z = 4$, $D_c = 1{\cdot}38$ g cm^{-3}, $F(000) = 400$. Systematic absences, $0k0$, k odd; $h0l$, l odd. Space group $P2_1/c$. Mo $K\alpha$ radiation, $\lambda = 0{\cdot}71069$ Å; μ(Mo $K\alpha$) = 5·8 cm^{-1}.

The structure was determined by direct methods (Karle & Karle, 1966) with *SHELX* (Sheldrick, 1975). Phases were assigned to 417 reflexions with $E > 1{\cdot}1$ and from the resulting E map all the atoms of the asymmetric unit (apart from H atoms) could be located. Least-squares refinement of positional and anisotropic thermal parameters reduced R to 9·5%. At this stage the H atoms were introduced in calculated positions but their parameters were not refined. Refinement was terminated when all calculated shifts were $<0{\cdot}1\sigma$ and R was 7·9%.

The weighting scheme was $w = 1/[\sigma^2(F) + 0{\cdot}0016F^2]$, where $\sigma(F)$ is the standard deviation in the observed amplitude derived from counting statistics.

Computations were carried out largely on the CDC 7600 computer at the University of Manchester Regional Computer Centre with *SHELX* (Sheldrick, 1975).

NMR spectroscopy

The ^{1}H NMR spectra were recorded at 100 MHz on a Varian XL-100 spectrometer operating in the c.w. mode with an internal deuterium lock. Solutions were 0·5 M in D_2O. The side-chain $[AB]_2$ multiplet was anlaysed with an interactive Jeol FX-60 computer/CRT display system and the appropriate spin simulation program.

Table 1. *Fractional atomic coordinates* (×10^4)

	x	*y*	*z*
C(1)	2585 (5)	4020 (15)	4022 (9)
C(2)	3206 (5)	2730 (16)	4360 (11)
C(3)	3765 (5)	3576 (21)	3882 (13)
C(4)	3700 (5)	5651 (20)	3121 (11)
C(5)	3086 (6)	6934 (15)	2771 (12)
C(6)	2536 (5)	6129 (17)	3245 (11)
C(7)	1975 (6)	3173 (17)	4533 (10)
C(8)	1298 (6)	2691 (19)	3021 (11)
N	651 (3)	2321 (11)	3474 (8)
Cl(1)	4397 (2)	6644 (8)	2579 (4)
Cl(2)	−656 (1)	2361 (4)	22 (2)
H[C(2)]	3188	1010	4632
H[C(3)]	4177	2596	3990
H[C(5)]	3074	8538	2520
H[C(6)]	2120	7479	3092
H^1[C(7)]	2183	1874	5368
H^2[C(7)]	1949	4373	5246
H^1[C(8)]	1198	1250	2560
H^2[C(8)]	1198	3762	2265
H^1[N]	581	3824	4111
H^2[N]	756	833	4276
H^3[N]	149	2043	2338

Results

Crystallographic

The atomic coordinates are listed in Table 1.* The conformation of the cation is illustrated in Fig. 1 which also shows the atom numbering. Bond lengths, bond angles and torsion angles are listed in Table 2 and the results of mean-plane calculations in Table 3.

Bond lengths and angles generally agree with standard values to within the limits of experimental error, which are, however, relatively large (e.s.d.'s 0·01–0·02 Å for lengths and *ca* 1° for angles). The phenyl ring is planar to within ±0·01 Å and the ring substituents, Cl(1) and C(7) lie close to the plane of the ring. The ethylamine side chain is in the extended (*trans*) conformation, with C(1), C(7), C(8) and N coplanar to within ±0·07 Å. The angle between the mean plane of the ethylamine chain and that of the ring is 69°.

The shape of the cation can also be described by the two torsion angles C(1)–C(7)–C(8)–N, which defines the conformation of the side chain, and C(6)–C(1)–C(7)–C(8), which defines the orientation of the side chain relative to the aromatic ring. In the present structure these are −169 and 68°.

The crystal packing is illustrated in Fig. 2. The intermolecular distances correspond to normal van der Waals interactions apart from three short $N^+\cdots Cl^-$ contacts; $N^+\cdots Cl^-$ (x,y,z), 3·04, $N^+\cdots Cl^-$ $(-x, y-\frac{1}{2}, \frac{1}{2}-z)$, 3·17 and $N^+\cdots Cl^-$ $(-x, y+\frac{1}{2}, \frac{1}{2}-z)$, 3·22 Å. The corresponding $H\cdots Cl^-$ distances involving H³[N], H²[N] and H¹[N], respectively, are 1·99, 2·14, and 2·17 Å. These distances are characteristic of hydrogen bonds which here link cations and Cl^- ions in infinite columns parallel to **b**.

* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33398 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

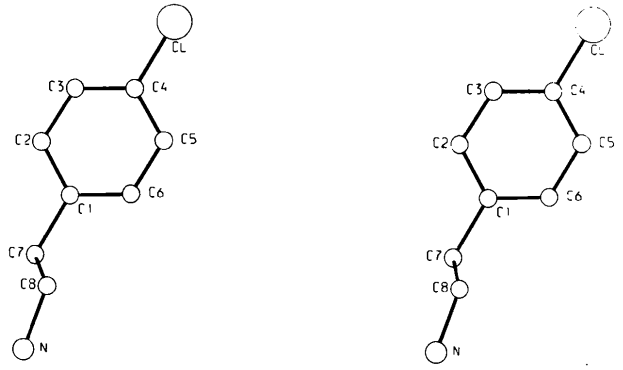

Fig. 1. Stereoscopic view of the pCPE cation as it occurs in the crystal of the chloride salt.

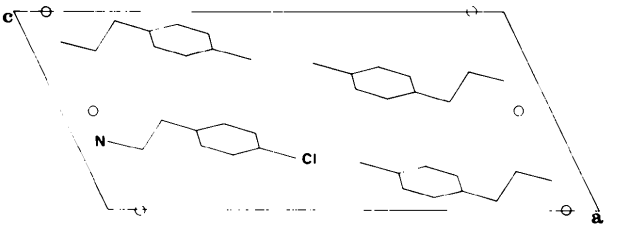

Fig. 2. The contents of the unit cell projected along **b**. Circles denote chloride ions.

NMR

^{1}H NMR spectra of pCPE.HCl showed the expected $[AB]_2$ spin systems arising from the 1,2-disubstituted ethane and 1,4-disubstituted benzene fragments. The side-chain multiplet was not symmetrical in that the high-field component signals had a significantly greater line-width than the low-field component (Fig. 3). This excess broadening can be attributed to incomplete

Table 2. *Molecular dimensions*

(*a*) Bond lengths (Å)

C(1)–C(2)	1·36 (1)	C(6)–C(1)	1·39 (1)
C(2)–C(3)	1·44 (2)	C(1)–C(7)	1·55 (1)
C(3)–C(4)	1·36 (2)	C(7)–C(8)	1·46 (2)
C(4)–C(5)	1·35 (1)	C(8)–N	1·52 (1)
C(5)–C(6)	1·41 (1)	C(4)–Cl(1)	1·75 (1)

(*b*) Bond angles (°)

C(2)–C(1)–C(6)	117·2 (9)	C(3)–C(4)–Cl(1)	120·8 (8)
C(2)–C(1)–C(7)	120·8 (8)	C(5)–C(4)–Cl(1)	120·1 (9)
C(6)–C(1)–C(7)	122·0 (8)	C(4)–C(5)–C(6)	119·4 (9)
C(1)–C(2)–C(3)	119·4 (9)	C(5)–C(6)–C(1)	122·9 (8)
C(2)–C(3)–C(4)	122·1 (9)	C(1)–C(7)–C(8)	108·8 (6)
C(3)–C(4)–C(5)	119·0 (9)	C(7)–C(8)–N	109·7 (6)

(*c*) Selected torsion angles (°). Mean e.s.d. 1·5°. Sign convention as defined by Klyne & Prelog (1960).

C(6)–C(1)–C(7)–C(8)	68
C(2)–C(1)–C(7)–C(8)	−113
C(1)–C(7)–C(8)–N	−169

Table 3. *Mean-plane calculations*

Deviations (Å) of atoms from least-squares planes. In the equations of the planes x, y and z are fractional coordinates relative to the cell axes.

Plane (i): C(1)–(6)

$$-1{\cdot}782x - 2{\cdot}589y - 6{\cdot}777z = -4{\cdot}231$$

C(1) −0·004, C(2) 0·002, C(3) −0·003, C(4) 0·006, C(5) −0·008, C(6) 0·007, C(7) 0·015, C(8) −1·256, N −1·160, Cl(1) 0·020

Plane (ii): C(1), C(7), C(8), N

$$-5{\cdot}074x + 5{\cdot}600y + 0{\cdot}514z = 1{\cdot}076$$

C(1) −0·070, C(7) 0·069, C(8) 0·073, N −0·072

Interplanar angle: plane (i)–plane (ii) 69°

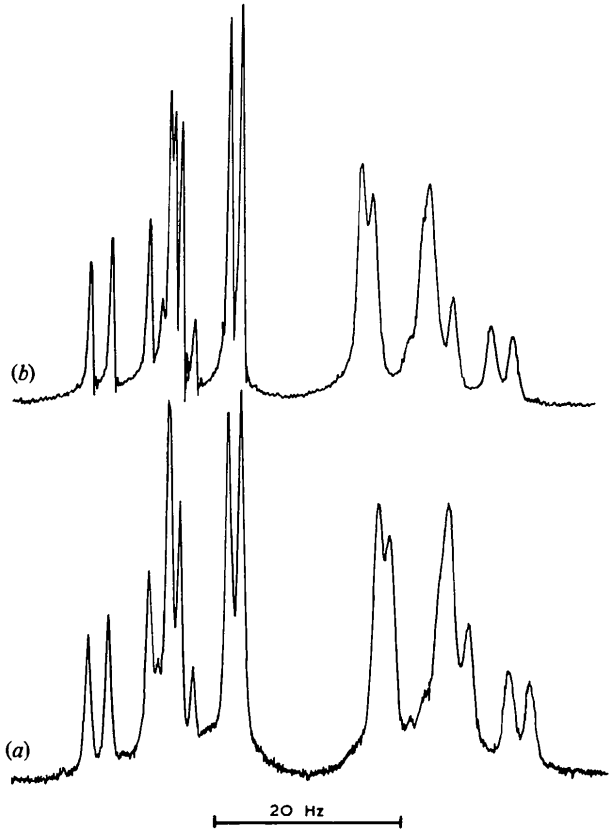

Fig. 3. 100 MHz NMR spectra of the CH_2–CH_2 side chain in (*a*) pCPE.HCl and (*b*) PE.HCl recorded in D_2O solution at 35 °C.

quadrupolar relaxation of the ^{14}N spin states, and since $^3J_{NCCH}$ is known to be larger than $^2J_{NCH}$ in ammonium salts the high-field component can be assigned to the benzylic protons on C(7) (Mooney & Winson, 1969; Bustard & Egan, 1971; Bailey & By, 1975).

The side-chain multiplet was analysed with an interactive computer and the vicinal coupling constants (J_{AB} and $J_{AB'}$), their sum (N) and the signal separation (δ_{AB}) are given in Table 4. The spectrum of PE.HCl recorded under the same conditions was analysed in a similar fashion, although the spectrum of this compound has been analysed previously on a lower-field instrument (Bailey & By, 1975). The results for pCPE.HCl and PE.HCl are almost identical (Fig. 3), except for a small change in the signal separation (δ_{AB}).

The fractional population of the *trans* rotamer (n_t) was calculated from the observed vicinal coupling constants (J_{AB} and $J_{AB'}$) with the procedure adopted by Bailey & By (1975). This analysis involves the assumption that the various *gauche* couplings (J^g) are equal and that the *trans* coupling constant (J^t) in the *trans* rotamer has a value of 12·0 Hz (J^g is calculated from $2J^g + J^t = 2J_{AB} + J_{AB'}$). Alternatively, n_t can also be evaluated according to Abraham & Gatti (1969)

Table 4. ^1H *NMR data for the side-chain conformation in* D_2O *solution*

Spectra were recorded at 100 MHz with a Varian XL-100 spectrometer operating in internal deuterium lock mode; probe temperature 35 °C.

Compound	δ_{AB} (p.p.m.)	J_{AB} (Hz)	$J_{AB'}$ (Hz)	N (Hz)	n_t	
pCPE.HCl	0·288	6·48	8·47	14·95	0·52*	(0·52)†
PE.HCl	0·264	6·58	8·26	14·84	0·49*	(0·50)†

* Calculated according to Bailey & By (1975).
† Calculated according to Abraham & Gatti (1969).

from $n_t J_t^t + (1 - n_t) J_g^g = J_{AB'}$, with $J_t^t = 12{\cdot}75$ Hz and $J_g^g = 3{\cdot}77$ Hz cited by these authors for C–CH_2–CH_2–N systems. The n_t values evaluated by these slightly different methods (Table 4) are in close agreement.

Discussion

X-ray crystallographic results obtained for pCPE.HCl in this study show that the bond lengths in the molecule do not differ significantly from those of PE.HCl (Tsoucaris, 1961; Carlström, Bergin & Falkenberg, 1973). The pCPE cations pack with the side chain in the *trans* conformation, the torsion angles defining the shape of the cation (see above) being −169 and 68° respectively (or 169 and −68° if the mirror-image rotamer also present in the crystal is considered) compared with 171 and −72° for PE.HCl. The overall conformations of the two molecules in the solid state therefore appear to be virtually identical though the bond lengths were not determined with sufficient accuracy to allow discussion of any differences in electronic properties. From the NMR data the *vicinal* coupling constants (J_{AB} and $J_{AB'}$) and their sum (the so-called N value) in 1,2-disubstituted ethanes are known to be very sensitive to the *trans*:*gauche* conformational distribution. Therefore, the close similarity in these parameters for pCPE.HCl and PE.HCl shows that both compounds have almost identical conformational distributions around the CH_2–CH_2 bond in solution. Furthermore, these correspond to *ca* 50% of the *trans* rotamer at equilibrium (Table 4). Were the *trans* and *gauche* rotamers to be equally populated a 33:67 distribution would result since the *gauche* rotamer is favoured on statistical grounds by a factor of two as it exists as a (±) racemate. Therefore the observed 50:50 distribution corresponds to a small energetic preference of *ca* 1·8 kJ mol^{-1} at 35 °C for the *trans* conformation. This is indeed the conformation found in the crystalline state.

The failure in this study to find any changes in molecular parameters induced by the introduction of a 4-chloro substituent into PE would therefore indicate that the 4-chloro substituent alone is responsible for the marked difference in the ability of PE and pCPE to interact with the uptake and release of DA and 5HT in the mammalian CNS. X-ray crystallographic studies of a number of phenylethylamines (Carlström, Bergin & Falkenberg, 1973; Paxton & Hamor, 1977) have shown that in all of these in the solid state, the ethylamine side chain adopts an almost identical *trans* conformation. It therefore appears that the side-chain conformation is not an important determinant in the biological activity.

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An X-ray Study of a Very Short, Asymmetric Hydrogen Bond between a Protonated Molecule of 1,5-Dimethyl-1,5-naphthyridine-4(1*H*),8(5*H*)-dione and a CF_3COO^- Anion

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Crystals of 1,5-dimethyl-1,5-naphthyridine-4(1*H*),8(5*H*)-dione (DMNDO) obtained from a CF_3COOH solution have been studied by X-ray diffraction methods and were found to consist of hydrogen-bonded $CF_3COOH\cdots CF_3COO^-\cdots {}^+H(DMNDO)H^+\cdots CF_3COO^-\cdots CF_3COOH$ units situated about crystallographic centers of symmetry. The crystals are monoclinic, space group $P2_1/n$, with $Z = 2$. At −35 °C, the unit-cell dimensions are: $a = 16{\cdot}804$ (3), $b = 13{\cdot}959$ (2), $c = 5{\cdot}123$ (1) Å, and $\beta = 90{\cdot}57$ (2)°. Full-matrix least-squares refinement using 2320 reflections [$I > 2\sigma(I)$] converged at a conventional R of 0·046. All non-hydrogen atoms, including the disordered F atoms of the CF_3COOH and CF_3COO^- moieties, were refined with anisotropic thermal parameters; the H atoms with isotropic parameters. The protonated keto groups of the DMNDO molecule form very short, asymmetric hydrogen bonds to the O atoms of the CF_3COO^- anions. Details of these O–H···O bonds are: O···O = 2·477 (2), O–H = 1·09 (3), H···O = 1·39 (3) Å, O–H···O = 175 (3)°. The second O atom of the anion accepts a more normal hydrogen bond from the –OH group of the CF_3COOH molecule: O···O = 2·594 (2), O–H = 0·88 (3), H···O = 1·72 (3) Å, O–H···O = 177 (3)°.

Introduction

The structural analysis of 1,5-dimethyl-1,5-naphthyridine-4(1*H*),8(5*H*)-dione (hereinafter referred to as DMNDO) was undertaken as part of a study of the chemistry and spectral properties of substituted naphthyridines (Brown & Dewar, 1976). Recrystallized by slow evaporation from a trifluoroacetic acid