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Structure of 1-(1-Phenylcyclohexyl)piperidine (PCP)

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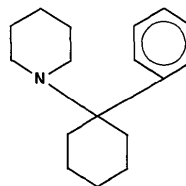
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Abstract. $C_{17}H_{25}N$, $M_r = 243.39$, monoclinic, $P2_1/c$, $a = 12.727$ (5), $b = 11.480$ (5), $c = 10.175$ (6) Å, $\beta = 102.58$ (3)°, $V = 1451$ (1) Å³, $Z = 4$, $D_x = 1.11$ g cm⁻³, $\lambda(\text{Cu } K\alpha) = 1.54178$ Å, $\mu = 4.5$ cm⁻¹, $F(000) = 536$, $T = 295$ K, $R = 0.046$ for 1763 unique reflections. A comparison with the structure of protonated PCP [Argos, Barr & Weber (1970). *Acta Cryst.* **B26**, 53–61] shows that there is significant shortening in the C–N bond distances in neutral PCP. The orientations of the three rings with respect to each other also differ in the two molecules with the piperidine ring occupying the axial position on the cyclohexane ring in PCP but the equatorial position in protonated PCP.

Introduction. 1-(1-Phenylcyclohexyl)piperidine, (1), commonly known as PCP, is an analgesic and a drug of abuse (Perry, 1975). It was developed at Park-Davis and Company in the late 1950's and was sold under the name Sernyl. In clinical trials it proved to be an effective anaesthetic and a pre- and post-surgical analgesic. Its use was discontinued, however, owing to adverse side effects, such as extreme agitation, disorientation and hallucination. The drug is biologically active both as the free base and as the hydro-

chloride salt (Goldstein, Aronow & Kalman, 1974; Labianca, 1981).



(1)

We are currently investigating the physical and chemical properties of PCP and related compounds and have therefore synthesized a number of them (Jones, Beaver, Schmoeger, Ort & Leander, 1981) following the procedure of Kalir, Edery, Pelah, Balderman & Porath (1969). As a first step in our further investigation of these biologically active molecules, we have determined the crystal and molecular structure of the free base of PCP. The structure of protonated PCP was determined by Argos, Barr & Weber (1970) as the hydrochloride salt using visually estimated film data. The present structure of the free base improves the precision of the derived parameters and allows an assessment of the

effect of protonation on the structure and conformation of PCP.

Experimental. Large colorless crystals of PCP were grown by slow evaporation of a concentrated methanol solution. A crystal fragment of approximate dimensions $0.48 \times 0.40 \times 0.35$ mm was mounted on a goniometer head and was used for data collection at room temperature with Cu $K\alpha$ radiation on a Nicolet R3M/ μ diffractometer equipped with a graphite monochromator and a pulse-height analyzer. Unit-cell dimensions were determined from a least-squares refinement of the setting angles of 25 reflections with 2θ values between 40 and 60° . Intensity data were collected to a limit of 115° in 2θ by the $\omega/2\theta$ scan technique at a variable scan rate between 4 and $29.3^\circ \text{ min}^{-1}$. Range in the Miller indices hkl was $-13 \leq h \leq 13$, $0 \leq k \leq 12$ and $0 \leq l \leq 11$. Backgrounds were measured by the stationary crystal/stationary counter techniques at the beginning and end of a scan, each for one-half of the total scan time. Two reflections (020 and 004) were measured after every 48 reflections to check the stability of the crystal and the counting system. A drop of approximately 15% in the intensity of both check reflections indicated some crystal decomposition. The intensities were corrected for background, crystal decomposition and Lorentz and polarization effects but not for absorption. Out of the 1976 reflections measured 1769 had intensities $\geq 2.5\sigma(I)$. The structure was solved by direct methods using the *SOLV* routine of the crystallographic program package *SHELXTL* (Sheldrick, 1985) and refined by the block-diagonal least-squares technique to an R of 0.046 and wR of 0.071 for 1763 data and 264 variables (R and wR for all 1976 data are 0.056 and 0.075, respectively). The function minimized was $\sum w(|F_o| - |F_c|)^2$, where $w = 1/[\sigma^2(F_o) + GF_o^2]$. G is an adjustable parameter with a final value of 0.00024. The goodness-of-fit parameter, S , was 2.4. The e.s.d.'s, $\sigma(F_o)$, were derived from the counting statistics. Six low- 2θ reflections appeared to be suffering from extinction effects even after a secondary-extinction correction was applied. They were, therefore, excluded from the final refinement. The refined secondary-extinction parameter is $7.8(6) \times 10^{-6}$. The H atoms were located from a difference Fourier map and refined with isotropic thermal vibration parameters. The non-hydrogen atoms were refined with anisotropic thermal vibration parameters. The largest shift/ σ was 0.10. A final difference Fourier was featureless in electron density, the largest positive and negative peaks being $+0.13$ and $-0.10 \text{ e } \text{Å}^{-3}$, respectively.

The atomic scattering factors were taken from the *International Tables for X-ray Crystallography* (1974). All computing was performed in-house on a Data General Microclipse computer with the crystallographic program package *SHELXTL* (Sheldrick,

Table 1. Atomic fractional coordinates ($\times 10^4$) and equivalent isotropic thermal parameters ($\text{Å}^2 \times 10^3$) for non-hydrogen atoms

	x	y	z	U_{eq}^*
N	2267 (1)	-94 (1)	3728 (1)	52 (1)
C(1)	2570 (2)	-1225 (2)	3283 (2)	69 (1)
C(2)	2756 (2)	-2080 (2)	4437 (3)	86 (1)
C(3)	3626 (2)	-1672 (2)	5582 (3)	88 (1)
C(4)	3384 (2)	-455 (2)	5960 (2)	81 (1)
C(5)	3166 (2)	347 (2)	4745 (2)	66 (1)
C(6)	1804 (1)	722 (1)	2613 (2)	50 (1)
C(7)	1510 (2)	1881 (2)	3198 (2)	65 (1)
C(8)	699 (2)	1746 (2)	4081 (2)	81 (1)
C(9)	-327 (2)	1174 (3)	3329 (3)	100 (1)
C(10)	-85 (2)	35 (2)	2703 (2)	80 (1)
C(11)	734 (2)	203 (2)	1843 (2)	64 (1)
C(12)	2592 (1)	931 (2)	1705 (2)	53 (1)
C(13)	3419 (2)	1733 (2)	2035 (2)	67 (1)
C(14)	4190 (2)	1875 (2)	1269 (2)	77 (1)
C(15)	4130 (2)	1222 (2)	130 (2)	82 (1)
C(16)	3313 (2)	440 (2)	-234 (2)	85 (1)
C(17)	2552 (2)	288 (2)	542 (2)	71 (1)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 2. Bond lengths (Å) and bond angles ($^\circ$) not involving the hydrogen atoms

N-C(1)	1.454 (2)	N-C(5)	1.456 (2)
N-C(6)	1.490 (2)	C(1)-C(2)	1.509 (3)
C(2)-C(3)	1.497 (3)	C(3)-C(4)	1.499 (4)
C(4)-C(5)	1.517 (3)	C(6)-C(7)	1.537 (3)
C(6)-C(11)	1.536 (2)	C(6)-C(12)	1.523 (3)
C(7)-C(8)	1.516 (3)	C(8)-C(9)	1.512 (3)
C(9)-C(10)	1.515 (4)	C(10)-C(11)	1.512 (3)
C(12)-C(13)	1.384 (3)	C(12)-C(17)	1.387 (3)
C(13)-C(14)	1.389 (3)	C(14)-C(15)	1.368 (3)
C(15)-C(16)	1.362 (4)	C(16)-C(17)	1.387 (4)
C(1)-N-C(5)	108.1 (1)	C(1)-N-C(6)	114.3 (1)
C(5)-N-C(6)	116.2 (1)	N-C(1)-C(2)	110.2 (2)
C(1)-C(2)-C(3)	111.5 (2)	C(2)-C(3)-C(4)	109.5 (2)
C(3)-C(4)-C(5)	111.6 (2)	N-C(5)-C(4)	110.2 (2)
N-C(6)-C(7)	109.8 (1)	N-C(6)-C(11)	107.7 (1)
C(7)-C(6)-C(11)	105.7 (1)	N-C(6)-C(12)	110.9 (1)
C(7)-C(6)-C(12)	110.3 (1)	C(11)-C(6)-C(12)	112.3 (1)
C(6)-C(7)-C(8)	113.3 (2)	C(7)-C(8)-C(9)	111.6 (2)
C(8)-C(9)-C(10)	110.8 (2)	C(9)-C(10)-C(11)	111.3 (2)
C(6)-C(11)-C(10)	113.6 (2)	C(6)-C(12)-C(13)	121.6 (2)
C(6)-C(12)-C(17)	121.9 (2)	C(13)-C(12)-C(17)	116.5 (2)
C(12)-C(13)-C(14)	122.3 (2)	C(13)-C(14)-C(15)	119.7 (2)
C(14)-C(15)-C(16)	119.3 (2)	C(15)-C(16)-C(17)	121.0 (2)
C(12)-C(17)-C(16)	121.2 (2)		

1985). Drawings were made on a Zeta-8 plotter using a Tektronix 4205 graphics terminal.

The atomic fractional coordinates for non-hydrogen atoms are given in Table 1 and the bond distances and bond angles not involving the H atoms are given in Table 2.* The C-H bond distances range from 0.92 (2) to 1.14 (2) Å.

* Lists of structure-factor amplitudes, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51118 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Discussion. The PCP molecule (1) contains three different ring systems: a benzene ring, a cyclohexane ring and a piperidine ring. The mean C—C bond distance in the benzene ring is 1.390 Å and the mean C—C—C bond angle is 120.0°. The internal ring angle at C(12), however, where the benzene ring is attached to the rest of the molecule (Fig. 1), is significantly smaller, 116.5 (2)°, than the other five ring angles. The same trend holds for the cyclohexane ring where the bond angle at C(6) is 105.7 (1)°, significantly smaller than the mean C—C—C bond angle, 111.1°. The corresponding values in the cyclohexane ring in PCP hydrochloride (Argos *et al.*, 1970) are 107 (5) and 111.6°, respectively, and in 1-piperidine-1-benzylcyclohexane (Ducruix & Pascard-Billy, 1974), a molecule very similar to PCP, 105.2 (4) and 111.7°, respectively, for molecule 1 and 105.7 (4) and 112.1 (4)° for molecule 2. It is clear, therefore, that the

cyclohexane ring angle is smaller at the C atom with non-hydrogen substituents than at C atoms with two H atoms.

The two exocyclic C—N—C bond angles in PCP, with values of 114.3 (3) and 116.2 (1)° (Table 2), are significantly different from each other. In PCP hydrochloride, however, they are quite similar with values of 114.3 (4) and 114.4 (4)°, respectively.

The two cyclohexane bonds at C(6), *i.e.* C(6)—C(7) (1.537 Å) and C(6)—C(11) (1.536 Å) are significantly longer than the other cyclohexane C—C bonds which have a mean value of 1.524 (3) Å (Table 2). This type of foreshortening of the outer cyclohexane bonds is also observed in 1-piperidine-1-benzylcyclohexane (Ducruix & Pascard-Billy, 1974) and is probably a result of neglect of correction for thermal motion. The two C—N bond distances in the piperidine ring, with a mean value of 1.455 (2) Å, are significantly shorter than the exocyclic C(6)—N bond distance, 1.490 (2) Å. The same trend in the C—N bond distances was observed in PCP hydrochloride (Argos *et al.*, 1970) where the corresponding values were 1.508 (8) and 1.550 (7) Å, respectively, and, to a lesser extent, in 1-piperidine-1-benzylcyclohexane (Ducruix & Pascard-Billy, 1974) where the values were 1.479 (7) and 1.464 (7) Å, respectively. These subtle differences between the exocyclic and endocyclic C—N bond distances may indicate different orbital hybridizations in these bonds. Somewhat longer C—N bond distances are expected theoretically in the hydrochloride salt owing to the protonation of the N atom.

Both the piperidine and the cyclohexane rings are in the usual chair conformation (Fig. 1). The C(6) atom of the cyclohexane ring has the phenyl ring attached in the equatorial position and the piperidine ring in the axial position, which orients the phenyl ring away from the lone-pair electrons on the N atom of the piperidine ring. The configuration of the unprotonated PCP molecule observed here is different from that observed for protonated PCP (Argos *et al.*, 1970). This is apparent from the overlay drawing of the two molecules (Fig. 2). The main difference lies in the orientation of the cyclohexane ring which flips from one chair form to the other. This puts the protonated piperidine ring in the equatorial position, whereas when unprotonated it assumed an axial position. This conformational chair-chair interconversion is consistent with the fact that bulkier substituents usually occupy an equatorial position (Vollhardt, 1987), the protonated piperidine in this case being bulkier than the unprotonated one. A distance calculation made by attaching a proton to the N atom of piperidine in neutral PCP shows that this proton has close contacts with the axial protons on C(8) and C(10) (the so-called 1,3-diaxial interaction) and with the carbon atoms C(7), C(8), C(10) and C(11). A conformational rearrangement is, therefore, necessary when neutral PCP is protonated.

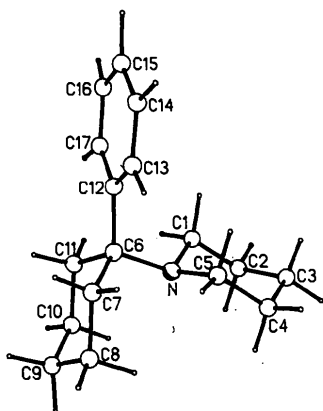


Fig. 1. The PCP molecule in the observed configuration.

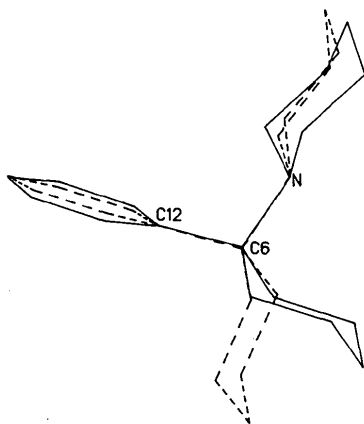


Fig. 2. A view of a comparative overlay of PCP (solid line) and protonated PCP (dotted line; Argos *et al.*, 1970). Labeled atoms in the two molecules were fitted by the least-squares method (SHELXTL; Sheldrick, 1985).

There are no short intermolecular contacts (Pauling, 1960), except between H(14) in the molecule whose coordinates are given in Table 1 and H(3B) at symmetry position $(1-x, -y, -z)$ (2.30 \AA).

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X-ray Structure of Cyanamide at 108 K

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Abstract. CH_2N_2 , $M_r = 42.04$, orthorhombic, $Pbca$, $a = 6.856$ (1), $b = 6.628$ (1), $c = 9.147$ (1) \AA , $V = 415.7 \text{ \AA}^3$, $Z = 8$, $D_x = 1.343 \text{ g cm}^{-3}$, $\lambda(\text{Mo K}\alpha) = 0.71069 \text{ \AA}$, $\mu = 1.09 \text{ cm}^{-1}$, $F(000) = 176$, $T = 108$ (1) K, $R = 0.051$ for 598 unique observed reflections. The cyanamide molecule is not totally planar. It has a pyramidal structure at the amino group. The N(1)–C–N(2) angle is 178.1 (1)°. One cyanamide molecule is linked to four neighbouring molecules by two pairs of symmetry-related hydrogen bonds.

Introduction. Experimental results with microwave, infrared and Raman spectroscopy suggest that the cyanamide molecule has a non-planar structure in the ground state (Daoudi, Pouchan & Sauvaitre, 1982; Birk & Winnevisser, 1986). *Ab initio* studies on cyanamide predict a planar or a non-planar structure, depending on the basis set used (Riggs & Radom, 1985; Ichikawa, Hamada, Sugawara, Tsuboi, Kato & Morokuma, 1982). An imprecise room-temperature X-ray structure analysis on cyanamide was performed by Zvonkova & Khvatkina (1961). Dyhr-Nielsen, Hansen & Larsen (1976) reported a neutron diffraction study on cyanamide at 100 K. The low-temperature X-ray crystal structure of cyanamide was determined to establish whether the structure is planar and whether the NCN angle is linear.

Experimental. Cyanamide (m.p. 318–319 K) is a weak acid with a great affinity for water. It may polymerize to form the dimer, dicyandiamide or even the trimer, melanine. Commercially available cyanamide (99+% purity, Aldrich) was slowly vacuum sublimed at 287 K to give good quality, colourless single crystals. A crystal of approximate dimensions $0.3 \times 0.3 \times 0.4 \text{ mm}$ was mounted inside a Lindemann tube. The crystal was aligned on a DEC MicroPDP computer-controlled Siemens four-circle diffractometer and was slowly cooled to 108 (1) K with the aid of a nitrogen gas stream low-temperature device designed by Dietrich & Dierks (1970). Lattice parameters from least-squares refinement of 33 reflections, $31 < 2\theta < 45^\circ$. Ten standard reflections with a good spread in reciprocal space and of different intensities were monitored every 120 min and showed insignificant intensity fluctuations throughout the measurement. All 2200 reflections in the hemisphere $h: -9$ to 9; $k: -9$ to 9, $l: 0$ to 12, in the range $2 < \theta < 30^\circ$ were measured with the ω - 2θ scan mode (Zr-filtered Mo K α radiation, $\lambda = 0.71069 \text{ \AA}$).

A variable scan range $\Delta\theta = (1.06 + 0.26\tan\theta)^\circ$ was used with minimum and maximum scan speeds of 0.44 and $3.55^\circ \text{ s}^{-1}$. Merging of data in the Laue class mmm gave 598 unique reflections, 50 unobserved ($I < 2\sigma$) ($R_{\text{int}} = 0.033$). Data corrected for Lorentz-polarization effects, but not for absorption. The structure was