The Crystal Structure and the Absolute Configuration of (+)-Amphetamine Dihydrogen Phosphate

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(+)-Amphetamine dihydrogen phosphate, $C_9H_{14}N^+.H_2PO_4^-$, crystallizes in the monoclinic space group $P2_1$, with $Z = 2$. The unit-cell dimensions are $a = 13.022$ (7), $b = 6.025$ (4), $c = 7.920$ (5) Å, $\beta = 102.62$ (5)°. The structure was determined by a combination of direct methods and the heavy-atom technique and was refined by a full-matrix least-squares procedure to an R value of 0.026 for 1370 observed reflexions collected by diffractometry. The absolute configuration was found to be S at the asymmetric carbon atom C(8). The amphetamine molecule consists of two almost planar and mutually perpendicular parts, the benzene ring and the ethylamine chain. Short hydrogen bonds between adjacent phosphate anions form columns running in the **b** direction. The amphetamine cations are attached to these chains by $N-H\cdots O$ hydrogen bonds.

Introduction

Amphetamine is one of the more potent sympathomimetic amines and has been used as an effective appetite depressant, as well as an antifatigue, euphoric and antidepressant drug, but it may on chronic administration lead to acute paranoid psychosis. The simplicity of its structure and its variety of biological effects have made amphetamine a ready target for studies on structure–activity relationships offering a ground for the development of novel pharmacological tools (Biel, 1970). There have been at least four suggestions to explain the biological action of amphetamine including synaptic release of noradrenaline, inhibition of the re-uptake of noradrenaline, inhibition of monoamine oxidase and direct action on receptors of the brain (Neville, Deslauriers, Blackburn & Smith, 1971). The absolute configuration of amphetamine is of considerable importance since the two enantiomers exhibit vast differences in their biological activities. In a previous work, the crystal structure of (+)-amphetamine sulphate was determined (Bergin & Carlström, 1971). However, owing to dislocations in the crystal, resulting in poor accuracy in the measured intensities, it was at that time not possible to determine the absolute configuration. Since the dihydrogen phosphate gives high-quality crystals, it was decided to use these for the determination of the absolute configuration.

Experimental

(+)-Amphetamine dihydrogen phosphate was prepared from the sulphate and rather large, transparent crystals were quite easily grown from an aqueous solution. One optically perfect crystal was reshaped by partial dissolution into a piece measuring 0.5 × 0.4 × 0.2 mm. Preliminary unit-cell dimensions and systematic absences were determined from Weissenberg photographs while accurate cell parameters were obtained from diffractometer data. The density was measured by flotation in a xylene–chloroform mixture.

Crystal data

(+)-Amphetamine (α-methyl-phenethylamine or 1-phenyl-2-aminopropane) dihydrogen phosphate, $C_9H_{14}N^+.H_2PO_4^-$, $M_r = 233.21$, $a = 13.022$ (7), $b = 6.025$ (4), $c = 7.920$ (5) Å, $\beta = 102.62$ (5)°, $V = 606.37$ Å³, $D_m = 1.272$ (5), $D_x(Z = 2) = 1.277$ g cm⁻³, μ(Mo $K\alpha$) = 0.986 cm⁻¹. Systematic absences: $0k0$ when k is odd, which gives two possible space groups $P2_1$ and $P2_1/m$. The latter, being centrosymmetric, was disregarded because of the asymmetry of the amphetamine molecule.

The crystal was mounted about its *b* axis in an automatic linear diffractometer (Pailred). Integrated intensities were measured using graphite-monochromated Mo $K\alpha$ radiation ($\lambda = 0.7107$ Å) for the layers $hk0$ through $hk7$ within sin $\theta/\lambda \leq 0.65$. The fainter reflexions were scanned two or three times and the background was measured for 1 min on each side. Standard reflexions measured at regular intervals during the data collection showed no significant change in intensity. Out of a total of 1528 unique reflexions, 151 had intensities not statistically different from the background level. Excluding these reflexions the net intensities were corrected for Lorentz and polarization factors, but not for absorption owing to the low μ value. The corrected structure amplitudes were placed on an approximately absolute scale by Wilson statistics.

Structure determination and refinement

In the three-dimensional Patterson maps, two peaks with almost identical intensities were found on the Harker section. To choose the one corresponding to the P—P rotation peak direct methods with the phase determination program *MULTAN* (Germain, Main & Woolfson, 1971) were applied. A comparison of the Patterson maps and the *E* maps calculated from the best *MULTAN* set showed that one of the peaks corresponded to a P—P rotation peak, whereas the other was caused by added P—O peaks. The Fourier map calculated by use of phase angles derived from the P atom contained a false mirror plane through the P atom, thus generating the false space group $P2_1/m$, but it was possible to select a suitable set of O atoms. By two three-dimensional electron density calculations all remaining non-hydrogen atoms could be located giving a conventional R value ($R = \Sigma \|F_o| - |F_c\|/\Sigma |F_o|$) of 0·26.

The refinement was carried out by a full-matrix least-squares procedure. The atomic scattering factors were those of *International Tables for X-ray Crystallography* (1974). After two cycles of isotropic refinement of the non-hydrogen atoms the R value had dropped to 0·114. An additional cycle with weights applied to $|F_o|$ according to $w = 1/(a + |F_o| + c|F_o|^2 + d|F_o|^3)$ with $a = 20\cdot0$, $c = 0\cdot1$, $d = 0\cdot001$ yielded an R value of 0·084. Two additional cycles of refinement with anisotropic temperature factors lowered the R value to 0·047. At this stage a difference synthesis was calculated and all H atoms were easily located. A further refinement of the positional and anisotropic temperature parameters of the non-hydrogen atoms with the H atoms fixed in the positions found in the difference maps revealed that the seven strongest reflexions ($|F_o| > 40\cdot0$) were affected by secondary extinction and they were excluded from further calculations. The refinement procedure, including all

Table 1. *Final positional parameters* $(\times 10^4)$ *for non-hydrogen atoms*

E.s.d.'s in parentheses are in units of the least significant digit.

	x	y	z
P	10605 (1)	2500 (0)	1788 (1)
O(1)	11100 (1)	4887 (3)	1930 (2)
O(2)	11368 (1)	1089 (3)	962 (3)
O(3)	9526 (1)	2547 (4)	602 (2)
O(4)	10621 (1)	1754 (3)	3595 (2)
C(1)	5205 (2)	1647 (6)	3531 (4)
C(2)	4200 (2)	1850 (7)	2529 (4)
C(3)	3921 (2)	3676 (8)	1518 (4)
C(4)	4642 (2)	5300 (7)	1455 (4)
C(5)	5658 (2)	5101 (6)	2458 (4)
C(6)	5943 (2)	3297 (5)	3523 (3)
C(7)	7028 (2)	3129 (5)	4683 (3)
C(8)	7873 (1)	2442 (6)	3742 (2)
C(9)	7749 (2)	120 (6)	2999 (4)
N	8904 (1)	2586 (5)	5013 (2)

Table 2. *Final fractional coordinates* $(\times 10^3)$ *for hydrogen atoms having a temperature factor B of* $3\cdot5 \text{ Å}^2$

E.s.d.'s in parentheses are in units of the last digit.

	x	y	z
H(1)	543 (2)	26 (7)	420 (4)
H(2)	371 (2)	72 (6)	254 (4)
H(3)	322 (2)	364 (7)	85 (4)
H(4)	453 (2)	671 (6)	80 (4)
H(5)	615 (2)	634 (7)	246 (4)
H(7A)	706 (2)	197 (6)	561 (4)
H(7B)	718 (2)	460 (6)	526 (4)
H(8)	793 (2)	353 (7)	287 (4)
H(9A)	704 (2)	20 (7)	212 (4)
H(9B)	831 (2)	−25 (6)	231 (4)
H(9C)	778 (2)	−99 (7)	388 (4)
H(NA)	947 (2)	226 (7)	448 (4)
H(NB)	896 (2)	156 (6)	589 (4)
H(NC)	901 (2)	393 (7)	554 (4)
H(O1)	95 (2)	575 (6)	95 (4)
H(O2)	106 (2)	8 (7)	41 (4)

parameters except the B values (3·5 Å²) for the H atoms, was continued until the shifts in the positional parameters of all atoms were less than one fifth of their standard deviations, resulting in a final R value of 0·026. The atomic fractional coordinates are given in Tables 1 and 2. All the computations were performed on an IBM 360/75 using our program system (Bergin, 1971a) except for the stereo pictures which were produced by the plotting program *ORTEP* (Johnson, 1965).*

The absolute configuration

The absolute configuration was first determined using Hamilton's (1965) statistical test by calculating weighted R values for the two enantiomers, giving $R_w(1) = 0\cdot03263$ and $R_w(2) = 0\cdot03242$ for the two possible configurations 8(R) and 8(S) around the asymmetric carbon atom C(8). The configuration with the lower R value has a probability of being correct on a significance level close to 0·5%. However, as pointed out by Engel (1972), this method is best suited for structures with heavier atoms or for light-atom structures where the refinement is extremely accurate. The present case was considered somewhat uncertain and the method of Bijvoet, Peerdeman & van Bommel (1951) was therefore applied. A new crystal was trimmed to an almost spherical shape and mounted

Table 3. *Ratios of calculated and observed structure factors of reflexions showing the effect of anomalous dispersion most accentuated*

h k l	$|F_c(hkl)|/|F_c(\bar{h}\bar{k}\bar{l})|$	$|F_o(hkl)|/|F_o(\bar{h}\bar{k}\bar{l})|$
8 1 2	1·14	1·13
11 1 2	0·93	0·94
12 1 2	1·06	1·07
6 2 2	1·06	1·18
15 2 2	1·06	1·10
12 4 2	1·08	1·07
11 5 2	0·95	0·95
6 6 2	0·93	0·95

about its c axis in an integrating Weissenberg camera. Ni-filtered Cu $K\alpha$ radiation was chosen since this gives a sufficient anomalous scattering factor for P (*International Tables for X-ray Crystallography*, 1974). With the multiple-film technique eight pairs ($hkl-\bar{h}\bar{k}\bar{l}$) from the second layer were measured on a microdensitometer. A comparison of the observed and calculated structure factor ratios (Table 3) indicates configuration S at the α-carbon atom C(8) in perfect agreement with the previous R-value test.

Description of the structure

The geometry of the amphetamine molecule

Bond distances and valency angles between atoms, uncorrected for thermal vibration, are given in Table 4 and in Fig. 1 which also shows the atomic numbering system. All interatomic distances and angles between non-hydrogen atoms are close to expected values and in excellent agreement with those found in structures of related molecules such as adrenaline (Andersen, 1975a), adrenaline bitartrate (Carlström, 1973), noradrenaline (Andersen, 1975b), noradrenaline hydrochloride (Carlström & Bergin, 1967), ephedrine monohydrogen phosphate monohydrate (Hearn, Freeman & Bugg, 1973), ephedrine dihydrogen phosphate (Hearn & Bugg, 1972), ephedrine hydrochloride (Bergin, 1971b), (+)-pseudoephedrine and (+)-pseudo-ephedrine hydrochloride (Mathew & Palenik, 1977). Unfortunately no comparison can be made with the only earlier crystal structure determination of amphetamine (Bergin & Carlström, 1971) owing to its rather poor accuracy.

Fig. 1. Schematic drawing of the amphetamine molecule showing the numbering of the atoms. Distances are in Å, angles in degrees.

Table 4. *Intramolecular bond distances (Å) and bond angles (°) of the amphetamine ion with estimated standard deviations in parentheses*

C(1)–C(2)	1·381 (3)	C(3)–H(3)	0·956 (24)
C(2)–C(3)	1·363 (5)	C(4)–H(4)	0·987 (34)
C(3)–C(4)	1·364 (5)	C(5)–H(5)	0·981 (34)
C(4)–C(5)	1·391 (4)	C(7)–H(7A)	1·007 (33)
C(5)–C(6)	1·376 (4)	C(7)–H(7B)	0·999 (35)
C(6)–C(1)	1·383 (4)	C(8)–H(8)	0·965 (34)
C(6)–C(7)	1·511 (3)	C(9)–H(9A)	1·032 (25)
C(7)–C(8)	1·515 (3)	C(9)–H(9B)	1·025 (25)
C(8)–C(9)	1·513 (6)	C(9)–H(9C)	0·962 (35)
C(8)–N	1·495 (2)	N–H(NA)	0·950 (23)
C(1)–H(1)	0·999 (37)	N–H(NB)	0·918 (35)
C(2)–H(2)	0·937 (30)	N–H(NC)	0·909 (40)
C(2)–C(1)–C(6)	120·4 (3)	C(1)–C(6)–C(7)	120·4 (3)
C(1)–C(2)–C(3)	120·5 (4)	C(5)–C(6)–C(7)	121·1 (3)
C(2)–C(3)–C(4)	120·2 (4)	C(6)–C(7)–C(8)	113·7 (3)
C(3)–C(4)–C(5)	119·6 (4)	C(7)–C(8)–C(9)	114·6 (3)
C(4)–C(5)–C(6)	120·9 (3)	C(7)–C(8)–N	107·2 (3)
C(5)–C(6)–C(1)	118·4 (3)	C(9)–C(8)–N	108·6 (3)

Fig. 2. Stereoscopic drawing of the amphetamine molecule. Heavy atoms are represented by thermal ellipsoids of 50% probability. H atoms are depicted as small spheres.
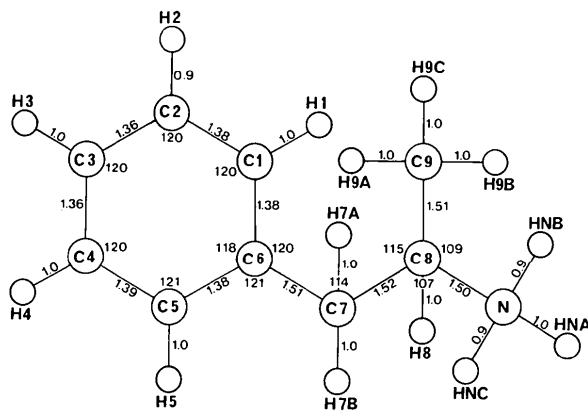
Table 5. Least-squares planes and deviations in Å of individual atoms

The equations of the planes are in the form $AX + BY + CZ = D$, where X, Y, Z are coordinates in orthogonal ångström space along a, b, c respectively.

Plane of benzene ring
$$-0.4617X + 0.4707Y + 0.7518Z = -0.3227$$

C(1)	−0.006	C(4)	−0.004
C(2)	−0.006	C(5)	−0.008
C(3)	0.011	C(6)	0.013

Plane of side chain
$$-0.1873X - 0.9547Y + 0.2310Z = -2.5663$$

C(6)	−0.036	C(8)	0.031
C(7)	0.041	N	−0.035

The bonds involving H atoms are all quite normal and corresponding bond angles have a maximal deviation of about 7° from expected values.

The amphetamine molecule contains two almost planar, mutually perpendicular parts, the benzene ring and the ethylamine side chain. This can be seen in the stereoscopic pair in Fig. 2. Table 5 gives atomic deviations from the two best planes. The maximum deviation of an individual atom in the phenyl ring is 0.013 Å and for an atom in the side chain 0.041 Å. The torsion angle τ_1, C(5)—C(6)—C(7)—C(8), is −78° and the antiperiplanar torsion angle τ_2, C(6)—C(7)—C(8)—N, is 174° showing that the ethylamine chain is nearly fully extended. This conformation is also found in aqueous solution where the *trans*-phenylamino rotamer is predominant not only for amphetamine but also for some of its derivatives (Neville, Deslauriers, Blackburn & Smith, 1971). In the solid state fully extended ethylamine chains oriented more or less perpendicular to the aromatic ring are frequently encountered in phenethylamines (Carlström, Bergin & Falkenberg, 1973).

The geometry of the phosphate group

Bond lengths and angles of the phosphate group are given in Table 6 together with data from some similar phosphate structures. As can be seen in this table the dihydrogen phosphate ions have similar geometries with two short P—O distances of about 1.50 Å and two long P—O distances, corresponding to the P—OH bonds, of about 1.56 Å.

Some of the O—P—O angles deviate several degrees from the tetrahedral arrangement so that the HO—P—OH angle is appreciably larger and the O—P—O angle correspondingly smaller than the tetrahedral value. A closer inspection of earlier accurate determinations of organic phsophate groups indicates that the dihydrogen phosphate ion regularly seems to have this distortion.

Hydrogen bonds and molecular packing

A stereoscopic drawing of the molecular packing and the hydrogen-bonding system is shown in Fig. 3. Table 7 gives pertinent distances and angles for the hydrogen bonds.

Earlier determinations of the crystal structures of dihydrogen phosphates show the characteristic feature of continuous columns of phosphate ions joined by short hydrogen bonds. In the present structure such columns of screw-related phosphate groups held together by strong hydrogen bonds, O(1)—H(O1)···O(3) and O(2)—H(O2)···O(3), 2.56 and 2.61 Å respectively, run in the **b** direction.

The infinite columns of phosphate groups are mutually connected in the **c** direction by three N—H···O hydrogen bonds tetrahedrally arranged around the charged amino N atom. The (+)-amphetamine cations are thus firmly linked to the phosphate columns, but

Table 6. P—O lengths (Å) and O—P—O angles (°) of some organic dihydrogen phosphate ions

E.s.d.'s in parentheses are in units of the least significant digit. P—O(1) and P—O(2) represent the longer P—OH bonds, while P—O(3) and P—O(4) correspond to the shorter P—O bonds.

Bond lengths	Amphetamine dihydrogen phosphate	Procaine dihydrogen orthophosphate	Ephedrine dihydrogen phosphate	Glycylglycine phosphate monohydrate	L-Arginine phosphate monohydrate
P—O(1)	1.570 (2)	1.563 (1)	1.578 (5)	1.571 (5)	1.594 (8)
P—O(2)	1.556 (2)	1.565 (1)	1.555 (5)	1.567 (5)	1.570 (9)
P—O(3)	1.509 (1)	1.504 (2)	1.505 (5)	1.502 (5)	1.513 (8)
P—O(4)	1.496 (2)	1.498 (1)	1.498 (5)	1.501 (5)	1.490 (10)
Bond angles					
O(1)—P—O(2)	103.9 (1)	107.66 (7)	102.6 (4)	107.2 (3)	106.3 (4)
O(1)—P—O(3)	109.8 (1)	109.17 (8)	108.4 (4)	111.4 (3)	111.0 (4)
O(1)—P—O(4)	106.7 (1)	107.67 (8)	109.8 (4)	107.1 (3)	105.3 (5)
O(2)—P—O(3)	110.0 (1)	106.21 (8)	108.2 (4)	107.1 (3)	107.9 (5)
O(2)—P—O(4)	111.2 (1)	110.40 (7)	111.8 (4)	110.1 (3)	111.6 (5)
O(3)—P—O(4)	114.6 (1)	115.49 (8)	115.3 (4)	113.8 (3)	114.4 (5)
	Present work	Freeman & Bugg (1975)	Hearn & Bugg (1972)	Freeman, Hearn & Bugg (1972)	Aoki, Nagano & Iitaka (1971)

Table 7. *Hydrogen-bonded interactions*

The columns labelled x', y', z' give the symmetry code of the acceptor atom Y'. Reference molecule is in x,y,z.

X	H	Y'	x'	y'	z'	$X\cdots Y'$	$H\cdots Y'$	$X-H\cdots Y'$
N	H(NA)	O(4)	x	y	z	2·76 Å	1·81 Å	175°
N	H(NC)	O(4)	$2-x$	$y+\frac{1}{2}$	$1-z$	2·76	1·86	171
N	H(NB)	O(1)	$2-x$	$y-\frac{1}{2}$	$1-z$	2·92	2·02	166
O(1)	H(O1)	O(3)	$2-x$	$y+\frac{1}{2}$	$-z$	2·56	1·66	167
O(2)	H(O2)	O(3)	$2-x$	$y-\frac{1}{2}$	$-z$	2·61	1·81	172
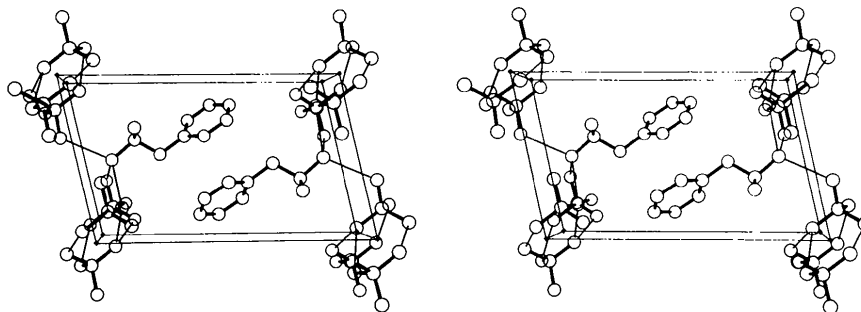
Fig. 3. Stereoscopic drawing of the molecular packing as seen along **b**. Thin lines represent hydrogen bonds.

there are no connexions other than van der Waals forces holding the screw-related amphetamine molecules together. This explains the pronounced cleavage parallel to (100) of the crystal. The general features of the above-described arrangement are frequently found in ethylamine salts where the amino N is the only donor. In many aspects the packing is similar to that found in amphetamine sulphate (Bergin & Carlström, 1971) and ephedrine hydrochloride, and mono- and dihydrogen phosphates (Bergin, 1971b; Hearn, Freeman & Bugg, 1973; Hearn & Bugg, 1972). Apart from the hydrogen bonds there are no intermolecular distances in the present structure violating ordinary packing requirements.

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