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The Structures of Ampicillin: a Comparison of the Anhydrate and Trihydrate Forms

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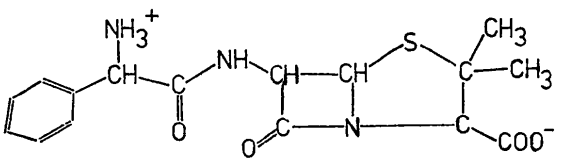
The structure of an anhydrate form of ampicillin, $C_{16}H_{19}N_3O_4S$, has been determined.



It crystallizes in the monoclinic system in space group $P2_1$ with two molecules in a unit cell of dimensions $a=12{\cdot}40$, $b=6{\cdot}20$, $c=12{\cdot}00$ Å, $\beta=114{\cdot}5°$ (standard deviation 0·30%). The structure was solved by Patterson heavy-atom methods and Fourier refinement from X-ray intensity measurements obtained from visual comparison and the equi-inclination Weissenberg method. Full-matrix least-squares refinement yielded an R value of 0·106 for observed data. The molecular configuration is very similar to the known configuration of the trihydrate form (space group $P2_12_12_1$). Both forms exist in the crystalline state as zwitterions with hydrogen bonding between the amino nitrogen atom and the ionized carboxyl group. In both forms the thiazolidine ring is puckered with four of the atoms forming an approximately planar arrangement with the remaining atom significantly out of this plane. The non-coplanar atoms are C(2) in the anhydrate and S(1) in the trihydrate. A comparison is made with the known thiazolidine ring configurations of other penicillins. The nitrogen atom N(4) of the β-lactam of both forms exists in a pyramidal configuration with its neighbouring atoms. The molecular packing of the two forms is completely different. The amino group in the anhydrate is hydrogen bonded to the ionized carboxyl groups of two molecules. In the trihydrate the amino group is hydrogen bonded to a single carboxyl group and to an intricate arrangement of the three hydrogen-bonded water molecules which also form hydrogen bonds to three other atoms within the molecule. There is no further hydrogen bonding in the anhydrate structure.

Introduction

Ampicillin, 6-[D-(−)-2-amino-2-phenylacetamido]penicillanic acid, is an antibiotic in common use and is effective against a wide variety of Gram-positive and Gram-negative organisms. Ampicillin was first described by Doyle, Fosker, Nayler & Smith (1962) who referred to obtaining a monohydrate which was identified by elemental analysis of a product which had been dried *in vacuo* over P_2O_5. Subsequently the anhydrate and trihydrate forms were described respectively by Grant & Alburn (1964, 1965) and Johnson & Hardcastle (1964) and the various hydrated forms were then discussed by Austin, Marshall & Smith (1965). Grant & Alburn (1965) reported results by Doyne of preliminary X-ray investigations on the anhydrate and monohydrate, but no information was given on the preparation of their poorly crystalline monohydrate (Grant & Alburn, 1967). Austin *et al.* (1965) concluded that the monohydrate was either amorphous or consisted of partially dehydrated trihydrate. More recently, Kamiya & Nishikawa (1970) have concluded that there is no real evidence for the existence of a crystalline monohydrate and the amorphous nature of ampicillin previously termed ampicillin monohydrate is also indicated by Shefter, Fung & Mok (1969). From time to time there have been reports of the existence of one or more further crystalline anhydrates, *viz.* form III ampicillin by Johnson & Hardcastle (1969), form 2 ampicillin by Shefter *et al.* (1973) and delta-ampicillin by Parker & Stanniforth (1975).

Crystallization of ampicillin from aqueous solution at temperatures below 50°C results in the formation of the trihydrate form while crystallization from aqueous solution at temperatures above 60°C yields the anhydrate (Austin *et al.*, 1965).

The anhydrate may also be obtained by heating other forms of ampicillin in a hot medium (Grant & Alburn, 1964, 1967). Poole & Bahal (1968) determined the transition temperature of the two forms in the presence of water as 42°C. Thus the trihydrate is the most stable form in water at room temperature. Though Poole & Bahal (1968) reported that the anhydrate is relatively unaffected by water, Bahal (1975) has indicated that this is not so. The anhydrate delta form reported by Parker & Stanniforth (1975) is prepared by rapidly heating purified trihydrate under specified conditions to a temperature of 120°C. The X-ray powder diffraction pattern of this form appears to be similar to that of the anhydrate form 2 reported by

Shefter *et al.* (1973). These authors stated that form 2 is rapidly converted to trihydrate in the presence of water. We have observed that the delta form also behaves in this way.

Only the crystalline structure of the trihydrate has been reported in detail (James, Hall & Hodgkin, 1968 and private communication). The present report, being part of a continuing investigation of the structure and physical properties of a series of penicillins and other antibiotic materials, describes the authors' investigations of the crystallographic structure of ampicillin anhydrate as prepared according to the process of Grant & Alburn (1967) and compares the structure of this with that of the trihydrate reported by James *et al.* (1969).

Experimental

Ampicillin trihydrate was obtained from Beecham Research Laboratories. Attempts were made to form suitable single crystals of ampicillin anhydrate from this material and the following method proved to be the most satisfactory. A slurry was made by adding 3·0 g ampicillin trihydrate to a solution of 5·0 ml isopropanol and 5·0 ml water. The slurry was added in one portion to 30 ml water which had previously been brought to boiling point. The mixture was stirred vigorously to assist the solution of trihydrate which occurred in 10–15 s. The solution was maintained at 85 °C. Crystal growth commenced after approximately 1½ min and the crystals were collected after 4 min by filtration through a preheated sintered glass funnel. The colourless crystals produced were very small and a large number of preparations and much searching of the crystals were required in order to obtain the best crystals of typical size 0·8 × 0·1 × 0·04 mm.

The unit-cell dimensions were determined from zero-level equi-inclination Weissenberg photographs, the camera radius was determined from high-angle reflexions from an annealed gold wire and the cell dimensions refined by a least-squares method. The unit-cell dimensions are $a = 12{\cdot}40$, $b = 6{\cdot}20$, $c = 12{\cdot}00$ Å, $\beta = 114{\cdot}5°$ with standard deviation 0·30%. Systematic absences $0k0$, $k = 2n+1$ indicated space group $P2_1$ or $P2_1/m$ in the monoclinic system. The density measured by flotation in a mixture of cyclohexane and chloroform was 1380 kg m^{-3}. The calculated density assuming two molecules per unit cell is 1388 kg m^{-3}; therefore space group $P2_1$ was indicated and later confirmed.

Data for intensity measurement were obtained by the equi-inclination method on a Stoe–Weissenberg camera using Ni-filtered Cu $K\alpha$ radiation ($\lambda = 1{\cdot}5418$ Å) and the multiple-film technique. The crystals for these measurements were rotated about the b axis with the long edge of the crystal parallel to the rotation axis. The X-ray films showed severe reduction in intensity of reflexions at high $\sin\theta$ after crystals had prolonged exposure to X-rays. Four crystals were used to collect the three-dimensional data. The intensities of the X-ray reflexions were obtained by visual comparison with a precalibrated density scale. The intensities of 1699 reflexions were examined, of which a total of 1452 were of measurable intensity. The absorption coefficient $\mu = 2001$ m^{-1}; no absorption correction was applied to the intensity measurements.

Structure determination and refinement

The structure was solved by initial determination of the sulphur atom position by means of a sharpened Patterson function and subsequent Fourier refinement using $|F_o|$ as coefficients with the phases calculated from the atoms whose positions were already known. Full-matrix least-squares refinement minimizing the function $\sum w||F_o| - |F_c||^2$ with individual isotropic temperature factors, unit weights and including refinement of interlayer scale factors resulted in $R = 0{\cdot}156$, where $R = \sum||F_o| - |F_c||/\sum|F_o|$. An $F_o - F_c$ Fourier synthesis

Table 1. *Final positional and temperature parameters obtained from final least-squares refinement*

Positional parameters are given as fractions of cell edges × 10^4. Isotropic temperature factors are of the form $\exp(-B\sin^2\theta/\lambda^2)$. Anisotropic temperature factors are expressed as $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)]$. The units of B are Å^2 × 10^2 and those of U_{ij} are Å^2 × 10^4. Standard deviations in parentheses are with respect to the last figures given.

	x	y	z	B or U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S(1)	5663 (2)	5000	3249 (2)	359 (9)	637 (32)	657 (13)	−149 (12)	182 (8)	−114 (14)
C(2)	4044 (8)	5154 (22)	2806 (8)	384 (17)					
C(3)	3510 (8)	4082 (19)	1518 (7)	362 (16)					
N(4)	4345 (6)	2384 (16)	1550 (6)	290 (28)	458 (60)	611 (38)	15 (33)	199 (27)	−6 (40)
C(5)	5496 (9)	2310 (23)	2608 (8)	444 (19)					
C(6)	6069 (9)	1788 (23)	1732 (9)	457 (20)					
C(7)	4831 (8)	2099 (22)	711 (8)	387 (16)					
O(8)	5619 (6)	7160 (17)	370 (6)	595 (38)	610 (59)	673 (38)	29 (40)	329 (32)	22 (41)
C(9)	3662 (13)	7433 (32)	2743 (13)	661 (30)					
C(10)	3736 (9)	3900 (23)	3714 (9)	448 (19)					
C(11)	2220 (8)	3246 (20)	1176 (8)	332 (16)					
O(12)	1441 (5)	4681 (14)	942 (6)	399 (29)	404 (53)	829 (42)	70 (31)	291 (29)	100 (37)
O(13)	2046 (7)	1354 (14)	1175 (8)	521 (40)	309 (59)	942 (53)	−88 (33)	218 (37)	−131 (40)
N(14)	6975 (7)	3154 (18)	1678 (8)	373 (37)	487 (66)	902 (56)	45 (37)	317 (37)	29 (48)
C(15)	7917 (8)	2375 (21)	1535 (8)	363 (16)					
O(16)	8129 (6)	488 (15)	1490 (8)	506 (36)	507 (66)	942 (50)	−42 (35)	370 (36)	−77 (43)

Table 1 (*cont.*)

	x	*y*	*z*	*B*
C(17)	8828 (9)	4098 (20)	1547 (8)	393 (17)
N(18)	9229 (7)	3423 (17)	573 (7)	383 (15)
C(19)	160	4187	2788	443 (19)
C(20)	18	6045	3493	670 (31)
C(21)	907	6099	4686	873 (44)
C(22)	1618	4297	5175	676 (31)
C(23)	1439	2440	4470	727 (33)
C(24)	550	2385	3277	564 (25)

Table 2. *Coordinates of hydrogen atoms inferred from F_o-F_c synthesis*

Coordinates are given as fractions of cell edges $\times 10^3$. The heavy atom associated with each hydrogen atom is also given.

	x	*y*	*z*
HC(3)	341	553	73
HC(5)	571	95	307
HC(6)	656	42	170
H(C9)(1)	426	237	387
H(C9)(2)	426	474	443
H(C9)(3)	294	316	333
H(C10)(1)	412	789	240
H(C10)(2)	279	763	227
H(C10)(3)	382	763	367
HN(14)	679	500	170
HC(17)	823	474	167
H(N18)(1)	882	210	0
H(N18)(2)	876	474	−27
H(N18)(3)	985	474	67
HC(20)	974	720	300
HC(21)	135	725	520
HC(22)	220	435	613
HC(23)	229	136	470
HC(24)	32	131	263

Table 3. *Bond distances and their standard deviations* (Å) *after final least-squares refinement*

Atoms C(19)–C(24) were refined as a rigid group and bond distances of 1·390 Å were used.

S(1)–C(2)	1·849 (10)	C(3)—C(11)	1·563 (14)
S(1)–C(5)	1·811 (14)	C(11)–O(12)	1·255 (13)
C(2)–C(3)	1·551 (13)	C(11)–O(13)	1·193 (15)
C(3)–N(4)	1·465 (14)	C(7)—O(8)	1·176 (11)
N(4)–C(5)	1·456 (10)	C(6)—N(14)	1·430 (17)
C(5)–C(6)	1·532 (18)	N(14)–C(15)	1·341 (15)
C(6)–C(7)	1·518 (12)	C(15)–O(16)	1·205 (16)
N(4)–C(7)	1·385 (15)	C(15)–C(17)	1·550 (17)
C(2)–C(9)	1·482 (24)	C(17)–N(18)	1·511 (15)
C(2)–C(10)	1·512 (18)	C(17)–C(19)	1·488 (8)

showed nine atoms with considerable anisotropic thermal vibrations. A weighting function $w=1/[\Delta F]^2$ was used in subsequent refinement cycles, where $\Delta F=0{\cdot}061F+0{\cdot}430$; this equation was obtained from a graph of $|\Delta F|$ *vs* $|F_o|$. Six reflexions which showed signs of being affected by extinction were omitted from the refinement. In the final refinement the carbon atoms of the benzene ring were refined as a rigid group due to the inability of the refinement process to produce atomic coordinates for this part of the molecule consistent with the expected bond lengths of 1·39 Å. The final R value was 0·106 using only the observed reflexions, anisotropic temperature factors on nine atoms and including all hydrogen atoms indicated on an F_o-F_c synthesis. The hydrogen atoms were given assumed temperature factors $B=3{\cdot}5$ Å, and neither their positional nor their temperature parameters were refined.* The major computations were carried out with the X-RAY 70 and 74 systems on the ICL 1906 A at the Atlas Computer Laboratory, Chilton. In all the calculations the scattering factor tables given in *International Tables for X-ray Crystallography* (1962) were used.

Discussion of the structure

The final parameters of ampicillin anhydrate are given in Table 1 and the hydrogen-atom coordinates inferred from the F_o-F_c synthesis are given in Table 2. The bond distances and angles are listed with their standard deviations in Tables 3 and 4 and are shown in context with the corresponding distances and angles for ampicillin trihydrate in Fig. 1. Fig. 2 shows the anhydrate structure viewed along the *b* axis, and the trihydrate structure viewed along the *c* axis is shown in Fig. 3.

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31658 (6 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 4. *Bond angles and their standard deviations* (°)

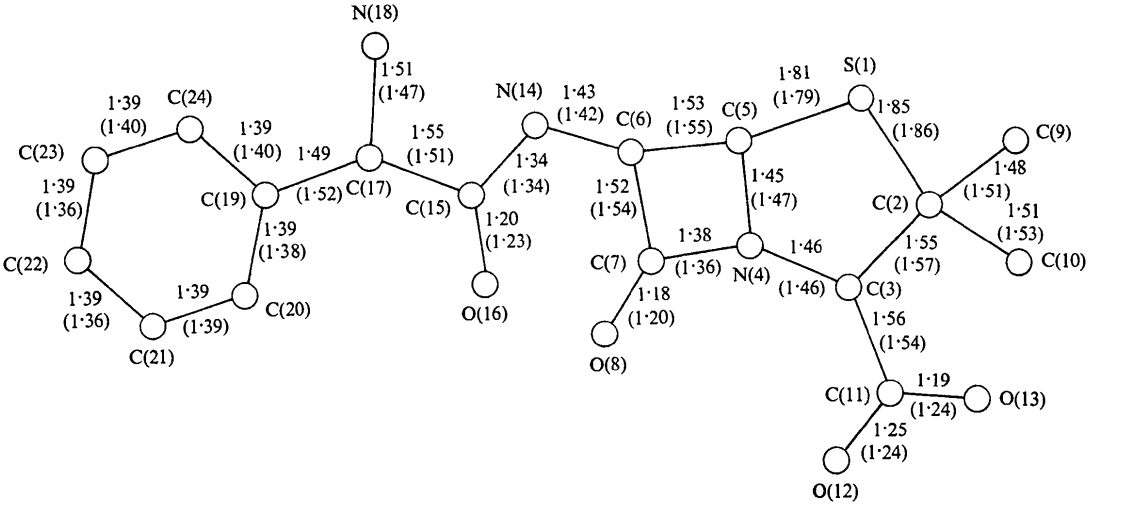
The interbond angles within the phenyl group C(19)–C(24) were assumed to be 120°.

C(5)—S(1)—C(2)	90·60 (0·53)
S(1)—C(2)—C(3)	102·59 (0·74)
C(2)—C(3)—N(4)	106·43 (0·67)
C(3)—N(4)—C(5)	117·84 (0·85)
C(3)—N(4)—C(7)	126·29 (0·87)
N(4)—C(5)—S(1)	103·57 (0·83)
S(1)—C(5)—C(6)	118·87 (0·97)
N(4)—C(5)—C(6)	88·61 (0·71)
C(5)—C(6)—C(7)	85·57 (0·83)
C(6)—C(7)—N(4)	91·84 (0·74)
C(7)—N(4)—C(5)	93·61 (0·73)
S(1)—C(2)—C(9)	110·38 (0·92)
S(1)—C(2)—C(10)	109·86 (0·65)
C(3)—C(2)—C(9)	111·45 (0·86)
C(3)—C(2)—C(10)	111·51 (0·98)
C(9)—C(2)—C(10)	110·78 (1·15)
C(2)—C(3)—C(11)	111·21 (0·88)
N(4)—C(3)—C(11)	113·72 (0·92)
C(3)—C(11)—O(12)	115·46 (1·02)
C(3)—C(11)—O(13)	119·37 (0·97)
O(12)–C(11)—O(13)	125·15 (1·00)
N(4)—C(7)—O(8)	130·40 (0·92)
C(6)—C(7)—O(8)	137·74 (1·15)
C(5)—C(6)—N(14)	120·46 (1·08)
C(7)—C(6)—N(14)	115·74 (1·00)
C(6)—N(14)–C(15)	122·41 (1·12)
N(14)–C(15)–O(16)	125·03 (1·15)
N(14)–C(15)–C(17)	114·93 (1·09)
O(16)–C(15)–C(17)	119·81 (1·00)
C(15)–C(17)–N(18)	106·18 (0·88)
C(15)–C(17)–C(19)	109·76 (0·75)
N(18)–C(17)–C(19)	111·77 (0·73)
C(17)–C(19)–C(20)	119·32 (0·49)
C(17)–C(19)–C(24)	120·53 (0·49)

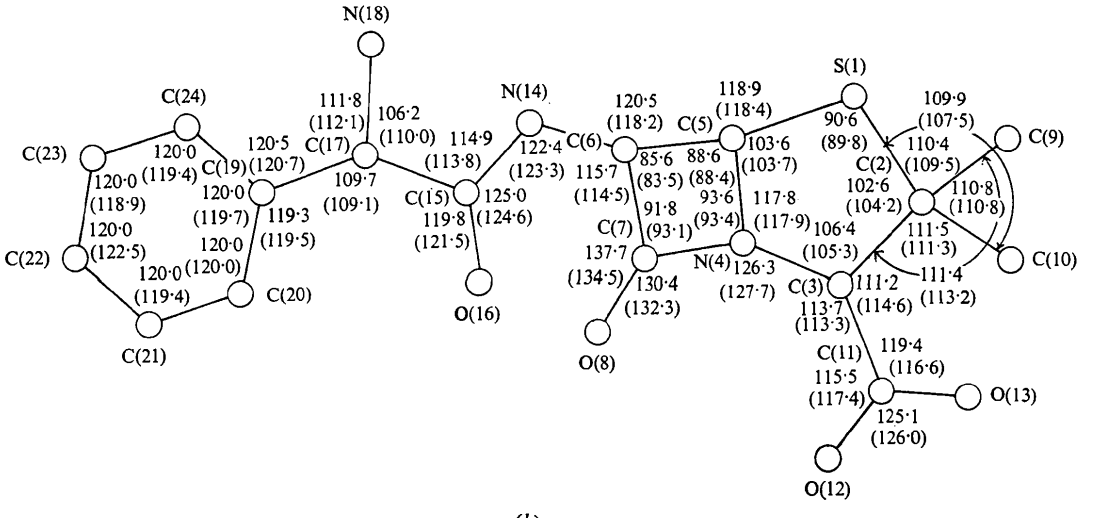
The ampicillin molecule exists as a zwitterion in both the anhydrate and trihydrate forms. The hydrogen atoms bonded to the amino nitrogen N(18) were indicated on the F_o-F_c synthesis and the bond lengths C(11)–O(12) at 1·255 Å (1·240 Å in trihydrate) and C(11)–O(13) at 1·193 Å (1·245 Å in trihydrate) are indicative of a high degree of π-orbital resonance. Comparison of the ampicillin molecules of Figs. 2 and 3 shows that the molecular configuration of the two forms is very similar.

The configurations of the thiazolidine rings of the anhydrate and trihydrate structures are not the same. In both forms four of the thiazolidine ring atoms form an approximately planar arrangement while the remaining atom is significantly out of this plane, full details are given in Table 5. In the anhydrate C(2) is 0·71 Å from the plane while in the trihydrate S(1) is 0·84 Å from the plane. This effect has been observed in other penicillins and Table 6 gives the results of other investigations of thiazolidine rings in penicillin derivatives which are known to the authors. A recent NMR study has shown that, in contrast to the solid-state observations, the thiazolidine ring of potassium benzyl penicillin in solution has the same configuration as the thiazolidine rings of ampicillin trihydrate and penicillin V sulphoxide (Dobson, Ford, Summers & Williams, 1975).

The distance of the nitrogen atom N(4) from the plane defined by C(3)C(5)C(7) is 0·35 Å in ampicillin anhydrate and 0·38 Å in ampicillin trihydrate. Thus in both forms the configuration of this nitrogen atom conforms to the pyramidal arrangement which appears



(*a*)



(*b*)

Fig. 1. (*a*) Interatomic distances and (*b*) interbond angles in the ampicillin anhydrate molecule; the corresponding values for ampicillin trihydrate are shown in parentheses. The C(19)–C(24) atoms of the anhydrate were refined as a rigid group and the assumed bond distances and angles are 1·39 Å and 120° respectively.

Table 5. *Planarity of the thiazolidine ring in ampicillin anhydrate and trihydrate*

The equations of the planes are expressed as $Px+Qy+Rz=S$ in direct space.

Ampicillin anhydrate

P	*Q*	*R*	*S*	Deviations (Å) of atoms from planes	
				S(1)	−0·049
				*C(2)	0·710
				C(3)	0·068
				N(4)	−0·117
				C(5)	0·099
−7·824	−2·521	10·386	−2·268		

Ampicillin trihydrate

P	*Q*	*R*	*S*	Deviations (Å) of atoms from planes	
				*S(1)	0·841
				C(2)	−0·005
				C(3)	0·009
				N(4)	−0·010
				C(5)	0·006
11·725	5·826	−3·834	4·763		

* Atoms not used to define the planes.

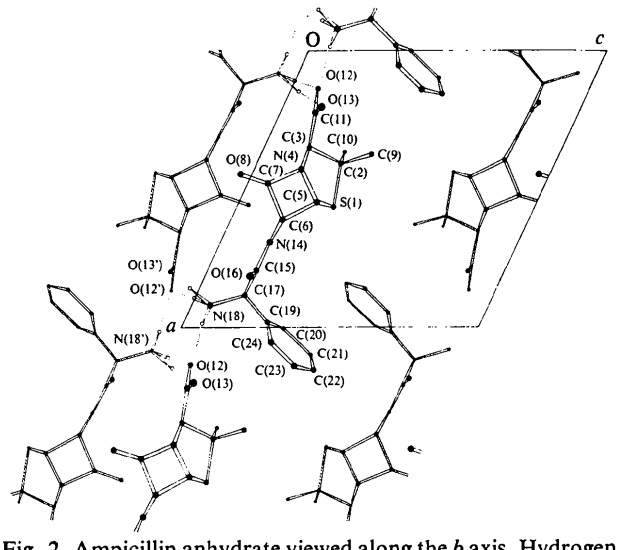


Fig. 2. Ampicillin anhydrate viewed along the *b* axis. Hydrogen atoms involved in hydrogen bonding are shown and the bonds are indicated by dotted lines.

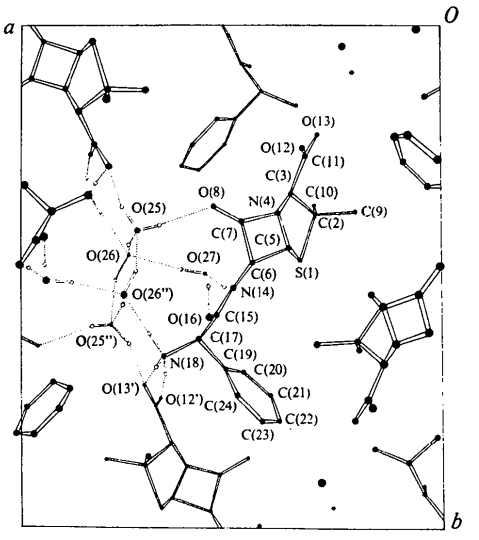


Fig. 3. Ampicillin trihydrate viewed along the *c* axis. Hydrogen atoms involved in hydrogen bonding are shown. [The diagram has been reconstructed from the paper by James *et al.* (1968) to facilitate a direct comparison with the anhydrate structure; the atomic coordinates were kindly provided by Professor James.]

to be a common feature of biologically active penicillins and cephalosporins (Sweet & Dahl, 1970; Vijayan, Anderson & Hodgkin, 1973).

In both the anhydrate and trihydrate forms the amino nitrogen atoms N(18) participate in hydrogen bonding with the oxygen atoms O(12) and O(13) of the ionized carboxyl group and in both forms this results in an infinite linkage of the molecules through the hydrogen bonding of N(18) to oxygen atoms in different molecules, *i.e.* along the **b** direction in the anhydrate and along the **c** direction in the trihydrate. In both crystalline forms one of the carboxyl oxygen atoms participates in the formation of two hydrogen bonds, in the anhydrate the donors are two symmetry-related N(18) atoms while in the trihydrate the donors are

Table 6. *Conformation of thiazolidine rings in various penicillins*

Penicillin	Planar portion formed by	Atom out of plane	Distance of atom from plane (Å)	Reference
Ampicillin anhydrate	S(1)C(3)N(4)C(5)	C(2)	0·71	(*a*)
Ampicillin trihydrate	C(2)C(3)N(4)C(5)	S(1)	0·84	(*b*)
Phenoxymethylpenicillin (penicillin V)	S(1)C(2)N(4)C(5)	C(3)	0·51	(*c*)
6-Aminopenicillanic acid	S(1)C(2)C(3)C(5)	N(4)	0·4	(*d*)
p-Bromopenicillin V	S(1)C(2)N(4)C(5)	C(3)	0·4	(*e*)
Potassium benzylpenicillin (penicillin G)			0·5	(*f*)
Penicillin V sulphoxide	C(2)C(3)N(4)C(5)	S(1)	?	(*g*)

(*a*) This paper. (*b*) James, Hall & Hodgkin (1968). (*c*) Abrahamsson, Crowfoot Hodgkin & Maslen (1963). (*d*) Diamond (1963). (*e*) K. J. Watson (unpublished). (*f*) Crowfoot, Bunn, Rogers-Low & Turner-Jones (1949); Pitt (1952). (*g*) Cooper, de Marco, Cheng & Jones (1969).

N(18) and O(25). In the anhydrate structure this hydrogen bonding effectively holds together opposite ends of the symmetry-related molecules. In contrast to the trihydrate, the anhydrate structure contains no other close contacts where hydrogen bonding can take place. The hydrogen-bond distances involved between the donor and acceptor atoms for the anhydrate are shown in Table 7.

Table 7. *Distances and their standard deviations* (Å) *between donor and acceptor atoms involved in hydrogen bonding in ampicillin anhydrate*

Donor	Acceptor	Distance
N(18)	O(12′)	2·846 (12)
N(18)	O(13′)	2·720 (12)
N(18)	O(12)	2·701 (11)

Apart from the close proximity of N(18) with O(12) and O(13) the molecular packing of the two forms is completely different. There is thus no way in which the trihydrate form could be converted into this anhydrous form in the solid state.

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