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The Crystal and Molecular Structure of Toyocamycin Monohydrate, a Nucleoside Antibiotic

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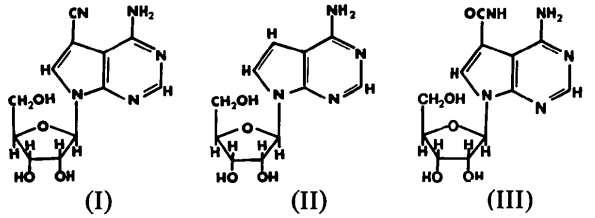
The crystal structure of toyocamycin, a nucleoside antibiotic having antineoplastic properties and a structural analog of tubercidin, has been determined by X-ray diffraction techniques. The crystal data are $a = 5{\cdot}245$ ($\pm 0{\cdot}001$), $b = 19{\cdot}781$ ($\pm 0{\cdot}005$), $c = 7{\cdot}547$ ($\pm 0{\cdot}002$) Å, $\beta = 118{\cdot}58$ ($\pm 0{\cdot}03$)°, $Z = 2$; space group $P2_1$. The structure was solved by a combination of the Nordman vector-space search and direct methods. Least-squares refinement with isotropic and then anisotropic temperature factors resulted in a final R value of 0·026 for the 1120 observed reflections measured on a diffractometer. The D-ribosyl group assumes the C(2′)-*endo* pucker with the *anti–gauche*$^+$ conformation for the base and the exocyclic C(4′)–C(5′) torsions. These features are one of the favored conformational combinations for the nucleosides. The cyano group at C(7) is nonlinear and does not participate in hydrogen bonding, but is involved in stacking interactions with adjacent bases in a manner similar to halogen-substituted nucleosides. The conformational and crystal packing properties of toyocamycin closely resemble those of tubercidin which does not have a cyano group at C(7)

Introduction

Toyocamycin (I) (4-amino-5-cyano-7β-D-ribofuranosylpyrrolo[2,3-D]pyrimidine) is a structural analog of tubercidin (II) (Ohkuma, 1961) and both are pyrrolopyrimidine nucleoside antibiotics. This antimicrobial agent markedly inhibits the growth of some animal tumors (Sareyoshi, Tokuzen & Fukuoka, 1965) with its antineoplastic activity dependent upon the presence of the amino and cyano groups. Toyocamycin differs from tubercidin only in the presence of the cyano group at position C(7) (purine numbering will be used hereafter for convenience of comparison with other purine systems). They display several common biological properties as well as some major differences (Roy-Burman, 1970). For instance, both are substrates for adenosine kinase (Hill & Bennett, 1969) and may be incorporated into the 3′ termini of transfer RNA molecules in place of the adenosine (Uretsky, Acs, Reich, Mori & Altweiger, 1968). Toyocamycin is incorporated in only limited amounts into ribosomal RNA, but tubercidin can be incorporated into the RNA or DNA of mouse fibroblasts (Acs, Reich & Mori, 1964) and may inhibit protein synthesis at the transcriptional rather than the translational level. Thus, the nucleosides display different degrees of inhibition in different organisms (Matsuoka, 1960; Anzai, Nakamura & Suzuki, 1957). The mechanism of action of toyocamycin is not known, but since it is closely related to tubercidin and is metabolized like adenine, its inhibitory effects are probably similar to those of tubercidin. The differences between toyocamycin and tubercidin may arise from the presence of the cyano substituent which may impose steric as well as functional factors in its interactions in certain enzymatic systems. The crystal structure determination of toyocamycin was undertaken with the purpose of furnishing stereochemical as well as intermolecular packing and hydrogen bonding details for comparison with those of tubercidin (Stroud, 1973; Abola & Sundaralingam, 1973). Further, the structural details of toyocamycin and tubercidin provide invaluable insights into the stereochemical properties of the related antibiotic sangivamicin (III).



(I) (II) (III)

Experimental

Crystals of toyocamycin were grown by slow evaporation of an aqueous methanol solution from a sample kindly provided by Dr R. K. Robins. Weissenberg and oscillation photographs established the crystals to be monoclinic. The systematic absences of $0k0$ reflections for $k = 2n + 1$, and the intensity statistics from

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diffractometer data indicated the space group to be $P2_1$. The unit-cell constants measured on the diffractometer are $a = 5{\cdot}245$ (1), $b = 19{\cdot}781$ (5), $c = 7{\cdot}547$ (2) Å, $\beta = 118{\cdot}58$ (3)°. The calculated density of 1·503 g cm^{-3}, with the assumption of two molecules of toyocamycin monohydrate per unit cell, agrees well with the observed density of 1·501 g cm^{-3} determined by flotation in a carbon tetrachloride-cyclohexane mixture.

The crystal chosen for data collection had approximate dimensions of 0·30 × 0·20 × 0·20 mm and was mounted along **a**. Three-dimensional intensity data were collected in the θ–2θ scan mode to a maximum 2θ of 127° on a Picker FACS-I automated diffractometer using Ni-filtered Cu $K\alpha$ ($\lambda = 1{\cdot}5418$ Å) radiation. The intensities of 1142 independent reflections were scanned and corrected for Lorentz and polarization effects, but not for absorption since its effects were considered to be small. 1120 reflections had intensities greater than 1·5 times their estimated standard deviation and only these were used in the structure analysis.

Structure solution

The structure was solved by a combination of Patterson search techniques with the vector-space search program of Schilling, Hoge & Nordman (1970) and direct methods. The model Patterson function was calculated for an 11-atom adenine fragment with eight vectors which were assigned weights proportional to the product of the atomic numbers of the contributing atoms. Additional contributions to the weights by overlapping vectors were also considered.

This function was rotated in the Patterson map through the Eulerian angles A, B and C with the MIN(M,N) function. While the (A,B) search unambiguously located the vector set in the correct plane of the Patterson function, a threefold ambiguity in the azimuthal rotation C of the vector set in the plane of the ring was encountered. The value of C = 160° was the highest in the MIN(M,N) map and was chosen for subsequent translation searches. The coordinates of this molecular fragment properly oriented and positioned in the cell (Prusiner, 1974) were then used as a model to refine the phases of 206 $|E|$'s > 1·3, where $|E|$ is the normalized structure factor, with the tangent formula and the computer program of Stewart, Kundell & Baldwin (1970). The refinement converged in 14 iterations with an $R(E)$ of 0·05 and an E map computed at this stage revealed all 22 atoms of the asymmetric unit, including the water of crystallization, in the highest 22 peaks in the map.

After solution of the structure it was apparent that the azimuthal orientation of the vector set in the ring plane chosen from the C search was incorrect. The correct orientation was related to the model by a 60° rotation and corresponds to C = 100°, the second highest peak in the MIN(M,N) function (Fig. 1). Nevertheless, 8 of the 11 input atoms coincide with actual atomic sites to within 0·3 Å, and account for the success of the tangent refinement.

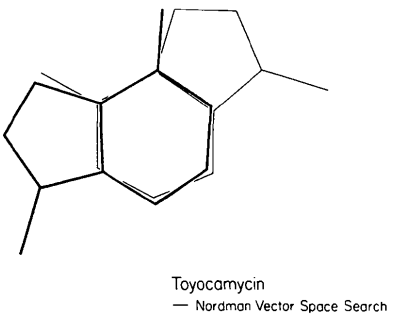

Fig. 1. A view normal to the base showing the relation between the actual atomic sites and those derived from the vector-space search.

Table 1. *Positional parameters of atoms in toyocamycin* (×10^4; *for* H ×10^3)

Standard deviations refer to the least significant digits.

	x	y	z
N(1)	3013 (4)	6111 (0)	5194 (3)
C(2)	4828 (5)	5578 (1)	5711 (3)
N(3)	4228 (4)	4946 (1)	4981 (3)
C(4)	1431 (4)	4875 (1)	3564 (3)
C(5)	−668 (4)	5373 (1)	2912 (3)
C(6)	208 (5)	6017 (1)	3798 (3)
N(6)	−1607 (4)	6551 (1)	3320 (3)
C(7)	−3301 (4)	5072 (1)	1375 (3)
C(71)	−6042 (5)	5411 (2)	285 (3)
N(71)	−8117 (5)	5711 (2)	−500 (4)
C(8)	−2689 (5)	4416 (1)	1168 (3)
N(9)	186 (4)	4290 (1)	2491 (3)
C(1′)	1675 (4)	3649 (1)	2791 (3)
O(1′)	1552 (3)	3449 (1)	947 (2)
C(2′)	288 (4)	3068 (1)	3357 (3)
O(2′)	1074 (3)	3057 (1)	5437 (2)
C(3′)	1517 (4)	2467 (1)	2755 (3)
O(3′)	4443 (4)	2394 (1)	4277 (2)
C(4′)	1345 (4)	2710 (1)	788 (3)
C(5′)	−1361 (5)	2511 (1)	−1117 (3)
O(5′)	−3878 (4)	2747 (1)	−1050 (2)
O(W)	−746 (5)	4083 (1)	6880 (3)
H(2)	685 (5)	564 (1)	673 (3)
H(61)	−93 (8)	700 (2)	387 (5)
H(62)	−367 (6)	652 (2)	252 (4)
H(8)	−372 (6)	406 (1)	26 (4)
H(1′)	370 (5)	373 (1)	386 (3)
H(2′)	−190 (5)	308 (1)	252 (4)
H(O2′)	22 (8)	341 (2)	569 (5)
H(3′)	45 (6)	210 (1)	243 (4)
H(O3′)	507 (7)	200 (2)	442 (5)
H(4′)	311 (4)	254 (1)	73 (3)
H(51′)	−139 (5)	274 (1)	−237 (3)
H(52′)	−129 (7)	198 (2)	−131 (5)
H(O5′)	−537 (7)	284 (2)	−234 (5)
H(W1)	−13 (11)	401 (3)	810 (7)
H(W2)	−250 (7)	435 (2)	623 (5)

Structure refinement

The atomic positions derived from the E map were subjected to four cycles of full-matrix least-squares refinement with individual isotropic temperature factors, and the $R(=\Sigma||F_o| - |F_c||/\Sigma|F_o|)$ values dropped from the initial value of 0·21 to 0·089. Two cycles of refinement with anisotropic temperature factors lowered the R value to 0·054. At this stage all the 15 H atoms were clearly defined in a difference Fourier map. Examination of the refinement statistics suggested that the weighting scheme used here, which was based on counting statistics (Stout & Jensen, 1968), was not performing well. Consequently we adopted a modified Hughes (1941) weighting scheme, where $w^{-1/2} = 1{\cdot}0$ for $|F_o| < 30{\cdot}84$ and $w^{-1/2} = |F_o|/30{\cdot}84$ for $|F_o| > 30{\cdot}84$, and submitted the H atoms to two cycles of refinement with isotropic temperature factors, thus lowering R to 0·039. After correction of the data for secondary extinction (Zachariasen, 1963), two additional cycles of refinement with anisotropic and isotropic temperature factors for the nonhydrogen and hydrogen atoms, respectively, resulted in complete convergence of all positional and thermal parameters and yielded a final R of 0·026 and 'goodness of fit' of 1·443. The final average shift/σ values for the nonhydrogen and hydrogen positional and thermal parameters were 0·016 and 0·242, respectively, with corresponding maximum values of 0·057 and 0·397.

The least-squares program used was that of Busing, Martin & Levy (1962) modified for the Univac machine by Rao (1968). Scattering-factor curves for C, N and O were those of Cromer & Waber (1965) while that for H was taken from Stewart, Davidson & Simpson (1965).

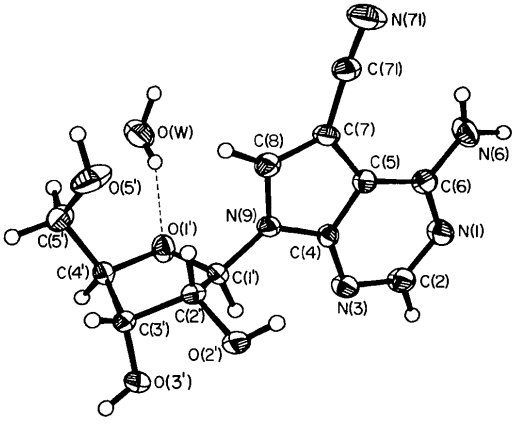

Fig. 2. The ellipsoids of thermal vibrations of the nonhydrogen atoms. The numbering system used is analogous to that of the adenine base in order to facilitate comparisons with the normal purine nucleosides.

Results

The atomic coordinates for both the nonhydrogen and hydrogen atoms are listed in Table 1.* In Fig. 2 are shown the thermal ellipsoids of the atoms, including the hydrogen-bonded water O drawn with 50% probability surfaces with the *ORTEP* program (Johnson, 1965). The bond distances and bond angles for the base and ribose moieties are displayed in Fig. 3. A summary of the ranges and mean values of the various types of covalent hydrogen bond lengths and

*Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32998 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

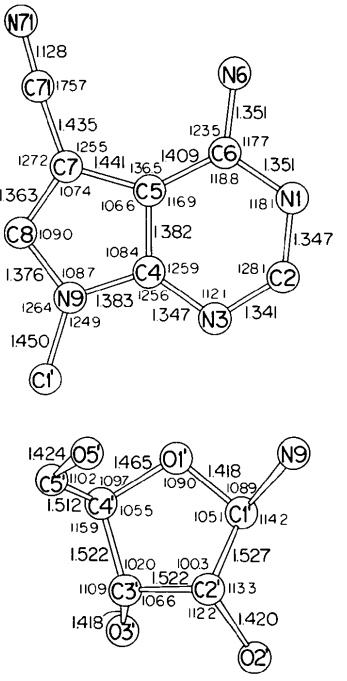

Fig. 3. The bond lengths and bond angles involving the nonhydrogen atoms.

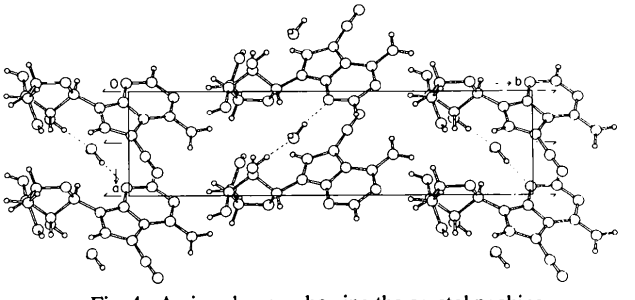

Fig. 4. A view down c showing the crystal packing.

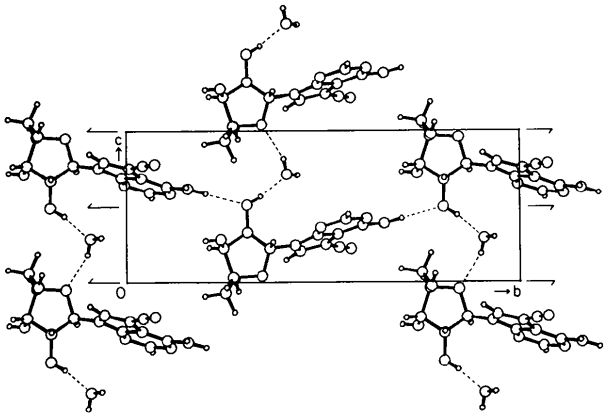

Fig. 5. A view down **a** showing the alternating hydrophobic and hydrophilic zones and the hydrogen bond involving the ribose ring O(1′).

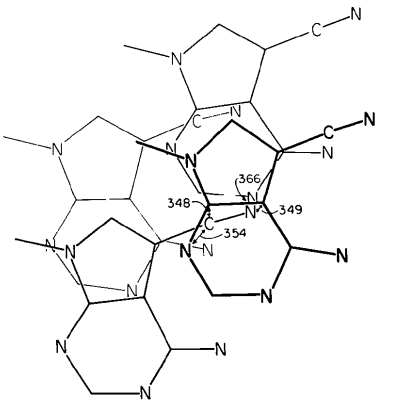

Fig. 6. A view normal to the base ring showing the base stacking and intermolecular distances.

Table 2. *Summary of the bond distances and bond angles involving the hydrogen atoms*

$\sigma(l) = 0{\cdot}04$ Å, $\sigma(\theta) = 1°$.

Bonds	Range	Mean	E.s.d.
C–H	0·87–1·06 Å	0·98 Å	0·02 Å
N–H	0·96–0·98	0·97	0·02
O–H	0·83–0·93	0·88	0·02°
O(*W*)–H	0·83–0·97	0·90	0·03
Angles			
C–C–H (tetrahedral)	108–115°	111°	1°
O–C–H (tetrahedral)	106–116	111	1
C–O–H (tetrahedral)	108–114	111	1
N–C–H (tetrahedral)		106	1
N–C–H (trigonal)	112–119	116	1
C–N–H (trigonal)	123–124	124	1
C–C–H (trigonal)		134	1
H–C–H (tetrahedral)		107	1
H–N–H (trigonal)		113	2
H–O(*W*)–H		116	2

angles are given in Table 2. Least-squares planes for the base and sugar are given in Tables 3 and 4 respectively. The intermolecular hydrogen bonding distances and angles are given in Table 5 while views of the molecular packing and stacking interactions are in Figs. 4–6.

Geometry of the base

The average estimated standard deviations are 0·003 Å in bond distances and 0·2° in bond angles. The bond distances and bond angles in the pyrimidine portion of the base ring compare favorably with those found for adenosine (Lai & Marsh, 1972), 3′-*O*-acetyladenosine (Rao &Sundaralingam, 1970) and 2′-deoxyadenosine [redetermined structure of Watson, Sutor & Tollin (1965), Lin & Sundaralingam (1971, unpublished results)]. But, as might be expected, there are substantial changes in the geometry of the five-membered ring due to the replacement of N with C at position 7. Variations between the geometry of the five-membered imidazole and pyrazole rings resulting from replacement of N by C have been discussed in some detail earlier (Prusiner, Brennan & Sundaralingam, 1973). The C(5)–C(7) and C(7)–C(8) bonds are 0·05 Å longer than the corresponding C(5)–N(7) and N(7)–C(8) bonds in adenosine. There is an increase of 3–4° in the endocyclic valence angles at positions 7 and 9 accompanied by a decrease of 3–5° in the endocyclic angles at positions 4, 5 and 8. The C(8)–N(9) and C(4)–N(9) bonds also display slightly more single-bond character than the corresponding bonds in adenosine. However, no significant differences in the bonding parameters are observed from those found for tubercidin. Even the cyano group at position 7 barely perturbs the pyrazole ring. The cyano group itself deviates from linearity by about 5°. Bond distances and angles involving the hydrogen atoms are in the usual range (Table 2).

Planarity of the base

The least-squares planes through the nine ring atoms of the base (plane I) as well as the six (plane II) and five (plane III) atoms of the pyrimidine and pyrazole rings are given in Table 3. It is apparent that the pyrrolopyrimidine ring is distorted slightly from planarity, as seen by the significant displacements experienced by the N(1) and C(5) atoms. The ribosyl C(1′) atom and the amino N(6) atom are displaced on the same side of the base ring. The individual pyrimidine and pyrrole rings themselves are virtually devoid of any distortion from planarity. The dihedral angle between those two rings is 1·8°. The amino group is twisted approximately 7° from the base ring.

Geometry of the sugar

The bond distances and bond angles in the ribose moiety of toyocamycin are generally in agreement with those found in the normal nucleosides and nucleotides. The observed shortening in the endocyclic anomeric bond C(1′)–O(1′) (1·418 Å) compared with the endocyclic C(4′)–O(1′) bond (1·465 Å) is a universal property of the *β-N*-glycosyl nucleosides and nucleotides (Sundaralingam, 1965; Sundaralingam & Jensen, 1965; Sundaralingam, 1968). The average ring C–C bond distance (1·524 Å) is in excellent agreement with established values. The smallest endocyclic angle of 100·3° is associated with the puckered C(2′) atom and is accompanied by an increase in the associated exocyclic angles of C(2′) from the tetrahedral values (Sundaralingam, 1965; Sundaralingam & Jensen, 1965). However, the C–OH hydroxyl bond distances are nearly equal here compared with the shortening sometimes encountered for the C–OH bond involving the puckered C atom. The slight shortening of the exocyclic C(4′)–C(5′) bond (1·512 Å) is also in accord with established geometrical features of nucleosides and nucleotides (Sundaralingam, 1965; 1975*a*).

Sugar conformation

Table 4 shows the deviations of atoms from the least-squares planes of the ribose. It is found that the ribosyl group assumes the C(2′)-*endo*–C(3′)-*exo* ($^2T_3$) pucker, while a slight variant of this, *viz* $^2T_1$, is observed in tubercidin (Abola & Sundaralingam, 1973; Stroud, 1973). The phase angle of pseudorotation (**P**) and maximum puckering amplitude (τ_m) (Altona & Sundaralingam, 1972) are 165·7 and 42·5°, respectively, compared with 149·3 and 43·8° for tubercidin. These values are within the normal range found for the C(2′)-*endo* *β*-nucleosides.

Table 3. *Least-squares planes for the base and deviations* (Å) *of the atoms from the planes*

Atoms used in fitting the least-squares planes are denoted by asterisks. The dihedral angle between planes II and III is 1·8°.

Plane I: $0{\cdot}658X + 0{\cdot}263Y - 0{\cdot}706Z = 0{\cdot}526$,
Plane II: $0{\cdot}652X + 0{\cdot}252Y - 0{\cdot}715Z = 0{\cdot}386$,
Plane III: $0{\cdot}661X + 0{\cdot}276Y - 0{\cdot}697Z = 0{\cdot}661$,

where X, Y, Z are atomic coordinates in Å referred to the system a, b, c^*.

	Plane I	Plane II	Plane III
N(1)	0·023*	0·009*	0·081
C(2)	0·008*	−0·003*	0·057
N(3)	−0·013*	−0·006*	0·015
C(4)	−0·015*	0·007*	−0·000*
C(5)	−0·020*	−0·001*	0·000*
C(6)	−0·008*	−0·008*	0·035
N(6)	−0·020	−0·024	0·032
C(7)	−0·000*	0·039	0·000*
C(71)	−0·001	0·043	−0·002
N(71)	−0·007	0·040	−0·007
C(8)	0·017*	0·068	−0·001*
N(9)	0·009*	0·051	0·001*
C(1′)	−0·022	0·027	−0·044
R.m.s. deviation of fitted atoms	0·014	0·006	0·001

Table 4. *Deviations* (Å) *of the atoms from the least-squares planes for the ribose*

Atoms used in fitting the least-squares planes are denoted by asterisks.

Plane I: $-0{\cdot}790X + 0{\cdot}040Y - 0{\cdot}612Z = -0{\cdot}539$,
Plane II: $-0{\cdot}900X + 0{\cdot}040Y - 0{\cdot}433Z = -0{\cdot}406$,

where X, Y, Z are atomic coordinates in Å referred to the system a, b, c^*.

	Plane I	Plane II
C(1′)	−0·119*	0·011*
O(1′)	0·058*	−0·017*
C(2′)	0·261*	0·641
O(2′)	−0·316	0·348
C(3′)	−0·224*	−0·009*
O(3′)	−1·625	−1·340
C(4′)	0·104*	0·016*
C(5′)	1·439	1·206
O(5′)	2·492	2·416
O(*W*)	0·346	1·344
R.m.s. deviation of fitted atoms	0·185	0·014

Table 5. *Hydrogen-bond lengths and angles of toyocamycin*

Estimated standard deviations are given in parentheses. Symmetry operations: (i) x,y,z (ii) $-x, \frac{1}{2}+y, -z$.

Symmetry	Translation x	y	z		Angle (°)	Length (Å)	Length from hydrogen (Å)
ii	+1	−1	+1	O(3′)–H(O3′)···N(1)	173 (1)	2·806 (3)	1·98 (4)
i	−1	0	0	O(*W*)–H(*W*2)···N(3)	175 (1)	2·881 (3)	1·91 (4)
ii	0	0	+1	N(6)–H(61)···O(2′)	160 (1)	3·097 (3)	2·16 (3)
i	0	0	+1	O(*W*)–H(*W*1)···O(1′)	160 (1)	2·985 (3)	2·19 (4)
i	0	0	0	O(2′)–H(O2′)···O(*W*)	165 (1)	2·685 (3)	1·81 (4)
i	−1	0	−1	O(5′)–H(O5′)···O(3′)	165 (1)	2·774 (3)	1·86 (4)

The exocyclic C(3′)–C(4′)–C(5′)–O(5′) torsion is *gauche*$^+$ (56·1°) which contrasts with the *trans* conformation adopted in tubercidin. This difference is attributed to the differences in the molecular packing and hydrogen bonding in the two compounds.

Glycosyl conformation

The glycosyl torsion, χ[O(1′)–C(1)–N(9)–C(8)], in toyocamycin is 60·7° resembling that found for tubercidin (73·1°). The high values of χ in these modified bases are correlated with the C(2′)-*endo* puckered sugars (Prusiner, Brennan & Sundaralingam, 1973; Singh & Hodgson, 1975). Thus the *anti* disposition of the base, the C(2′)-*endo* puckering of the sugar and the g^+ conformation around the exocyclic C(4′)–C(5′) bond found for toyocamycin are one of the favored conformational combinations for nucleoside crystal structures (Sundaralingam, 1969, 1973, 1975*a*,*b*).

Hydrogen bonding and crystal packing

The contents of the unit cell projected down **c** are shown in Fig. 4 and down **a** in Fig. 5. The water of crystallization links together three adjacent molecules by hydrogen bonds to the O(2′), N(3) and O(1′) atoms of the respective molecules. Although the latter hydrogen bonding is generally not favored in the common nucleotide crystal structures, several analogs have been reported to display this hydrogen-bonding scheme (Prusiner, Brennan & Sundaralingam, 1973; Sprang & Sundaralingam, 1973). Only one of the amino H atoms, that on the N(1) side of the base ring, is engaged in hydrogen bonding (Table 5); the other amino H facing C(7) is not, presumably because it is shielded by the cyano substituent. There is no interbase hydrogen bonding in this crystal. The cyano group itself is not involved in any hydrogen bonding but is involved instead in 'stacking' interactions (Fig. 6) in a manner reminiscent of that displayed by halogen-substituted bases (Bugg, Thomas, Sundaralingam & Rao, 1971; Bugg, 1972). The closest contact between the bases of 3·49 Å involves the N(71) atom of the cyano group and the adjacent base-ring atom C(5). The base rings are spaced 3·46 Å apart. The crystal packing consists of alternating layers of hydrophobic base stacks and ribose rings running parallel to the *ac* plane (Figs. 4 and 5). The water molecule sits over one base and lies in the plane of an adjacent base to which it is hydrogen bonded at the N(3) site. The base stacking in toyocamycin is analogous to that observed for tubercidin.

Conclusions

Toyocamycin exhibits one of the preferred overall conformations found for the nucleosides (*anti*, g^+, $^2T_3$). It differs from its analog tubercidin (*anti*, *t*, $^2T_1$) mainly in the exocyclic C(4′)–C(5′) bond conformation. This difference probably arises from the requirements of hydrogen bonding and crystal packing. Since the rotation around the C(4′)–C(5′) bond does not involve a major energy hurdle in nucleosides, the distinction between the biological properties of toyocamycin and tubercidin must stem not from conformational but rather from steric and probably hydrogen-bonding differences exerted by the cyano substituent. It is also noteworthy that the rod-shaped cyano group obstructs one of the amino H atoms from participating in hydrogen bonding and this might bring about an additional difference in the biological activities of toyocamycin and tubercidin. The analogous compound sangivamycin (III) should be expected to display conformational features very similar to those of toyocamycin and tubercidin, *viz* ^2E sugar pucker, *anti*/high-*anti* glycosyl conformation, and one of the staggered conformations with the C(4′)–C(5′) bond preferably *gauche*$^+$/*trans* rather than *gauche*$^-$. Sangivamycin possesses a carboxamide group at position C(7) which is likely to be engaged in an intramolecular hydrogen bond involving its carbonyl O and the N(6) amino group. Structural studies on sangivamycin are planned to obtain information on its stereochemical properties.

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Disorder in Crystalline Tetraiodoethylene; Constrained Refinements of Neutron Powder Diffraction Data

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The 4 K results of Haywood & Shirley [*Acta Cryst.* (1977), B**33**, 1765–1773] have been reanalysed using the constrained-refinement program *EDINP*. The molecules are constrained to *mmm* symmetry and disorder is allowed on both molecular sites. One site is fully ordered, whereas the other is disordered to 21%. New room-temperature results indicate disorder on both sites, but as certain unexplained features appear in the diffraction scan at this temperature, scans at intermediate temperatures are required before a satisfactory explanation can be found. The significance of the low-temperature result is thought to be high and a possible significance test is suggested.

Introduction

The crystal structure of tetraiodoethylene at room temperature has been studied by Khotsyanova, Kitaigorodsky & Struchkov (1952, 1953) and Kitaigorodsky, Khotsyanova & Struchkov (1953) using single-crystal X-ray diffraction. Later work by Kipps (1973) did not give a definitive answer to the question posed by Kitaigorodsky's (1961) suggestion that the molecules in the structure are disordered between two orientations on each of the two independent sites in the crystal. The structure is monoclinic, $P2_1/c$, and although both molecules are sited on symmetry centres they are not related by symmetry.