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The X-ray Structure of the Molecular Complex 8-Bromo-9-ethyladenine–Cyanuric Acid Monohydrate

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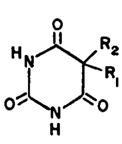
Crystals of the hydrogen-bonded complex 8-bromo-9-ethyladenine–cyanuric acid monohydrate, $C_{10}H_{13}BrN_8O_4$, have the space group $P2_1$ with unit-cell parameters $a=4{\cdot}932$ (4), $b=13{\cdot}411$ (9), $c=11{\cdot}693$ (7) Å, $\beta=108{\cdot}66$ (4)° with two complexes per unit cell. Intensity data were measured with an automated diffractometer using monochromated Mo $K\alpha$ radiation. The structure was solved with the heavy-atom technique and was refined by full-matrix least-squares procedures to a final $R=0{\cdot}042$ based on 1335 non-zero unique reflections. The adenine and cyanuric acid molecules associate through a Watson–Crick pairing and a pseudo-Hoogstein pairing in which a water molecule forms a hydrogen-bonded bridge. The hydrogen-bonding parameters in this structure are normal. In addition the structure incorporates a close Br···O contact and extensive stacking interactions.

Introduction

Despite the chemical similarity between the barbiturates (I) and uracil (or thymine) (II) the interactions between barbiturates and adenine derivatives (Voet, 1975) have been found to be quite different from those between uracil and adenine derivatives (Voet & Rich, 1970). The weak hydrogen-bond acceptor properties of the barbiturates have been described by Voet (1975) and by Gartland & Craven (1974). Parabanic acid (III), a derivative of barbituric acid, shares these weak hydrogen-bond acceptor properties (Shieh & Voet, 1975, 1976). It has been suggested that these unusual hydrogen-bonding properties are due to the electronic interactions among several closely associated carbonyl groups (Voet, 1972).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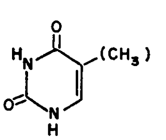
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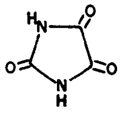
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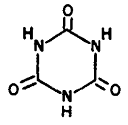
(IV)

Cyanuric acid (IV) resembles the barbiturates in that the latter's tetrahedral carbon atom has been replaced by an NH group so as to form an *s*-triazine ring. Associations between cyanuric acid and adenine derivatives can be expected from the results of Temperli, Turler & Ercegovich (1966) who found that cyanuric acid was incorporated into the RNA and DNA of a strain of thymine and uracil-requiring *E. coli* if the thymine and uracil in its growth medium were replaced by cyanuric acid.

The structural study of the crystalline complex 8-bromo-9-ethyladenine–cyanuric acid was undertaken to investigate the origin of the unusual hydrogen-bonding properties of adenine–barbiturate complexes. It will be seen below that the hydrogen-bonding properties of the above complex more nearly resemble those of adenine–uracil complexes than those of adenine–barbiturate complexes.

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Experimental

Crystals of the complex 8-bromo-9-ethyladenine–cyanuric acid monohydrate (A.X.H_2O) in the form of colorless rectangular plates were grown by the evaporation in air of an ethanol–dimethylformamide solution containing equimolar quantities of 8-bromo-9-ethyladenine (Cyclo Chemical) and cyanuric acid (Eastman Kodak). The ultraviolet spectrum of an aqueous solution of a washed single crystal suggested that the two starting materials were present in the crystal in approximately equimolar amounts.

A crystal of the complex with dimensions 0·35 × 0·13 × 0·08 mm was used in this study. Weissenberg and precession photographs of the crystal indicated that it had monoclinic lattice symmetry. The systematic absences of the $0k0$ reflections for k odd together with the determination that the unit cell contains two complexes (see below) indicated that the space group of the crystal is $P2_1$. This was subsequently confirmed by the successful refinement of the structure.

All further X-ray measurements were made with a Picker FACS-I diffractometer employing Mo $K\alpha$ radiation and equipped with a pyrolytic graphite monochromator. The unit-cell dimensions, as determined by the least-squares refinement of the angular positions of twelve reflections, are given in Table 1. The density of the crystals, which was measured by flotation in a mixture of CCl_4 and 1,4-dibromobutane, is in good agreement with the calculated density for the crystal containing two A.X.H_2O complexes in the unit cell. The waters of crystallization were probably absorbed from the air by the hygroscopic solution from which the complex crystallized.

Table 1. *Crystal data for 8-bromo-9-ethyladenine–cyanuric acid monohydrate*

Molecular formula $C_{10}H_{13}BrN_8O_4$

a = 4·932 (4) Å	F.W. 389·2
b = 13·411 (9)	Space group $P2_1$
c = 11·693 (7)	$Z=2$
β = 108·66 (4)°	μ(Mo $K\alpha$) = 30·1 cm^{-1}
d_{obs} = 1·75 g cm^{-3}	$F(000) = 392$
d_{calc} = 1·76	

The X-ray diffraction data were measured with the θ–2θ mode, a scan rate of 1° min^{-1} and a scan range of 1·5°. Stationary background counts of 20 s each were collected at both limits of each scan. A total of 1349 unique reflections with $2\theta < 50°$ were measured.

The measured intensities, I, were corrected for Lorentz and polarization effects. No absorption corrections were made due to the small size of the crystal. Standard deviations, $\sigma(I)$, were calculated according to the method of Stout & Jensen (1968) assuming an instrumental instability factor of 0·02. A total of 59 measured unique reflections had $I < 2{\cdot}33\sigma(I)$.

The bromine atom was located by the Harker analysis of the straight line sharpened Patterson map with the origin removed. The y coordinate of this atom was arbitrarily assigned a value of 0·25. An electron density map based on phases generated by the Br atom contained two sets of molecules related by a false center of symmetry located at the Br position. Most of the atoms of these two sets of molecules were intermingled in such a way that it would have been quite difficult to extricate a unique structure. However, cyanuric acid atom O(2) was well resolved. The position of this atom was used to break the false center of symmetry.

An electron density map with phases based on the position of the above oxygen atom, together with that of the bromine atom, clearly revealed the positions of the atoms of the cyanuric acid molecule. Three more iterations of the heavy-atom method revealed the positions of all 23 unique non-hydrogen atoms of the complex.

The structure was refined by the full-matrix least-squares method. The quantity minimized was $\sum w(|F_o|-|F_c|)^2$ where $w=I/\sigma^2(I)=1/\sigma^2(F_o)$. The atomic scattering factors for non-hydrogen atoms were taken from Cromer & Waber (1965) and those for hydrogen atoms were taken from Stewart, Davidson & Simpson (1965). Refinement of the scale factor, all atomic positions (except the arbitrarily fixed y coordinate of the Br atom) and the isotropic temperature factors, followed by a similar refinement in which the anisotropic temperature factors were varied, converged at a discrepancy index of $R=0{\cdot}045$. The difference Fourier map at this point revealed the positions of three of the expected thirteen hydrogen atoms. A least-squares refinement in which the non-hydrogen atoms were refined anisotropically and the hydrogen atoms were refined isotropically reduced the discrepancy index to $R=0{\cdot}043$. The difference Fourier map at this point revealed three more hydrogen atoms at their predicted positions. After further least-squares refinement, in which the positional parameters of the latter three hydrogen atoms were not varied, R converged to its final value of 0·042, based on 1335 non-zero unique reflections.* The highest peak in the final difference Fourier map, which was 1·0 Å away from the Br atom, had an electron density of 0·40 e $Å^{-3}$.

The molecular structures

The molecular structure of several contiguous A.X.H_2O complexes is illustrated in Fig. 1 together with the atomic numbering scheme used in this report. The final atomic parameters of the structure are given in Table 2. The covalent bond distances and angles in the structure are presented in Fig. 2. The observed

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31702 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

dimensions of the 8-bromo-9-ethyladenine molecule are in excellent agreement with the corresponding average quantities of previously reported adenine-containing crystal structures (Voet & Rich, 1970). The thermal parameters of adenine atom C(2′) are considerably larger than those of the other atoms. This is probably an indication of a large degree of rotational freedom that is commonly observed for methyl groups.

The bond parameters for cyanuric acid in the present structure are in good agreement with the corresponding

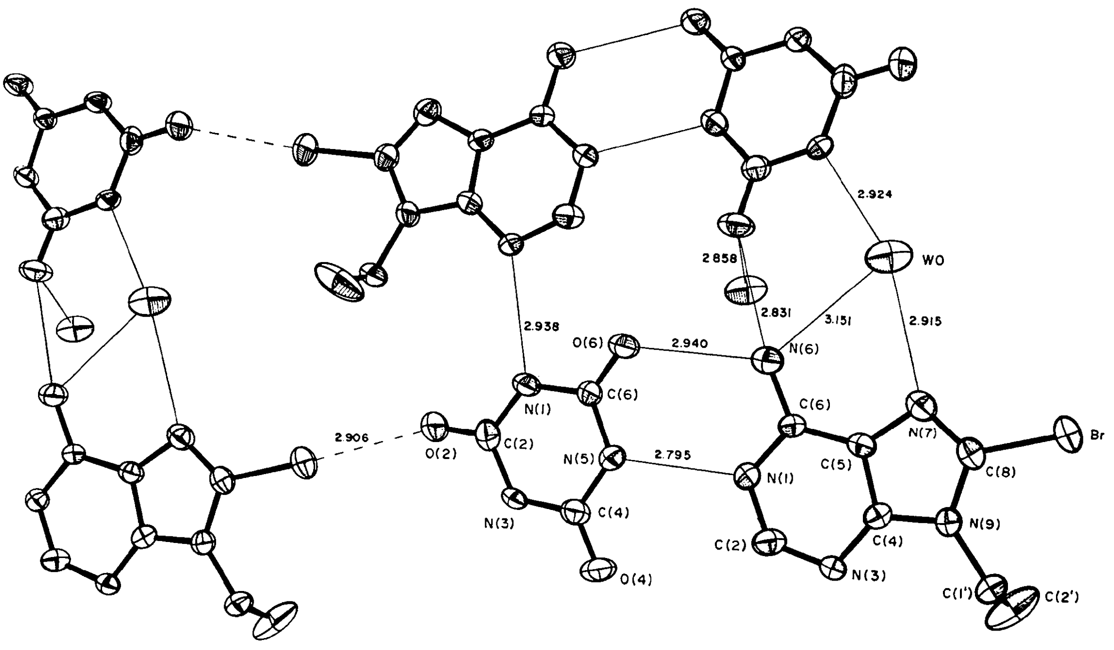

Fig. 1. A perspective drawing of approximately three contiguous asymmetric units of the crystalline complex 8-bromo-9-ethyladenine–cyanuric acid monohydrate. Atoms are illustrated as thermal ellipsoids at the 50% level. Hydrogen bonds are represented by thin lines. The Br···O interaction is represented by a dashed line. Hydrogen atoms have been deleted for the sake of clarity.

Table 2. *Positional and thermal parameters for the complex 8-bromo-9-ethyladenine–cyanuric acid monohydrate*

The positional parameters are expressed as fractions of a unit-cell edge. The anisotropic temperature factors have the functional form $T=\exp[-(h^2\beta_{11}+k^2\beta_{22}+l^2\beta_{33}+2hk\beta_{12}+2hl\beta_{13}+2kl\beta_{23})\times10^{-4}]$. Isotropic temperature factors have the functional form $T=\exp[-B\sin^2\theta/\lambda^2]$. Standard deviations, as determined from the variance–covariance matrix of the final cycle of least-squares refinement, are given in parentheses and refer to the least significant digits of their corresponding parameters. The prefixes A, X and W refer to the 8-bromo-9-ethyladenine, the cyanuric acid and the water molecules respectively.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
AN(1)	−0·1682 (13)	0·2941 (5)	0·0898 (5)	258 (27)	25 (3)	53 (5)	−12 (8)	2 (10)	1 (4)
AC(2)	−0·1164 (18)	0·3890 (7)	0·1238 (8)	376 (45)	25 (5)	62 (7)	−11 (12)	44 (15)	−1 (5)
AN(3)	0·1163 (11)	0·4275 (4)	0·2053 (5)	263 (29)	20 (3)	55 (5)	12 (8)	−1 (10)	1 (3)
AC(4)	0·3080 (15)	0·3558 (5)	0·2557 (6)	288 (34)	24 (4)	45 (6)	−5 (10)	26 (12)	−6 (4)
AC(5)	0·2791 (12)	0·2555 (8)	0·2305 (5)	239 (26)	22 (3)	51 (5)	6 (14)	23 (9)	3 (6)
AC(6)	0·0275 (15)	0·2238 (4)	0·1419 (6)	287 (33)	19 (5)	43 (5)	−4 (9)	18 (12)	0 (3)
AN(7)	0·5139 (13)	0·2028 (5)	0·3032 (5)	277 (30)	33 (4)	59 (5)	16 (9)	29 (11)	5 (4)
AC(8)	0·6736 (14)	0·2724 (5)	0·3688 (6)	222 (29)	35 (7)	52 (5)	16 (10)	16 (11)	3 (4)
AN(9)	0·5670 (12)	0·3672 (5)	0·3440 (5)	210 (26)	27 (4)	54 (5)	4 (8)	1 (10)	−3 (4)
AN(6)	−0·0329 (15)	0·1286 (5)	0·1045 (7)	317 (36)	27 (4)	78 (7)	11 (10)	9 (12)	−3 (4)
Br	1·0187 (1)	0·2500	0·4897 (1)	259 (3)	47 (0)	68 (1)	23 (1)	−10 (1)	5 (1)
AC(1′)	0·6959 (16)	0·4612 (6)	0·4009 (7)	328 (37)	25 (4)	72 (7)	−20 (10)	−2 (13)	−4 (5)
AC(2′)	0·6059 (23)	0·4861 (9)	0·5082 (10)	904 (73)	68 (9)	121 (10)	−116 (23)	177 (25)	−59 (8)
XN(1)	−1·0374 (13)	0·1448 (5)	−0·1958 (6)	234 (30)	22 (4)	79 (7)	7 (9)	−11 (11)	3 (4)
XC(2)	−1·2376 (18)	0·2176 (6)	−0·2403 (7)	246 (39)	43 (6)	47 (6)	2 (11)	11 (13)	3 (4)
XN(3)	−1·1464 (15)	0·3145 (5)	−0·2015 (6)	265 (37)	19 (4)	65 (7)	21 (10)	−14 (13)	4 (4)
XC(4)	−0·8906 (17)	0·3380 (6)	−0·1219 (8)	240 (43)	27 (5)	64 (8)	1 (11)	34 (15)	5 (5)
XN(5)	−0·7037 (11)	0·2603 (7)	−0·0816 (5)	254 (24)	25 (4)	69 (5)	−4 (11)	−7 (9)	−6 (5)
XC(6)	−0·7691 (16)	0·1631 (6)	−0·1153 (7)	211 (40)	25 (5)	61 (7)	−10 (13)	−10 (13)	3 (5)
XO(2)	−1·4730 (11)	0·2008 (4)	−0·3102 (5)	312 (28)	40 (3)	87 (5)	3 (8)	−35 (11)	3 (4)
XO(4)	−0·8241 (12)	0·4235 (4)	−0·0862 (5)	415 (31)	22 (3)	97 (6)	−9 (8)	45 (11)	−6 (3)
XO(6)	−0·5941 (11)	0·0969 (4)	−0·0789 (5)	294 (26)	24 (3)	104 (6)	8 (8)	−24 (10)	0 (3)
WO	−1·5006 (12)	0·4937 (5)	−0·2336 (6)	554 (34)	39 (3)	114 (6)	13 (10)	131 (13)	6 (4)

Table 2 (*cont.*)

	x	y	z	B
AH(N6)	0·124	0·080	0·129	3·8 (1·8)
AH(C1′)	0·650	0·513	0·334	4·4 (1·9)
AH(C2′)	0·680	0·538	0·548	4·3 (2·0)
XH(N2)	−1·284 (15)	0·354 (6)	−0·215 (6)	1·7 (1·5)
XH(N3)	−0·512 (12)	0·276 (5)	−0·014 (5)	1·3 (1·3)
WH	−1·561 (17)	0·494 (7)	−0·172 (7)	3·7 (2·0)

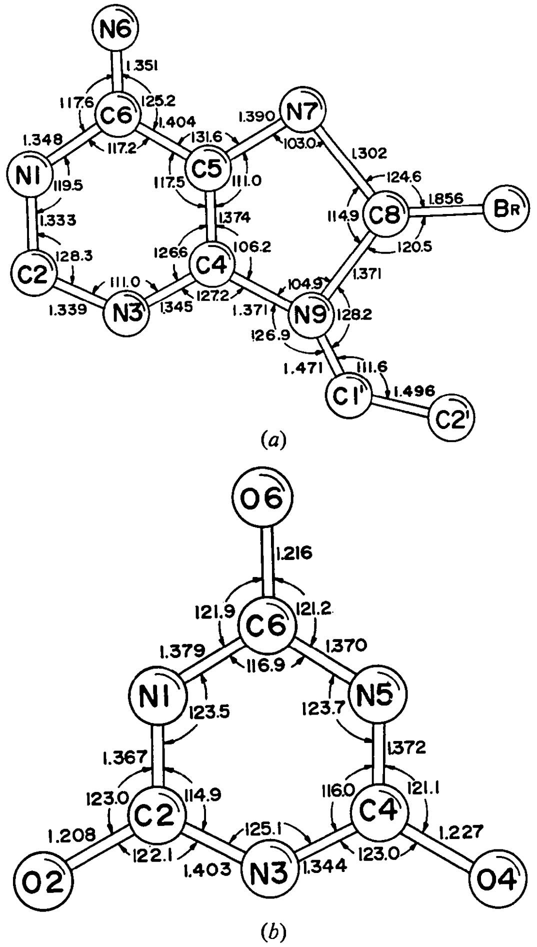

Fig. 2. The covalent bond distances (Å) and angles (°) involving non-hydrogen atoms for (*a*) 8-bromo-9-ethyladenine and (*b*) cyanuric acid. The average standard deviations of these quantities are 0·010 Å and 0·7° respectively.

quantities determined for crystalline cyanuric acid. The latter values were determined in highly accurate crystallographic determinations at room temperature and low temperature using X-rays (Verschoor & Keulen, 1971) and at low temperature using neutrons (Coppens & Vos, 1971). In Table 3 the average values of the bond parameters in these various studies are compared with those quantities for cyanuric acid in A.X.H_2O. It can be seen that corresponding quantities are in agreement within experimental error although the bond parameters of the present structure are, as expected, less accurate than those of the other studies.

Table 4 indicates that both the adenine and the cyanuric acid rings are approximately planar. However in both molecules atoms deviate significantly from their least-squares planes.

Table 4. *Deviations of atoms from the least-squares planes through the indicated atoms*

Adenine atom	Deviation†	Cyanuric acid atom	Deviation‡
N(1)	0·005 Å	N(1)	−0·005 Å
C(2)	0·023	C(2)	0·012
N(3)	0·002	N(3)	−0·016
C(4)	−0·020	C(4)	0·011
C(5)	−0·017	N(5)	−0·003
C(6)	−0·015	C(6)	0·001
N(7)	0·012	O(2)	0·017*
C(8)	0·027	O(4)	0·045*
N(9)	−0·018	O(6)	−0·038*
N(6)	−0·038*	R.m.s. deviation	0·010
Br	0·126*		
C(1′)	−0·027*		
R.m.s. deviation	0·017		

* Atoms not included in calculating the least-squares plane.

† The equation of the least-squares plane is:
$-3{\cdot}4627x-1{\cdot}6434y+10{\cdot}3975z=1{\cdot}0275$ Å.

‡ The equation of the least-squares plane is:
$-3{\cdot}1143x-1{\cdot}6972y+10{\cdot}8373z=0{\cdot}8683$ Å.

The molecular interactions

The A.X.H_2O crystal structure is held together by a variety of intermolecular interactions. These include hydrogen bonding, stacking and Br···O associations. The hydrogen-bond and Br···O distances are indicated in Fig. 1.

Table 3. *Average bond parameters for cyanuric acid*

Averages were taken with unit weights. Standard deviations, σ, which are shown in parentheses as the least significant digits of the tabulated values, were calculated in the usual manner:

$$\sigma=\left[\sum_{i=1}^{n}(x-\bar{x})^2/(n-1)\right]^{1/2}.$$

	Reference	Distances			Angles	
		C–O	C–N	C–N–C	N–C–N	N–C–O
This study		1·217 (9) Å	1·372 (19) Å	124·1 (9)°	115·9 (1·0)°	122·1 (8)°
Room-temperature X-ray*	(*a*)	1·213 (10)	1·374 (6)	124·6 (2)	115·4 (8)	122·3 (4)
Low-temperature X-ray*	(*a*)	1·221 (3)	1·372 (2)	124·7 (1)	115·4 (1)	122·3 (4)
Low-temperature neutron*	(*b*)	1·217 (2)	1·370 (2)	124·6 (0)	115·4 (1)	122·3 (5)

* The cyanuric acid molecule lies across a crystallographic twofold axis of symmetry.

(*a*) Verschoor & Keulen (1971); (*b*) Coppens & Vos (1971).

The structure, as can be seen in Fig. 1, is composed of sheets of complexed planar molecules. Each such sheet is comprised of endless parallel linear ribbons of alternating adenine and cyanuric acid rings. Each cyanuric acid molecule interacts with a neighboring adenine ring in the linear ribbon *via* hydrogen bonding to form a normal Watson–Crick base pair. The rather close contact of 3·100 Å between atoms AC(2) and XO(4) suggests that a C–H···O hydrogen-bond-like interaction (Voet, 1972) supplements this pairing. The dihedral angle between the least-squares planes of the adenine and the cyanuric acid rings in this base pair is 5·4°.

The cyanuric acid molecule interacts with its other neighboring adenine residue in the linear ribbon through a close Br···O contact of 2·906 Å. The accepted minimal van der Waals distance for such a contact is 3·35 Å (Pauling, 1960). The near linearity of the 174·1° AC(8)–Br–XO(2) angle indicates that this association is of the type that Hassel (1970) described as a charge-transfer interaction.

The complexed linear ribbons associate to form planar sheets *via* hydrogen-bonding interactions. An adenine and a cyanuric acid molecule in neighboring ribbons interact through the formation of a pseudo-Hoogsteen base pair. This interaction differs from a true Hoogsteen base pair in that the water molecule is insinuated between and forms hydrogen bonds to atoms AN(7) and XN(3). Model building indicates that steric hindrance by the bromine atom prevents 8-bromoadenine derivatives from forming Hoogsteen base pairs. Hence the interposition of the bridging water molecule relieves this steric interference.

Atom AN(6) is within hydrogen-bonding distance of three hydrogen-bond acceptor groups. The nearly linear AC(6)–AN(6)···XO(4) $(-1-x, -\frac{1}{2}+y, -z)$ angle of 165·1° and the normal AC(6)–AN(6)···XO(6) and AC(6)–AN(6)···WO hydrogen-bond angles of 115·5 and 108·9°, respectively, suggest that atom XO(4) participates in bifurcated hydrogen bonds with both hydrogen atoms substituent to atom AN(6). Here the XO(4)···AN(6)···XO(6) and XO(4)···AN(6)···WO angles of 69·6 and 68·2°, respectively, are essentially equal. Thus the presence of the water molecule, not unexpectedly, distorts thc geometry of the ··· AN(6)···XO(4) hydrogen bond from that found in a normal Hoogsteen base pair. The dihedral angle between the adenine and the cyanuric acid rings in this interaction is 15·3°.

Neighboring ribbons are further held together by a hydrogen bond between atoms XN(1) and AN(3). Such an interaction has not been observed in adenine–uracil base pairs (Voet & Rich, 1970; Sobell, 1972) but is not uncommon in crystalline complexes between adenine and barbiturate derivatives (Shieh & Voet, 1976; Epstein, Zeiger, Crocker & Voet, 1976).

The linear ribbons of complexed molecules stack over one another so as to form infinite walls of layered ring molecules. This is illustrated in Fig. 3. The adenine–adenine association in these stacks is dominated by a dipole–induced dipole interaction in which the polar Br atom overlies the polarizable adenine imidazole ring. Such interactions have been discussed by Bugg (1972) and Bugg, Thomas, Rao & Sundaralingam (1971). The crystal structures of 8-bromoadenosine (Tavale & Sobell, 1970) and 8-bromoguanosine (Bugg & Thewalt, 1969) exhibit stacking patterns that are quite similar to that found between the adenine molecules in the present structure [see Fig. 12 in Bugg (1972)].

The adenine–cyanuric acid stacking association is characterized by extensive atom–atom overlap. Inspection of Fig. 3 indicates that this association places ring carbons in apposition to more electronegative nitrogen and oxygen atoms. Hence this stacking interaction appears to be stabilized by electrostatic forces. However none of the atom–atom contacts in this association are less than their respective minimal van der Waals distances.

Cyanuric acid molecules in neighboring layers show little overlap. However there is a rather close contact of 3·116 Å between atoms XO(2) and XC(6) of molecules in neighboring layers [the minimum C···O van der Waals distance is 3·1 Å (Pauling, 1960)]. This association is also suggestive of an electrostatic interaction. However the analysis of this interaction according to the method of Bürgi, Dunitz & Shefter (1974) indicates that atom XC(6) is displaced from the plane of its three covalently-bonded atoms by 0·017 Å to the side opposite the neighboring XO(2) atom. This suggests that the XO(2)···XC(6) interaction is quite weak.

The water molecules are contained in channels between the walls of layered molecules. Besides its above-described participation in the pseudo-Hoogsteen pairing, each water molecule forms a hydrogen bond with a neighboring XO(4) atom. There are no other notable intermolecular interactions in the crystal structure. The full hydrogen-bonding capacity of the complex has been utilized, as is usually the case in crystal structures.

Discussion

The present structural study is part of a program to determine the hydrogen-bonding properties of barbitu-

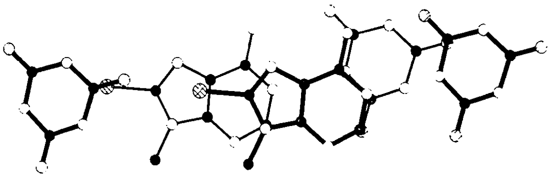

Fig. 3. A projection of two consecutive layers of stacked linear ribbons of molecules onto the least-squares plane of the adenine molecules. Atoms are represented as circles of arbitrary radii with carbon atoms as filled circles, nitrogen atoms as unfilled circles, oxygen atoms as shaded circles and bromine atoms as cross-hatched circles.

rate-like molecules in complexes with adenine derivatives. It was initiated in an effort to determine the origin of the unusual hydrogen-bonding characteristics of such complexes (Voet, 1975).

All of the crystal structures of adenine–barbiturate complexes so far reported (Voet, 1975; Shieh & Voet, 1975) exhibit structural abnormalities such as very long hydrogen bonds or failure to utilize their full hydrogen-bonding capacity. These structural anomalies appear to be due, at least in part, to the fact that barbiturate carbonyl groups are weak hydrogen-bond acceptors (Voet, 1972; Hsu & Craven, 1974*b,c*; Gartland & Craven, 1974; Shieh & Voet, 1975). In contrast, the crystalline complex A.X.H_2O shows no structural feature that could easily be interpreted in terms of the cyanuric acid carbonyl groups being weak hydrogen-bond acceptors [although the pseudo-Hoogsteen pairing described above has not been previously observed and adenine atom N(3) may be a poor hydrogen-bond acceptor (Shieh & Voet, 1976)].

The replacement of the tetrahedral ring carbon atom C(4) in barbiturates by the more electron-rich NH group to form cyanuric acid would tend to allow more electron density to reach the highly electronegative carbonyl oxygen atoms in the molecule. This suggests that there is insufficient mobile electron density available in a barbiturate ring to place sufficient charge on its three carbonyl oxygen atoms so as to render them good hydrogen-bond acceptors. Implicit in this hypothesis is the assumption that hydrogen-bonding interactions are largely electrostatic in character (Pauling, 1960; Hagler, Huler & Lifson, 1974; Hagler & Lifson, 1974). The hypothesis is corroborated by the fact that the carbonyl oxygen atoms of parabanic acid, which is formed by eliminating the tetrahedral carbon atom from the barbiturate ring, also appears to be a poor hydrogen-bond acceptor (Shieh & Voet, 1975, 1976; Colman & Medlin, 1970). However it should be noted that CNDO/2 molecular orbital calculations on 5,5-diethylbarbituric acid (Voet, 1972) and thymine (Geissner-Prettre & Pullman, 1968) show no significant differences between the net atomic charges at analogous positions of these molecules.

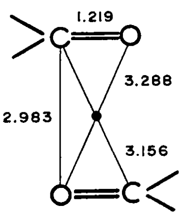

Fig. 4. The interatomic distances (Å) between atoms of the closer than van der Waals carbonyl–carbonyl association of two centrosymmetrically related C(2)–O(2) carbonyl groups in the crystalline complex 9-ethyladenine–5,5-diethylbarbituric acid (Voet, 1972). Non-bonding contacts are indicated by thin lines. The center of symmetry is indicated by a filled circle.

There have been several crystal structures reported in which carbonyl groups that appeared to avoid hydrogen-bonding associations exhibited closer than van der Waals carbonyl–carbonyl contacts. These include the structures of barbituric acid (Bolton, 1963), alloxan (Bolton, 1964), parabanic acid–urea (Colman & Medlin, 1970), 9-ethyladenine–5,5-diethylbarbituric acid (Voet, 1972) and 9-ethyladenine–parabanic acid–oxaluric acid monohydrate (Shieh & Voet, 1975). Yet there have been no reports of structures with a potential for extensive hydrogen-bonding associations that simultaneously exhibit close carbonyl–carbonyl contacts and normal hydrogen-bonding interactions. This suggests that the forces between closely approaching carbonyl groups are relatively weak and can therefore be revealed only when competing intermolecular forces such as hydrogen bonding are somehow attenuated.

A crude model calculation serves to illustrate the foregoing point. The electrostatic energy gained in bringing two carbonyl groups into proximity is simply calculated according to Coulomb's law. Let us choose as an example the interaction found between two centrosymmetrically related C(2)–O(2) carbonyl groups in the crystalline complex 9-ethyladenine–5,5-diethylbarbituric acid (Voet, 1972). The relevant geometry of this structure is shown in Fig. 4. The net atomic charges of barbiturate atoms C(2) and O(2), as estimated by a CNDO/2 molecular orbital calculation, are 0·47 and −0·37 electron units respectively (Voet, 1972). Accordingly, the electrostatic energy of this interaction is calculated to be −2·0 kcal mol^{-1}.

This calculation is of course highly simplistic. It assumes that the charges on an atom are localized at its nucleus rather than being distributed in space. Furthermore it neglects such secondary effects as bond polarizabilities, exchange forces and interactions with other parts of the structure. But as such corrections for the system in Fig. 4 are likely to be small and are expected to largely cancel one another it can be concluded that the energy of the foregoing carbonyl–carbonyl interaction is significantly less than that of a hydrogen bond (3–6 kcal mol^{-1}). Hence it seems unlikely that such an association could form at the expense of a normal hydrogen bond.

The above is consistent with the fact that close carbonyl–carbonyl approaches are found in only a few barbiturate-containing crystal structures rather than in the great majority of them as would be expected if the carbonyl–carbonyl interactions in these structures were strong interactions. Thus close carbonyl–carbonyl contacts are not observed in the crystal structures of the complexes acetamide–5,5-diethylbarbituric acid (Hsu & Craven, 1974*a*); imidazole–5,5-diethylbarbituric acid (Hsu & Craven, 1974*b*); urea–5,5-diethylbarbituric acid (Gartland & Craven, 1974); (2-aminopyridine)$_2$–5,5-diethylbarbituric acid (Hsu & Craven, 1974*c*); *N*-methyl-2-pyridone–5,5-diethylbarbituric acid (Hsu & Craven, 1974*d*); 9-ethyladenine–parabanic acid (Shieh & Voet, 1976); and 8-bromo-9-ethyladenine–5-allyl-5-isobutylbarbituric acid (Epstein, Zeiger, Crocker & Voet, 1976) even though the carbonyl groups of the barbiturate derivatives in these crystal structures exhibited low hydrogen-bond acceptor affinities. Likewise, close carbonyl–carbonyl contacts are only occasionally observed in the structures of pure barbiturates [see references in Voet & Rich (1970) and in Gartland & Craven (1974)].

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