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Hydrogen Bonding NH...N of Barbiturates: The 1:1 Crystal Complex of Imidazole and 5,5-Diethylbarbituric Acid (Barbital)

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The 1:1 crystal complex of imidazole and barbital (m.p. 122°C) is monoclinic, space group $P2_1/c$, with $a = 10{\cdot}133$ (4), $b = 11{\cdot}261$ (4), $c = 13{\cdot}715$ (5) Å, $\beta = 123{\cdot}12$ (1)° and four molecules of each component in the unit cell ($D_{meas} = 1{\cdot}276$, $D_x = 1{\cdot}278$ g cm^{-3}). The X-ray crystal structure has been determined from 2115 integrated intensities measured on a four-circle computer-controlled diffractometer using nickel-filtered Cu $K\alpha$ radiation. The phase problem was solved by a combination of direct and Patterson methods. The atomic parameters were refined by a full-matrix least-squares procedure to give a final R index of 0·065 for all reflections. The crystal structure consists of NH···O=C hydrogen-bonded dimers of barbital which are cross-linked by pairs of imidazole molecules to form hydrogen-bonded ribbons. Barbital provides the NH donor in a strong hydrogen bond to imidazole, with N···N distance 2·78 Å. Similar short hydrogen-bond distances occur in crystal complexes in which uracil, thymine or barbiturate provides the NH donor, and adenine provides the nitrogen atom acceptor.

Introduction

Kyogoku, Lord & Rich (1968) have reported that the association between barbiturates and 9-ethyladenine in carbon tetrachloride solution is strong, with equilibrium constants ($K_{HB} \sim 1000$ M^{-1}) which are an order of magnitude greater than those between uracil and adenine derivatives (100 M^{-1}). Highly specific interactions of this kind may be involved in the drug action of barbiturates. An important factor in the interaction is likely to be the barbiturate/adenine hydrogen bonding. Kyogoku, Lord & Rich (1968) point out that barbiturates may form stronger hydrogen bonds than uracil derivatives because of their greater acidity in aqueous solution (pK_a 7·8, 9·4 for barbital and uridine respectively). This would be in accord with Taft, Gurka, Joris, Schleyer & Rakshys (1969) who have found linear relationships between pK_a and pK_{HB} for the interactions of families of closely related hydrogen-bonding bases with a common hydrogen-bonding acid. In crystal complexes of barbiturates with adenine derivatives (Kim & Rich, 1968; Voet & Rich, 1972; Voet, 1972) there are indeed short NH···N hydrogen bonds between the two components, although not markedly shorter than those found in crystal complexes of uracil or thymine with adenine derivatives.

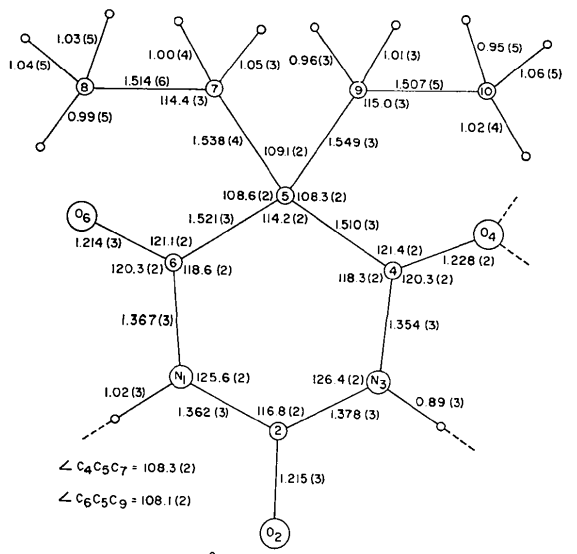
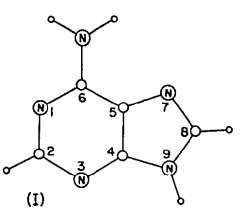
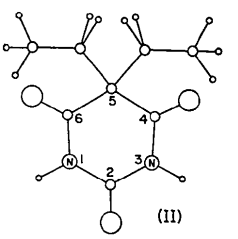
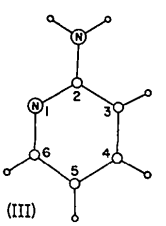
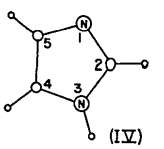


Fig. 1. Bond lengths (Å) and angles (°) for barbital. These values have not been corrected for the effects of anisotropic thermal motion. The e.s.d.'s are given in parentheses and refer to the least significant digit in the parameters.









It is interesting that in addition to the crystal complex with 9-ethyladenine [(I), Voet, 1972], 5,5-diethylbarbituric acid [barbital, (II)] also forms crystal complexes with 2-aminopyridine (III) and imidazole (IV). Molecules (III) and (IV), if fused together, comprise a molecule which closely resembles adenine. We report the crystal structure determinations of the latter complexes in this and the following paper (Hus & Craven,

1974). As in the barbiturate/adenine complexes, these structures involve short NH···N hydrogen bonds in which barbital NH groups are donors.

Experimental

The 1:1 crystal complex of imidazole with barbital, m.p. 122°C, was obtained by slow cooling to room temperature of an alcoholic solution which had been slightly supersaturated with respect to both components. We know of no previous report in the literature concerning this complex. The crystals are monoclinic with space group $P2_1/c$ and lattice translations $a=10{\cdot}133$ (4), $b=11{\cdot}261$ (4), $c=13{\cdot}715$ (5) Å, $\beta=123{\cdot}12$ (1)°. The crystal density (1·276 g cm^{-3}), which was determined by flotation in a mixture of CCl_4 and benzene, agrees with the calculated value (1·278 g cm^{-3}) assuming four molecules of each component in the unit cell. The lattice translations and X-ray intensity data were measured on a four-circle computer-controlled diffractometer using nickel-filtered Cu $K\alpha$ radiation ($\lambda=1{\cdot}5418$ Å). Integrated intensities were measured for 2115 symmetry-independent reflections in the range $\theta\leq 63°$, with the prism axis of the crystal (b) making an angle of 5° with the φ axis of the goniostat. The crystal dimensions were $0{\cdot}37\times 0{\cdot}29\times 0{\cdot}20$ mm. Reflections were scanned in the θ–2θ mode at a rate of 2° min^{-1} with 20 s background counts being taken at each of the scan limits. The 2θ scan width was based on 2·0° and was increased to allow for spectral dispersion. There were 385 reflections for which the integrated intensity, I, was less than $2{\cdot}0\sigma(I)$ as calculated from the counting statistics. These reflections were arbitrarily assigned intensity of $\sigma(I)/2$. No corrections were applied for X-ray absorption or extinction.

The crystal structure was determined by a combination of direct and Patterson methods. The most promising phase-set resulting from direct-method procedures as described by Germain, Main & Woolfson (1971) corresponded to an E map in which a barbital

Table 1. *Atomic parameters for the imidazole–barbital complex*

Positional parameters are given as fractions of the lattice translations. Anisotropic temperature factors correspond to the expression: $T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$, and isotropic temperature factors to the expression: $\exp(-B\sin^2\theta/\lambda^2)$. E.s.d.'s given in parentheses refer to the least significant figures in parameter values.

(*a*) Carbon, nitrogen and oxygen atom parameters (× 10^4)

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
(i) Imidazole									
N(1)	−172 (2)	1523 (2)	−2149 (2)	116 (3)	133 (2)	85 (2)	−18 (2)	25 (2)	−30 (2)
C(2)	661 (3)	1179 (2)	−1047 (2)	128 (3)	95 (2)	107 (2)	−13 (2)	55 (2)	1 (2)
N(3)	1839 (2)	1890 (2)	−410 (1)	129 (3)	128 (2)	61 (1)	−28 (2)	30 (2)	12 (1)
C(4)	1736 (3)	2736 (2)	−1154 (2)	157 (4)	122 (3)	79 (2)	−49 (3)	51 (2)	2 (2)
C(5)	519 (3)	2518 (3)	−2219 (2)	179 (4)	159 (3)	68 (1)	−16 (3)	36 (2)	19 (2)
(ii) Barbital									
N(1)	4033 (2)	1623 (2)	1966 (1)	128 (3)	87 (2)	54 (1)	−17 (2)	35 (2)	7 (1)
C(2)	3515 (2)	870 (2)	2465 (2)	114 (3)	64 (2)	62 (2)	−6 (2)	39 (2)	−3 (1)
O(2)	2195 (2)	453 (1)	1934 (1)	120 (2)	98 (1)	84 (1)	−29 (1)	37 (1)	−5 (1)
N(3)	4564 (2)	595 (1)	3622 (1)	117 (2)	70 (1)	60 (1)	−16 (1)	40 (1)	9 (1)
C(4)	6039 (2)	1036 (2)	4324 (2)	113 (3)	57 (1)	59 (1)	−2 (2)	44 (2)	4 (1)
O(4)	6844 (2)	754 (1)	5356 (1)	135 (2)	89 (1)	56 (1)	−7 (1)	35 (1)	17 (1)
C(5)	6658 (2)	1871 (2)	3802 (2)	114 (3)	76 (2)	54 (1)	−17 (2)	36 (2)	7 (1)
C(6)	5486 (2)	2145 (2)	2521 (2)	141 (3)	83 (2)	58 (2)	−21 (2)	46 (2)	3 (1)
O(6)	5822 (2)	2817 (2)	1996 (1)	226 (3)	146 (2)	72 (1)	−69 (2)	62 (2)	22 (1)
C(7)	8137 (3)	1313 (3)	3943 (2)	131 (3)	149 (3)	102 (2)	−1 (3)	69 (3)	16 (2)
C(8)	7844 (5)	151 (4)	3298 (4)	275 (7)	171 (4)	177 (5)	57 (5)	147 (5)	−6 (4)
C(9)	7114 (3)	3056 (2)	4485 (2)	214 (4)	81 (2)	65 (2)	−52 (2)	41 (2)	1 (2)
C(10)	5800 (5)	3656 (3)	4505 (4)	365 (8)	89 (3)	149 (4)	2 (4)	139 (5)	−14 (3)

(*b*) Hydrogen atoms (positional parameters × 10^3)

(i) Imidazole

	x	y	z	B (Å^2)
H(1)	−112 (4)	126 (3)	−276 (3)	7·4 (8)
H(2)	40 (3)	49 (3)	−74 (3)	7·4 (7)
H(4)	252 (3)	332 (3)	−88 (3)	7·1 (7)
H(5)	13 (4)	292 (3)	−288 (3)	8·4 (9)

(ii) Barbital

	x	y	z	B (Å^2)
H(1)	326 (3)	175 (3)	109 (3)	7·3 (7)
H(3)	419 (3)	8 (2)	391 (2)	6·2 (6)
H(71)	891 (3)	122 (2)	484 (2)	6·1 (6)
H(72)	861 (4)	191 (3)	368 (3)	8·3 (8)
H(81)	884 (5)	−17 (4)	337 (4)	12 (1)
H(82)	737 (5)	−48 (4)	358 (3)	11 (1)
H(83)	705 (5)	30 (4)	246 (4)	11 (1)
H(91)	802 (3)	288 (2)	531 (2)	6·0 (6)
H(92)	749 (3)	356 (3)	412 (2)	7·0 (7)
H(101)	546 (5)	317 (4)	489 (4)	11 (1)
H(102)	486 (5)	387 (3)	364 (4)	10 (1)
H(103)	621 (4)	447 (4)	490 (3)	10 (1)

molecule could be recognized. The molecular orientation was consistent with the origin region of the Patterson function, but the position of the molecule was inconsistent with hydrogen-bonding requirements. The correct position was determined using the Q-function of Tollin (1966). Atomic parameters (Table 1) were refined by a full-matrix least-squares procedure. The function minimized was $\sum_H w_H \Delta_H^2$, where $\Delta_H = |F_H^{obs}| - |F_H^{calc}|$. The weights were $w_H^{-1} = 0{\cdot}5 + 0{\cdot}002|F_H|^2$. The atomic scattering factors were those of Cromer & Waber (1965) for C, N, O, and of Stewart, Davidson & Simpson (1965) for H. All hydrogen atomic positions were obtained from difference Fourier syntheses which were calculated after refinement of anisotropic thermal parameters had been introduced for the non-hydrogen atoms. Hydrogen-atom positional and isotropic thermal parameters were subsequently refined. Before the last three cycles of least-squares refinement, 11 strong reflections for which $|F^{calc}| > |F^{obs}|$ were given zero weight. In the final cycle, all parameter changes were less than $0{\cdot}2\sigma$. The final overall R index was 0·065.*†

The molecular structures

The crystal structure consists of a hydrogen-bonded molecular complex and not of the imidazolium barbiturate salt. This conclusion is based upon the position of the hydrogen atom which was found to be at covalent bonding distance from barbital N(1), and also upon the barbiturate bond distances and angles, which closely resemble those of the acid rather than the barbiturate anion (Berking & Craven, 1971).

(i) *Barbital*

The bond lengths and angles are shown in Fig. 1. The oxopyrimidine bond lengths are very similar to those reported in the crystal structures of barbiturates in which oxygen atom O(4) is acceptor for two NH···O=C hydrogen bonds, and atom O(6) is acceptor for none (Craven, Cusatis, Gartland & Vizzini, 1973). There are slight differences of about 0·01 Å in corresponding bond lengths in the two halves of the oxopyrimidine ring which appear to be related to the mode of hydrogen bonding. Thus the bond C(4)=O(4) is longer (1·228 Å) than C(6)=O(6), (1·214 Å). Bond lengths and angles in the ethyl groups are similar to those found in the crystal structures of the three polymorphs of barbital (Craven, Vizzini & Rodrigues, 1969; Craven & Vizzini, 1971).

The atoms of the oxopyrimidine ring are nearly coplanar (Table 2), being more so than in all but one of the 14 molecules from barbiturate crystal structures which are shown in Fig. 3 of Craven *et al.* (1973). The largest atomic displacement from the best least-squares plane of the six pyrimidine ring atoms is 0·038 Å for atom O(2). The carbon atoms of the ethyl groups and C(5) form a chain which is nearly in the extended configuration, with torsion angles of 180·9° and 184·7° about the bonds C(5)–C(7) and C(5)–C(9) respectively.

Table 2. *Best least-squares planes through selected atoms*

The equations for the planes have the form $Lx + My + Nz = D$, where (L, M, N) are direction cosines of the plane normal with respect to the orthogonal axes a^*, b and c, and D is the distance of the plane from the crystallographic origin in Å.

(i) Plane equations

	L	M	N	D
(1)	−0·5812	0·7744	0·2500	0·462
(2)	−0·2787	−0·4932	0·8240	1·505
(3)	0·8117	−0·5552	−0·1814	0·662

(1): Plane through pyrimidine ring carbon and nitrogen atoms.
(2): Plane through atoms C(5) and the ethyl carbon atoms.
(3): Plane through imidazole ring carbon and nitrogen atoms.

(ii) Dihedral angles

(1)∠(2) = 90·8° (1)∠(3) = 18·7°

(iii) Atomic displacements from the planes (Å)

Plane (1)			
N(1)	−0·001	O(2)*	0·038
C(2)	0·008	O(4)*	0·036
N(3)	−0·013	O(6)*	0·008
C(4)	0·010	H(1)*	−0·07
C(5)	−0·003	H(3)*	−0·03
C(6)	−0·001		
Plane (2)			
C(5)	−0·032		
C(7)	0·023		
C(8)	0·006		
C(9)	−0·029		
C(10)	0·032		
Plane (3)			
N(1)	−0·001	H(1)*	−0·12
C(2)	−0·001	H(2)*	−0·04
N(3)	0·003	H(4)*	0·06
C(4)	−0·003	H(5)*	−0·03
C(5)	0·002		

* Atom not included in the best least-squares plane.

* At the request of the referee, a second refinement was carried out with zero weight assigned to reflections with $I < 2\sigma(I)$ as well as the 11 strong reflections. After two cycles, all parameter changes were less than $0{\cdot}2\sigma$. The final value of $R = \sum_H |\Delta_H| / \sum_H |F_H^{obs}|$ remained 0·065 for all reflections and 0·043 excluding reflections with zero weight. In the first refinement, the final weighted R index was 0·060 or 0·053, if reflections with $I < 2\sigma(I)$ were included or excluded respectively. In the second refinement, the weighted R index remained 0·053. A comparison of the two refinements showed that 25 out of 227 parameters were different by more than $1{\cdot}0\sigma$. The largest differences in thermal and positional parameters were $1{\cdot}6\sigma$ for β_{33} of C(5) for imidazole and $1{\cdot}3\sigma$ for x of C(4) in barbital. The most significant differences ($1{\cdot}0\sigma$) in bond lengths and angles observed in the second refinement are the bond lengths N(3)–C(4) of imidazole (1·360 Å) and the internal ring angles at N(3) and C(2) of imidazole (105·0°, 111·6° respectively). Parameter values in Table 1 are those of the first refinement. All interatomic distances and angles are based on these values.

† The table of structure amplitudes has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30314 (14 pp., 1 microfiche). Copies may be obtained through the Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

(ii) *Imidazole*

The atoms of the imidazole molecule are coplanar except possibly for the hydrogen atom at N(1), which is displaced by 0·12 Å (4σ) from the best least-squares plane of the carbon and nitrogen atoms (Table 2). The bond distances and angles (Fig. 2) show small but significant differences from those reported by Will (1969) and Martínez-Carrera (1966) for imidazole itself at room temperature and −150°C respectively. In the case of the bond length C(4)–C(5) which showed the poorest agreement in the previous determinations (1·31 *vs.* 1·35 Å) the value from the barbiturate complex agrees well (1·32 Å) with the room temperature value. In the case of the internal ring angles at N(1), C(2) and N(3), each of which differ by almost 3° in the previous determinations, the values from the barbiturate complex agree well with the low-temperature values. Other differences, which are possibly significant, are that the bond lengths N(1)–C(5) and N(3)–C(4) are somewhat shorter (1·353, 1·357 Å) than previously reported values (1·37, 1·38 Å). We can find no explanation for these differences.

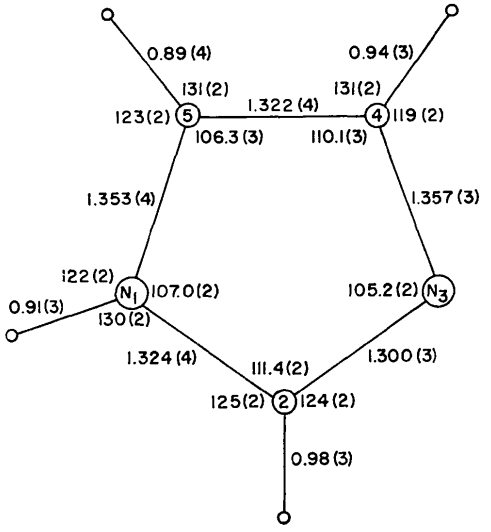


Fig. 2. Bond lengths (Å) and angles (°) for imidazole.

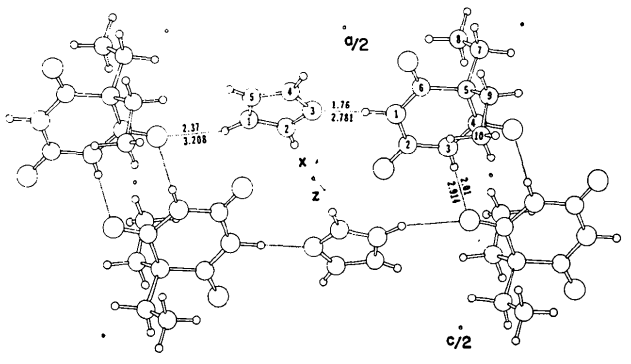


Fig. 3. The crystal structure viewed down **b**.

The molecular association

The crystal structure consists of hydrogen-bonded ribbons extending along [101] (Fig. 3). The intra-ribbon angle between the planes of the imidazole and barbiturate rings is 18·7° (Table 2). The ribbon plane is approximately parallel to (11$\bar{1}$), with the ribbons packed in a herringbone pattern, when viewed edge on. The barbiturate alkyl substituents from one ribbon fit against the region between two imidazole molecules of one adjacent ribbon and are close to the alkyl substituents of a second adjacent ribbon. The shortest intermolecular distances involving ethyl carbon atoms are $C(7)_{barb}\cdots C(2)_{imid}$ and C(7)···C(10) which are 3·78 and 3·97 Å respectively.

Barbital molecules hydrogen bond both with each other in cyclic dimers, and with imidazole molecules, whereas imidazole molecules hydrogen bond exclusively with barbital.* Within the barbital dimers, the NH···O=C hydrogen bonds have N···O distances (2·91 Å) which are within the range (2·9 ± 0·1 Å) of those observed in the crystal structures of the barbituric acids themselves (Gartland & Craven, 1974). The NH···O=C hydrogen bond in which imidazole is donor and barbital is acceptor is very weak. The N···O distance is long (3·21 Å) and the H···O distance (2·37 Å) is only 0·2 Å shorter than the corresponding van der Waals distance. Gartland & Craven (1974) have noted that NH···O=C hydrogen bonds in barbiturate crystal complexes are generally short when barbiturate participates only as donor, and long, as in the imidazole complex, when barbiturate participates only as acceptor. They have suggested that this is because the barbiturates are stronger hydrogen-bonding donors than acceptors.

If this were the case, similar variations should exist in N···N distances for NH···N hydrogen bonds involving barbiturates. With one exception,† distances are available only for NH···N hydrogen bonds in which barbiturate is donor. However, these do appear to be generally short, and thus consistent with the view that barbiturates are strong hydrogen-bonding donors.

In the barbital–imidazole complex, the NH···N hydrogen bond in which barbital is donor and imidazole is acceptor has N···N distance 2·78 Å and H···N distance 1·76 Å. This N···N distance is slightly shorter than in the hydrogen bonds in the crystal structure of imidazole itself at room temperature (2·81 Å) and at −150°C (2·86 Å) and the N(7)H···N(9) hydrogen bond involving the imidazole moiety of purine (2·85 Å; Watson, Sweet & Marsh, 1965).

* There is a short distance (3·06 Å) between atoms C(2) of imidazole and O(2) of barbital within the same ribbon. This would not appear to be a CH···O hydrogen bond since the H···O distance (2·46 Å) is rather long and the CHO angle is only 119°.

† In guanidinium barbiturate dihydrate (McClure & Craven, 1973) the guanidinium cation is donor and the barbital anion deprotonated nitrogen atom is acceptor for a hydrogen bond with N···N distance 3·00 Å.

A more extensive comparison of such distances is possible by considering those NH···N hydrogen bonds formed by adenine, both in self association and in complexes of adenine derivatives with uracil and uracil-like molecules, including the barbiturates. Table 3 lists the N···N distances for N(6)H···N(1) and N(6)H···N(7) hydrogen bonds in which adenine (I) is both donor and acceptor. There are six distances involving N(1) as acceptor and they range from 2·86 to 3·12 Å with a mean value of 3·00 Å. There are 11 distances involving N(7) as acceptor and they range from 2·93 to 3·13 Å with a mean value of 3·02 Å. These distances are combined and shown as a histogram in Fig. 4. The distribution is similar to that observed by Wallwork (1962) for 25 NH···N hydrogen bonds in crystal structures of various kinds, presumably including purines. He reported a mean N···N distance of 3·07 Å and a standard deviation of 0·11 Å.

The N···N hydrogen bond distance in the barbital/imidazole complex is significantly shorter than any of the distances in Table 3. However, it does fall within the range of distances for NH···N hydrogen bonds in which a uracil-like molecule provides the NH donor and an adenine N(1) or N(7) atom is acceptor. Hydrogen bonds involving N(1) and N(7) of adenine arise in pairings of the Watson–Crick and Hoogsteen type respectively. The N···N distances for these hydrogen

Table 3. *Hydrogen-bonding distance* N···N *between adenine derivatives*

The distances d_1 and d_7 are for hydrogen bonds NH···N in which the 6-amino group is donor and either atom N(1) or N(7) respectively is acceptor.

Crystal structure	d_1	d_7
9-Methyladenine (Stewart & Jensen, 1964)	2·96 Å	3·06 Å
Adenosine (Lai & Marsh, 1972)	–	3·13
Deoxyadenosine hydrate (Watson, Sutor & Tollin, 1965)	2·88	3·03
Adenine hydrochloride hemihydrate (Broomhead, 1948; Cochran, 1951)	–	2·99
N^6-(Δ^2-isopentenyl)-2-methylthioadenine (McMullan & Sundaralingam, 1971)	–	2·99
Uridyl-(3′,5′)-adenosine hemihydrate (Sussman, Seeman, Kim & Berman, 1972; Rubin, Brennan & Sundaralingam, 1972)	–	2·94, 2·98
1-Ethylthymine/8-methyl-9-ethyladenine (Tavale & Sobell; see Sobell, 1972)	3·04	–
1-Methyl-5-bromouracil/9-ethyladenine (Baklagina, Volkenshtein & Kondrashev, 1966)	3·00	–
1-Methyl-5-bromouracil/8-bromo-9-ethyladenine (Tavale, Sakore & Sobell, 1969)	–	3·03
1-Methyl-5-bromouracil/8-methyl-9-ethyladenine/9-ethyladenine (Ambady & Sobell; see Sobell, 1972)	3·12	2·93
5-Phenyl-5-ethylbarbituric acid/8-bromo-9-ethyladenine (Kim & Rich, 1968)	–	3·09, 3·02
8-Bromo-9-ethylhypoxanthine/8-bromo-9-ethyladenine (Sakore & Sobell, 1969)	3·01	–

Table 4. *Hydrogen bonding distances* N···N *between pyrimidine and adenine derivatives*

The distances d_1 and d_7 are for hydrogen bonds in which a pyrimidine NH is donor and either adenine N(1) or N(7) respectively is acceptor.

Crystal structure	d_1	d_7
Sodium adenosyl-(3′,5′)-uridinephosphate.$24H_2O$ (Rosenberg, Seeman, Park-Kim, Suddath, Nicholas & Rich, 1973)	2·82 Å, 2·83	–
5-Bromouridine/adenosine monohydrate (Haschemeyer & Sobell, 1965)	–	2·80 Å
1-Methylthymine/9-methyladenine (Hoogsteen, 1963)	–	2·92
1-Ethylthymine/8-methyl-9-ethyladenine (Tavale & Sobell; see Sobell, 1972)	–	2·89
1-Methyluracil/9-ethyladenine (Mathews & Rich, 1964)	–	2·83
1-Methyl-4-thiouracil/9-methyladenine (Saenger & Suck, 1970)	–	2·94
1-Methyl-5-fluorouracil/9-ethyladenine (Tomita, Katz & Rich, 1967)	–	2·78
1-Methyl-5-bromouracil/9-methyladenine (Baklagina, Volkenshtein & Kondrashev, 1966)	–	2·86
1-Methyl-5-bromouracil/9-ethyladenine (Katz, Tomita & Rich, 1965)	–	2·80
1-Methyl-5-bromouracil/8-methyl-9-ethyladenine/9-ethyladenine (Ambady & Sobell; see Sobell, 1972)	–	2·87
1-Methyl-5-bromouracil/8-bromo-9-ethyladenine (Tavale, Sakore & Sobell, 1969)	2·85	–
1-Methyl-5-iodouracil/9-ethyladenine (Sakore, Tavale & Sobell, 1969)	2·80	2·82
5-Phenyl-5-ethylbarbituric acid/8-bromo-9-ethyladenine (Kim & Rich, 1968)	2·78, 2·80	–
5,5-Diethylbarbituric acid/9-ethyladenine (Voet, 1972)	2·83	2·83
5-Isopropyl-5-bromoallylbarbituric acid/9-ethyladenine (Voet & Rich, 1972)	2·79	2·81
Riboflavin/5′-bromo-5′-deoxyadenosine trihydrate (Voet & Rich, 1971)	–	2·84

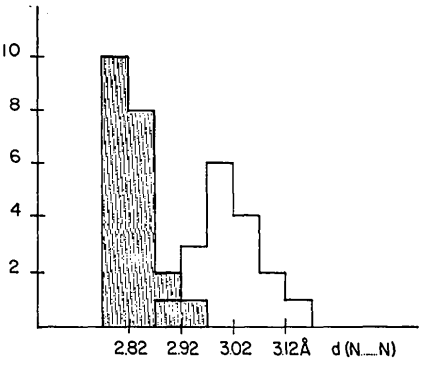


Fig. 4. Histogram of N···N distances in NH···N hydrogen bonds involving adenine. The shaded distribution is for distances from Table 4 (hydrogen bonds in which a uracil-like molecule provides the NH donor and adenine atom N(1) or N(7) is acceptor). The unshaded distribution is for distances from Table 3 (hydrogen bonds in which adenine provides both donor and acceptor). The two distributions overlap at the N···N distance of 2·9 Å.

bonds are listed in Table 4. There are eight distances involving adenine N(1) which range from 2·78 to 2·85 Å with a mean value of 2·81 Å and 13 distances involving N(7) which range from 2·78 to 2·94 Å with a mean value of 2·85 Å. These distances have been combined and their distribution shown as a histogram in Fig. 4. Katz, Tomita & Rich (1965) first noted that uracil-adenine hydrogen bonds at adenine N(7) were short. The distances in Table 3 and Fig. 4 show that their conclusion can be supported by data from more recent crystal structure determinations, and can also be extended to include hydrogen bonds at adenine N(1) and donor NH groups from uracil-like moieties, as found in the barbiturates and riboflavin.

The shortening of NH···N hydrogen bonds in crystal complexes of uracil and adenine derivatives is consistent with the hydrogen-bonding enthalpy change for their association in chloroform solution being greater by about 2 kcal mole^{-1} than for the self association of adenine (Kyogoku, Lord & Rich, 1966). However, the relationship between structural and thermodynamic properties is complex. In particular there may be a significant enthalpy change associated with the second hydrogen bond which accomplishes cyclic dimerization. This hydrogen bond changes from the type NH···N in the self association of adenine to NH···O=C in the adenine-uracil or adenine-barbiturate complexes.* In the case of the crystal complexes of barbiturates with adenine derivatives, with imidazole (IV) and 2-aminopyridine (III), the NH···O=C hydrogen bonds involving barbiturate as acceptor are weak (Hsu & Craven, 1974). This suggests that these complexes involve essentially the interaction of a hydrogen bonding acid (barbiturate) with a hydrogen bonding base [adenine or its analogs (III) and (IV)].

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* Enthalpy and entropy changes for barbiturate adenine interactions in solution have not been reported.

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