The Crystal and Molecular Structure of the Intermolecular Complex 9-Ethyladenine–5,5-Diethylbarbituric Acid[1]

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Abstract: The X-ray crystal structure of the intermolecular complex 9-ethyladenine–5,5-diethylbarbituric acid has been determined. The two types of molecules associate by forming extended planar sequences of mutually hydrogen-bonded barbiturate and adenine rings. The mode of hydrogen bonding in these sequences alternates between the Watson–Crick and the Hoogsteen types of base pairing. In both of these pairings the N–H···O contacts are anomalously long. The planes of hydrogen-bonded molecules form stacks of parallel layers that are held together by dipole–dipole interactions. The strengths of these interactions appear to be related to the strengths of the N–H···O hydrogen bonds.

Barbiturates are general metabolic depressants that appear to act as competitive inhibitors in oxidative metabolism.[2] Barbiturate derivatives that are physiologically effective as sedative–hypnotic agents are substituted at their 5 position by two nonpolar groups of at least the size of ethyl groups.[2] These hydrophobic side groups increase the solubility of the barbiturate ring in nonpolar environments and decrease it in aqueous media. Nerve tissue is quite lipid rich in comparison with other tissues such as muscle or blood. Hence, the marked effect of barbiturates on the central nervous system is due, at least in part, to their selective solubility in nerve tissue.

The nature of the barbiturate receptor site is largely unknown. Barbiturates, as do other uracil derivatives, have a selective affinity for hydrogen bonding to adenine derivatives. This has been demonstrated by infrared and nmr spectroscopy[3,4] and by the formation of a number of crystalline intermolecular complexes containing both adenine and barbiturate derivatives.[5,6] An attractive hypothesis concerning the nature of the barbiturate receptor site is that it involves adenine containing effectors or coenzymes, such as 3′,5′-cyclic AMP, ATP, FAD, and NAD. It has been postulated that the barbiturate molecules selectively hydrogen bond to these receptor molecules, thereby interfering with their normal function.[3,5] It is therefore of great interest to determine the crystal structure of a number of adenine–barbiturate complexes as this may shed light on the detailed molecular architecture of the barbiturate receptor site.

This article describes the structural determination of the crystalline intermolecular complex 9-ethyladenine–5,5-diethylbarbituric acid (I). In this structure the adenine and the barbiturate derivatives associate by the formation of extended hydrogen-bonded strips that contain adenine and barbiturate residues in alternating order. The layers of hydrogen-bonded strips appear to be held together by a series of stacked dipoles. It is shown that the strengths of these dipolar interactions and those of the N–H···O hydrogen bonds appear to be closely interrelated.

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(3) Y. Kyogoku, R. C. Lord, and A. Rich, *Nature (London)*, **218**, 69 (1968).
(4) Y. Kyogoku and B. S. Yu, *Chem-Biol. Interactions*, **2**, 117 (1970).
(5) S.-H. Kim and A. Rich, *Proc. Nat. Acad. Sci. U. S.*, **60**, 402 (1968).
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Experimental Section

9-Ethyladenine (Cyclo Chemical) and 5,5-diethylbarbituric acid (Merck and Co.) were dissolved in equimolar amounts in dimethyl sulfoxide. The resulting solution was evaporated to dryness at ~80°, yielding a number of small colorless crystals with the shape of flattened parallelepipeds. The ultraviolet spectrum and the paper chromatographic analysis of an aqueous solution of one of these crystals indicated that both 9-ethyladenine and 5,5-diethylbarbituric acid were present in the crystals in approximately equimolar amounts.

A small crystal (0.45 × 0.30 × 0.08 mm) was sealed inside a glass capillary tube. Preliminary Weissenberg and precession photographs of the crystal revealed that it had triclinic lattice symmetry. All subsequent X-ray measurements were made using a Picker FACS-1 diffractometer employing Ni-filtered Cu radiation (λ(Cu Kα) = 1.5418 Å). The reduced unit cell parameters as determined by the least-squares analysis of the angular positions of 12 independent reflections are given in Table I. The buoyant density of the crystals was measured by flotation in a mixture of CCl_4 and cyclohexane.

Table I. Crystal Data[a]

a = 7.520 (1) Å	α = 95.88 (1)°
b = 10.455 (2) Å	β = 102.35 (1)°
c = 12.255 (1) Å	γ = 115.48 (1)°
Space Group $P\bar{1}$	
Z = 2	
Density (obsd) = 1.393 g/cm³	
Density (calcd) = 1.391 g/cm³	

[a] The quantities in parentheses are the estimated standard deviations of the least significant figure of the tabulated data.

X-Ray diffraction peak counts, C, were measured using the θ–2θ scan mode, a scan rate of 1°/min, a scan range of 1.2°, and a take-off angle of 3°. Stationary background counts, B_1 and B_2, of 10-sec duration each, were taken at the limits of each scan. A total of 2464 unique reflections were measured to the limit 2θ = 125°. All computer calculations were performed using an IBM 360-75 computer.

Structure Determination and Refinement. The intensities, $I(h,k,l)$, were calculated according to the equation

$$I = [C - t(B_1 + B_2)]/Lp$$

where t is the ratio of the peak counting time to the total background

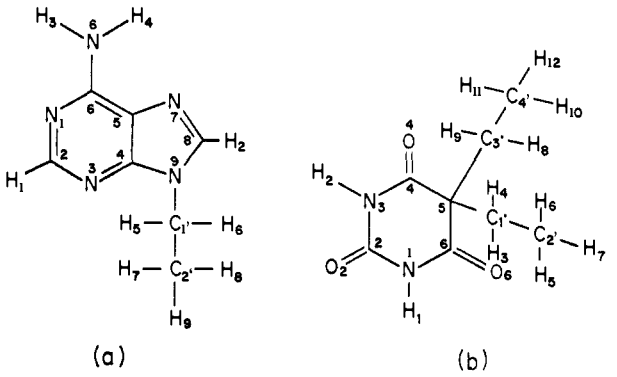

Figure 1. The molecular formulas and atomic numbering schemes for (a) 9-ethyladenine and (b) 5,5-diethylbarbituric acid.

counting time, L is the Lorentz factor, and p is the polarization factor. The standard deviation of these intensities, $\sigma(I)$, is defined as

$$\sigma(I) = [C + t(B_1 + B_2) + (kI)^2]^{1/2}/Lp$$

where k is a factor that accounts for instrumental instabilities.[7] In the present structural determination, k was assigned a value of 0.030. A total of 43 reflections had $I < 2.33\sigma(I)$ and hence were considered to be unobserved. (The rest are observed at the 98% confidence level.) It was not considered necessary to correct the intensities for absorption effects due the small size of the crystal.

The amplitudes of the normalized structure factors, E, were calculated according to the equation

$$E^2(h,k,l) = I(h,k,l)/\epsilon\langle I\rangle$$

where $\langle I\rangle$ is the average value of the intensity at the same $(\sin\theta/\lambda)$ value as that of the (h,k,l) reflection and ϵ is a small positive integer, the value of which depends on the symmetry class of the reflection.[8] For triclinic symmetry, ϵ is unity for all reflections.

The values of $\langle I\rangle$ were calculated according to the equation

$$\ln\langle I\rangle = \sum_{n=0}^{N}\alpha_n(\sin\theta/\lambda)^n$$

The coefficients, α_n, of the above polynomial are determined as follows. The reflections are ordered in increasing $(\sin\theta/\lambda)$ and the resulting list is divided into a small number of equally populated intervals. The average values of I and $(\sin\theta/\lambda)$ are computed for each interval. The α_n values are then fitted to these averages by the method of polynomial regression.[9] The degree of the final polynomial, N, is that integer such that there is no statistical improvement of fit of the equation to the data when $n = N + 1$. In the present case N was found to be 3 when the list of reflections was divided into 25 intervals.

The statistical distribution of the normalized structure factors,[10] which is shown in Table II, indicated that the unit cell had centric

Table II. Experimental and Theoretical Values of the Normalized Structure Factors

	Obsd	Centric	Acentric
$\langle E^2\rangle$	0.994	1.000	1.000
$\langle\|E\|\rangle$	0.797	0.798	0.886
$\langle E^2 - 1\rangle$	0.979	0.968	0.736
$\|E\| \geq 3.0$	0.50%	0.30%	0.01%
$\|E\| \geq 2.0$	4.46	5.00	1.80
$\|E\| \geq 1.0$	30.66	32.00	36.80

symmetry and hence that its space group was $P\bar{1}$. This finding was corroborated by the zero moment test[11] and was subsequently confirmed by the successful refinement of the structure. The above method of computing normalized structure factors, and also the Wilson plot[12] and the centrosymmetry tests, were carried out by the program STATISTX which was written by the author.

The structure was solved by the reiterative application of the Sayre equation[13] using a modified version of the program REL.[14] The positions of all of the expected nonhydrogen atoms except those of the barbiturate ethyl groups were evident in an E map based on the 310 (phased) reflections with $|E| > 1.5$. The positions of the remaining four ethyl carbon atoms were found in a Fourier map in which the phases of the observed structure factors were based on the positions of the 21 located atoms. The structure was refined by the method of full matrix least squares. The quantity minimized in this process was $\Sigma w(|F|_o - |F|_c)^2$ where $w = 1/\sigma^2(I)$. The initial scale factor and the initial overall isotropic temperature factor were those determined by Wilson's method.[12] The atomic scattering factors were taken from the International Tables for Crystallography.[15] After three cycles of refinement of the scale factor, the atomic positions and the isotropic temperature factors, the discrepancy index, R $(= \Sigma\,||F_o| - |F_c||/\Sigma|F_o|)$, was 0.132. An additional cycle of refinement employing anisotropic temperature factors reduced the discrepancy index to $R = 0.098$. A difference Fourier map based on the structure at this stage of refinement revealed the positions of all 21 unique hydrogen atoms at their expected positions. However, the hydrogen atoms about one of the barbiturate methyl carbon atoms, C-2′, were very poorly resolved from each other.

The positions and the isotropic temperature factors of the hydrogen atoms were refined for two cycles yielding a discrepancy index of $R = 0.074$. The full structure was then refined for three cycles using isotropic temperature factors for the hydrogen atoms and anisotropic temperature factors for the nonhydrogen atoms. The refinement process converged at a final discrepancy index of $R = 0.063$ based on 2421 reflections.[16] The final parameter shifts were, with three exceptions, all less than the estimated standard deviations of these parameters.

Results

The atomic numbering scheme used in this article is presented in Figure 1. Table III contains the final fractional coordinates and thermal parameters for all atoms in the asymmetric unit together with their standard deviations as estimated from the variance–covariance matrix of the final cycle of the least-squares refinement.[17]

Most of the thermal parameters are within the normal ranges for these quantities. However, the thermal parameters for barbiturate hydrogen atoms H-5, H-6, and H-7 are considerably larger than those of the other atoms in the crystal. Furthermore, the estimated standard deviations of the atomic parameters of these hydrogen atoms are significantly larger than those of any other atom in the structure. These hydrogen atoms form a methyl group with barbiturate atom C-2′, which itself has the largest thermal parameters of any nonhydrogen atom in the structure. Three of the

(7) G. H. Stout and L. H. Jensen, "X-Ray Structure Determination," Macmillan, New York, N. Y., 1968.

(8) A. J. C. Wilson, *Acta Crystallogr.*, **2**, 318 (1949).

(9) System 360 Scientific Subroutine Package (360 A-CM-03X), Version III, Programmers Manual, I.B.M. Manual H20-0205-3, White Plains, N. Y., 1968, pp 408–412.

(10) H. Hauptman and J. Karle, "Solution of the Phase Problem I. The Centrosymmetric Crystal," A. C. A. Monograph No. 3, Polycrystal Book Service, Pittsburgh, Pa., 1953.

(11) E. R. Howells, D. C. Phillips, and D. Rogers, *Acta Crystallogr.*, 3, 210 (1950).

(12) A. J. C. Wilson, *Nature (London)*, 150, 151 (1942).

(13) D. Sayre, *Acta Crystallogr.*, **5**, 60 (1952).

(14) R. E. Long, *Diss. Abstr.*, **26**, 3651 (1966).

(15) "International Tables for Crystallography," Vol. III, The Kynoch Press, Birmingham, England, 1968, p 201.

(16) The observed and calculated structure factors for 9-ethyladenine–5,5-diethylbarbituric acid will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JACS-72-8213. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche.

(17) It has been noted by Hughes that the estimated standard deviations obtained from a least-squares refinement are often underestimates (E. W. Hughes in "Structural Chemistry and Molecular Biology," A, Rich and N. Davidson, Ed., W. H. Freeman, San Francisco, Calif., 1968, p 628).

Table III. Final Atomic Coordinates and Thermal Parameters[a]

Atom[b]	x	y	z	β_{11} or B	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
AN 1	0.2922 (3)	0.2873 (2)	0.0503 (2)	0.0232 (6)	0.0097 (3)	0.0066 (2)	0.0096 (3)	0.0026 (2)	0.0012 (2)
AC 2	0.3044 (4)	0.3011 (3)	−0.0562 (2)	0.0244 (7)	0.0101 (4)	0.0067 (2)	0.0095 (4)	0.0027 (3)	0.0017 (2)
AN 3	0.2979 (3)	0.2064 (2)	−0.1397 (2)	0.0249 (6)	0.0093 (3)	0.0060 (2)	0.0095 (3)	0.0027 (2)	0.0018 (2)
AC 4	0.2754 (3)	0.0839 (3)	−0.1047 (2)	0.0169 (6)	0.0090 (4)	0.0054 (2)	0.0074 (4)	0.0016 (2)	0.0011 (2)
AC 5	0.2608 (3)	0.0542 (3)	0.0005 (2)	0.0165 (6)	0.0091 (4)	0.0054 (2)	0.0071 (4)	0.0019 (2)	0.0015 (2)
AC 6	0.2701 (4)	0.1640 (3)	0.0825 (2)	0.0177 (6)	0.0105 (4)	0.0051 (2)	0.0079 (4)	0.0016 (2)	0.0010 (2)
AN 7	0.2394 (3)	−0.0833 (2)	0.0047 (2)	0.0235 (6)	0.0087 (3)	0.0060 (2)	0.0087 (3)	0.0025 (2)	0.0017 (2)
AC 8	0.2424 (4)	−0.1329 (3)	−0.0970 (2)	0.0226 (7)	0.0089 (4)	0.0061 (2)	0.0083 (4)	0.0024 (3)	0.0014 (2)
AN 9	0.2630 (3)	−0.0385 (2)	−0.1675 (2)	0.0218 (5)	0.0091 (3)	0.0055 (2)	0.0083 (3)	0.0024 (2)	0.0008 (2)
AN 6	0.2615 (4)	0.1505 (4)	0.1891 (2)	0.0338 (8)	0.0132 (4)	0.0058 (2)	0.0128 (5)	0.0043 (3)	0.0018 (2)
AC 1′	0.2770 (5)	−0.0583 (4)	−0.2851 (2)	0.0286 (8)	0.0131 (5)	0.0056 (2)	0.0113 (5)	0.0041 (3)	0.0012 (2)
AC 2′	0.0918 (5)	−0.0706 (5)	−0.3717 (3)	0.0337 (10)	0.0177 (6)	0.0055 (2)	0.0128 (6)	0.0018 (4)	0.0014 (3)
BN 1	0.1967 (3)	0.7189 (2)	0.1502 (2)	0.0267 (6)	0.0093 (3)	0.0051 (2)	0.0101 (3)	0.0035 (2)	0.0016 (2)
BC 2	0.2190 (4)	0.6059 (3)	0.0986 (2)	0.0186 (6)	0.0088 (4)	0.0052 (2)	0.0070 (4)	0.0016 (3)	0.0010 (2)
BN 3	0.2309 (3)	0.5087 (3)	0.1632 (2)	0.0254 (6)	0.0095 (3)	0.0058 (2)	0.0100 (4)	0.0038 (2)	0.0015 (2)
BC 4	0.2065 (4)	0.5079 (3)	0.2696 (2)	0.0220 (7)	0.0103 (4)	0.0054 (2)	0.0082 (4)	0.0027 (3)	0.0018 (2)
BC 5	0.1481 (4)	0.6176 (3)	0.3209 (2)	0.0273 (7)	0.0108 (4)	0.0052 (2)	0.0108 (4)	0.0034 (3)	0.0014 (2)
BC 6	0.1840 (4)	0.7413 (3)	0.2598 (2)	0.0194 (6)	0.0096 (4)	0.0056 (2)	0.0074 (4)	0.0021 (3)	0.0005 (2)
BO 2	0.2301 (3)	0.5939 (2)	0.0005 (1)	0.0268 (5)	0.0113 (3)	0.0050 (1)	0.0097 (3)	0.0033 (2)	0.0010 (1)
BO 4	0.2205 (4)	0.4154 (2)	0.3194 (2)	0.0453 (8)	0.0142 (3)	0.0075 (2)	0.0177 (4)	0.0068 (3)	0.0043 (2)
BO 6	0.1923 (3)	0.8558 (2)	0.3018 (2)	0.0334 (6)	0.0103 (3)	0.0077 (2)	0.0114 (3)	0.0048 (2)	0.0006 (2)
BC 1′	0.2526 (5)	0.6718 (4)	0.4497 (2)	0.0346 (10)	0.0165 (5)	0.0060 (2)	0.0136 (6)	0.0027 (4)	0.0007 (3)
BC 2′	0.4856 (7)	0.7526 (7)	0.4780 (4)	0.0329 (12)	0.0266 (9)	0.0102 (4)	0.0128 (8)	0.0003 (5)	0.0008 (5)
BC 3′	−0.0961 (5)	0.5223 (4)	0.2966 (3)	0.0277 (8)	0.0130 (5)	0.0078 (3)	0.0092 (5)	0.0049 (4)	0.0024 (3)
BC 4′	−0.2017 (6)	0.5998 (5)	0.3442 (3)	0.0289 (9)	0.0193 (6)	0.0103 (3)	0.0131 (6)	0.0070 (4)	0.0041 (4)
AH 1	0.326 (5)	0.896 (4)	−0.073 (3)	3.1 (8)					
AH 2	0.232 (5)	−0.229 (4)	−0.119 (3)	2.9 (8)					
AH 3	0.252 (5)	0.219 (4)	0.231 (3)	3.6 (8)					
AH 4	0.237 (6)	0.068 (5)	0.216 (3)	3.4 (1.0)					
AH 5	0.299 (4)	−0.144 (4)	−0.301 (2)	2.4 (7)					
AH 6	0.408 (6)	0.025 (4)	−0.288 (3)	3.9 (9)					
AH 7	−0.037 (6)	−0.165 (4)	−0.375 (3)	4.7 (9)					
AH 8	0.081 (6)	0.019 (5)	−0.356 (3)	5.2 (1.0)					
AH 9	0.117 (5)	−0.072 (4)	−0.444 (3)	3.8 (8)					
BH 1	0.204 (4)	0.789 (3)	0.106 (2)	1.3 (6)					
BH 2	0.257 (5)	0.439 (4)	0.129 (3)	2.2 (7)					
BH 3	0.211 (7)	0.578 (5)	0.486 (4)	5.5 (1.1)					
BH 4	0.182 (6)	0.738 (5)	0.476 (4)	5.2 (1.0)					
BH 5	0.539 (10)	0.821 (8)	0.548 (6)	12.0 (2.1)					
BH 6	0.525 (13)	0.824 (9)	0.437 (7)	16.9 (3.2)					
BH 7	0.553 (13)	0.693 (9)	0.476 (7)	14.2 (3.0)					
BH 8	−0.118 (5)	0.430 (4)	0.340 (3)	3.7 (8)					
BH 9	−0.157 (4)	0.486 (3)	0.211 (3)	2.3 (6)					
BH 10	−0.349 (7)	0.528 (4)	0.332 (3)	4.9 (1.0)					
BH 11	−0.183 (7)	0.690 (5)	0.300 (4)	7.0 (1.2)					
BH 12	−0.148 (5)	0.621 (4)	0.434 (3)	3.5 (7)					

[a] The positional parameters are expressed as fractions of unit cell edges. Anisotropic temperature parameters are expressed as $T = \exp[-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + 2hk\beta_{12} + 2hl\beta_{13} + 2kl\beta_{23})]$. Isotropic temperature factors for hydrogen atoms are of the form $\exp(-B\sin^2\theta/\lambda^2)$. 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. [b] The prefix A refers to the 9-ethyladenine molecule and the prefix B refers to the 5,5-diethylbarbituric acid molecule. The atomic numbering scheme is the same as that given in Figure 1.

six highest peaks in the final difference Fourier map were in the region about this methyl group. These peaks had heights in the range 0.10–0.15 e/Å^3. Hence it is concluded that this methyl group either can rotate rather freely or is rotationally disordered about the barbiturate C-1′–C-2′ bond.

The Molecular Structure

Table IV shows the bond distance and the bond angles found in I together with their standard deviations as estimated from the least-squares refinement.[17] These standard deviations are abnormally large for those bonds that involve barbiturate hydrogen atoms H-5, H-6, and H-7 due to the previously discussed disorder. The covalent bond distances and bond angles are, for the most part, well within the ranges normally found for these quantities.[18] The twofold molecular symmetry of the barbiturate ring is preserved almost to within experimental error. However, the methyl groups, especially the one involving barbiturate atom C-2′, appear to be somewhat distorted. This is not surprising in view of the disorder mentioned above and because of the difficulty of accurately determining the positions of hydrogen atoms in an X-ray structure determination.

The only other significant deviations from the expected covalent bond parameters in the structure are the barbiturate C-5–C-3′ bond length, which is at least 0.05 Å longer than is expected for a carbon–carbon single bond, and the barbiturate C-4–C-5–C-3′ bond angle, which is 7.3° smaller than the nominally expected tetrahedral angle. The highest feature in the final differ-

(18) D. Voet and A. Rich, *Progr. Nucl. Acid Res. Mol. Biol.*, 10, 183 (1970).

Table IV. Bond Lengths and Angles[a]

1. 9-Ethyladenine

	Å		Å
N-1–C-2	1.345 (3)	C-2–H-1	0.99 (4)
C-2–N-3	1.326 (3)	C-8–H-2	0.98 (4)
N-3–C-4	1.345 (3)	N-6–H-3	0.87 (4)
C-4–C-5	1.372 (3)	N-6–H-4	0.92 (4)
C-5–C-6	1.413 (4)	C-1′–H-5	0.98 (4)
C-6–N-1	1.338 (3)	C-1′–H-6	1.01 (4)
C-5–N-7	1.384 (3)	C-2′–H-7	1.03 (4)
N-7–C-8	1.309 (3)	C-2′–H-8	0.98 (4)
C-8–N-9	1.358 (3)	C-2′–H-9	0.95 (4)
N-9–C-4	1.379 (3)		
N-9–C-1′	1.468 (3)		
C-1′–C-2′	1.506 (4)		
	Deg		Deg
C-6–N-1–C-2	119.5 (2)	N-1–C-2–H-1	115 (2)
N-1–C-2–N-3	128.8 (3)	N-3–C-2–H-1	116 (2)
C-2–N-3–C-4	110.2 (2)	N-7–C-8–H-2	123 (2)
N-3–C-4–C-5	127.6 (2)	N-9–C-8–H-2	124 (2)
C-4–C-5–C-6	117.0 (2)	C-6–N-6–H-3	117 (2)
C-5–C-6–N-1	117.0 (2)	C-6–N-6–H-4	125 (2)
N-3–C-4–N-9	127.0 (2)	H-3–N-6–H-4	117 (3)
C-6–C-5–N-7	132.1 (2)	N-7–C-1′–H-5	109 (2)
C-5–N-7–C-8	103.8 (2)	N-7–C-1′–H-6	108 (2)
N-7–C-8–N-9	113.8 (3)	H-5–C-1′–H-6	104 (3)
C-8–N-9–C-4	106.0 (2)	C-2′–C-1′–H-5	112 (2)
N-9–C-4–C-5	105.4 (2)	C-2′–C-1′–H-6	112 (2)
C-4–C-5–N-7	111.0 (2)	C-1′–C-2′–H-7	110 (2)
N-1–C-6–N-6	119.8 (3)	C-1′–C-2′–H-8	109 (2)
C-5–C-6–N-6	123.2 (3)	C-1′–C-2′–H-9	109 (2)
C-4–N-9–C-1′	126.3 (2)	H-7–C-2′–H-8	116 (3)
C-8–N-9–C-1′	127.7 (2)	H-7–C-2′–H-9	110 (3)
N-9–C-1′–C-2′	112.4 (2)	H-8–C-2′–H-9	103 (3)

2. 5,5-Diethylbarbituric Acid

	Å		Å
N-1–C-2	1.374 (3)	N-1–H-1	0.95 (3)
C-2–N-3	1.371 (3)	N-3–H-2	0.92 (4)
N-3–C-4	1.356 (3)	C-1′–H-3	1.07 (5)
C-4–C-5	1.519 (4)	C-1′–H-4	1.10 (4)
C-5–C-6	1.513 (4)	C-2′–H-5	0.94 (7)
C-6–N-1	1.370 (3)	C-2′–H-6	0.93 (9)
C-2–O-2	1.219 (3)	C-2′–H-7	0.96 (9)
C-4–O-4	1.225 (3)	C-3′–H-8	1.11 (4)
C-6–O-6	1.225 (3)	C-3′–H-9	1.01 (4)
C-5–C-1′	1.528 (4)	C-4′–H-10	1.11 (5)
C-1′–C-2′	1.520 (5)	C-4′–H-11	1.06 (3)
C-5–C-3′	1.608 (4)	C-4′–H-12	1.00 (4)
C-3′–C-4′	1.510 (4)		
	Deg		Deg
C-6–N-1–C-2	125.5 (2)	C-6–N-1–H-1	120 (2)
N-1–C-2–N-3	116.7 (2)	C-2–N-1–H-1	114 (2)
C-2–N-3–C-4	125.8 (2)	C-2–N-3–H-2	115 (2)
N-3–C-4–C-5	118.2 (2)	C-4–N-3–H-2	119 (2)
C-4–C-5–C-6	113.2 (2)	C-5–C-1′–H-3	107 (2)
C-5–C-6–N-1	117.4 (2)	C-5–C-1′–H-4	103 (2)
N-1–C-2–O-2	121.5 (2)	C-2′–C-1′–H-3	108 (2)
N-3–C-2–O-2	121.8 (2)	C-2′–C-1′–H-4	115 (2)
N-3–C-4–O-4	121.1 (2)	H-3–C-1′–H-4	111 (3)
C-5–C-4–O-4	121.6 (2)	C-1′–C-2′–H-5	109 (4)
C-5–C-6–O-6	123.0 (2)	C-1′–C-2′–H-6	110 (5)
N-1–C-6–O-6	119.5 (2)	C-1′–C-2′–H-7	116 (5)
C-4–C-5–C-1′	111.1 (2)	H-5–C-2′–H-6	93 (6)
C-6–C-5–C-1′	112.1 (2)	H-5–C-2′–H-7	113 (6)
C-4–C-5–C-3′	102.2 (2)	H-6–C-2′–H-7	114 (7)
C-6–C-5–C-3′	107.7 (2)	C-5–C-3′–H-8	106 (2)
C-1′–C-5–C-3′	110.1 (2)	C-5–C-3′–H-9	107 (2)
C-5–C-1′–C-2′	112.4 (3)	C-4′–C-3′–H-8	107 (2)
C-5–C-3′–C-4′	115.4 (3)	C-4′–C-3′–H-9	111 (2)
		H-8–C-3′–H-9	111 (3)
		C-3′–C-4′–H-10	109 (2)
		C-3′–C-4′–H-11	107 (2)
		C-3′–C-4′–H-12	107 (2)
		H-10–C-4′–H-11	113 (3)
		H-10–C-4′–H-12	100 (3)
		H-11–C-4′–H-12	120 (3)

Table IV (*Continued*)

3. Intramolecular Contacts

(a) Hydrogen Bonds			
	—Å—		—Å—
AN-1–BN-3	2.832 (3)	AN-1–BH-2	1.91 (4)
AN-6–BO-4	3.218 (4)	BO-4–AH-3	2.35 (4)
AN-7–BN-1a	2.827 (3)	AN-7–BH-1a	1.89 (3)
AN-6–BO-6a	3.387 (4)	BO-6a–AH-4	2.47 (4)
	—Deg—		—Deg—
AC-2–AN-1–BN-3	112.2 (2)	AC-2–AN-1–BH-2	113 (1)
AC-6–AN-1–BN-3	126.9 (2)	AC-6–AN-1–BH-2	127 (1)
BC-2–BN-3–AN-1	114.0 (2)	AN-1–BH-2–BN-3	176 (3)
BC-4–BN-3–AN-1	120.1 (2)	BC-4–BO-4–AH-3	123 (1)
AC-6–AN-6–BO-4	111.8 (2)	AN-6–AH-3–BO-4	172 (3)
BC-4–BO-4–AN-6	120.6 (2)	AC-5–AN-7–BH-1a	140.(1)
AC-5–AN-7–BN-1a	142.8 (2)	AC-8–AN-7–BH-1a	116 (1)
AC-8–AN-7–BN-1a	113.4 (2)	AN-7–BH-1a–BN-1a	171 (3)
BC-2a–BN-1a–AN-7	108.3 (2)	BC-6a–BO-6a–AH-4	129 (1)
BC-6a–BN-1a–AN-7	125.7 (2)	AN-6–AH-4–BO-6a	176 (3)
AC-6–AN-6–BO-6a	127.4 (2)		
BC-6a–BO-6a–AN-6	129.3 (2)		
(b) Dipole–Dipole Interactions	—Å—		
BC-2–BO-2b	2.983 (4)		
BC-2–BC-2b	3.288 (5)		
BO-2–BO-2b	3.156 (4)		
BC-2–AC-2c	3.458 (3)		
BC-2–AN-3c	3.192 (3)		
BO-2–AC-2c	3.073 (3)		
BO-2–AN-3c	3.190 (3)		
	—Deg—		
BC-2–BO-2–BC-2b	93.4 (2)		
BC-2–BO-2–BO-2b	70.7 (2)		
BC-2–BO-2–AC-2c	97.9 (2)		
BO-2–BC-2–AN-3c	78.9 (2)		
AC-2c–AN-3c–BC-2	90.1 (2)		
AN-3c–AC-2c–BO-2	82.8 (2)		
(c) C–H···O Hydrogen Bond-Like Interaction	—Å—		—Å—
AC-8–BO-2a	3.180 (4)	BO-2a–AH-2	2.47 (4)
	—Deg—		—Deg—
AN-7–AC-8–BO-2a	85.4 (2)	BC-2a–BO-2a–AH-2	125 (2)
AN-9–AC-8–BO-2a	160.4 (2)	AC-8–AH-2–BO-2a	129 (2)
AC-8–BO-2a–BC-2a	109.2 (2)		
(d) Closest Stacking Contacts	—Å—		
AC-6–AN-7d	3.437 (4)		
AC-6–AC-5d	3.483 (4)		
AN-1–AN-7d	3.493 (3)		
AN-6–AN-9d	3.538 (4)		
AN-6–AC-4d	3.544 (4)		
AN-6–AC-8d	3.634 (4)		
AC-8–AC-5e	3.361 (3)		
AN-7–AC-8e	3.403 (3)		
AN-7–AN-9e	3.434 (3)		
AN-7–AN-7e	3.573 (4)		
AN-7–AC-4e	3.595 (3)		
AN-7–AC-5e	3.653 (3)		
(e) Other Close Contacts	—Å—		—Å—
BO-2–BC-3′b	3.496 (4)	BO-2–AH-1	2.60 (4)
BO-2–AC-2	3.372 (4)		

[a] The bond lengths are uncorrected for thermal motion. Standard deviations as determined from the final cycle of least-squares refinement are given in parentheses and refer to the least significant digit of their corresponding parameter. The prefix A refers to the 9-ethyladenine molecule and the prefix B refers to the 5,5-diethylbarbituric acid molecule. The atomic numbering scheme is that given in Figure 1. Lower case letters accompanying the atom numbers refer to atoms related to those in Table III by the following symmetry operations: (a) $x, -1 + y, z$; (b) $-x, 1 - y, -z$; (c) $1 - x, 1 - y, -z$; (d) $-x, -y, -z$; (e) $1 - x, -y, -z$.

ence Fourier map has a peak height of 0.21 e/Å.[3] It is located at the point (0.030, 0.605, 0.395) which is near barbiturate atoms C-5, C-1′, and C-3′. This peak appeared in all of the difference Fourier maps that were calculated in the latter stages of the structure refinement. It is likely that it is symptomatic of a small amount of disorder, that is most probably due to a different puckering conformation of the barbiturate ring at atom C-5. Such disorder could easily account for the apparent distortions in the above-mentioned bond parameters.

The adenine and the barbiturate molecules are highly planar as is shown in Table V. The planes of the molecules are very nearly parallel to the crystals' (2, 0,0) planes. The only large deviations of the atoms of the rings out of the least-squares planes are those of barbiturate atoms C-5 and O-6 from plane 2. This "flap" conformation of the barbiturate ring, in which atom C-5 and one or both of the carbonyl oxygen atoms O-4 and O-6 are displaced to opposite sides of the planar barbiturate ring by 0.1–0.4 Å, has been observed quite often in crystal structures of barbiturates.[18]

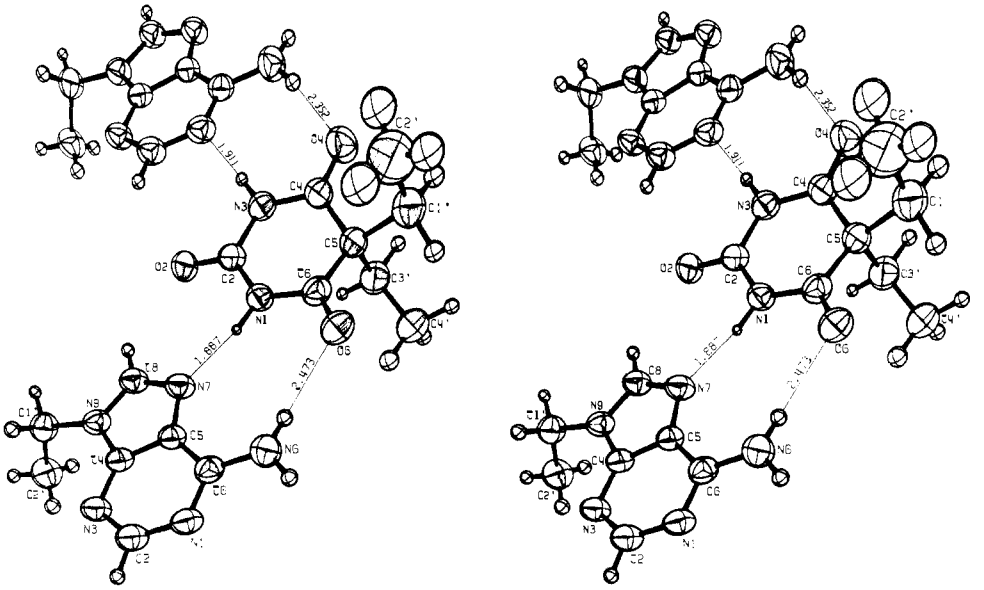

Figure 2. A stereodrawing depicting a section of the extended hydrogen-bonded chain in the crystalline intermolecular complex 9-ethyladenine-5,5-diethylbarbituric acid. The nonhydrogen atoms are represented as thermal ellipsoids of a size such that the vibrating atoms have a 50% probability of being found within them. The hydrogen atoms are represented as spheres of a size such that the atoms have a 25% probability of being found within them.

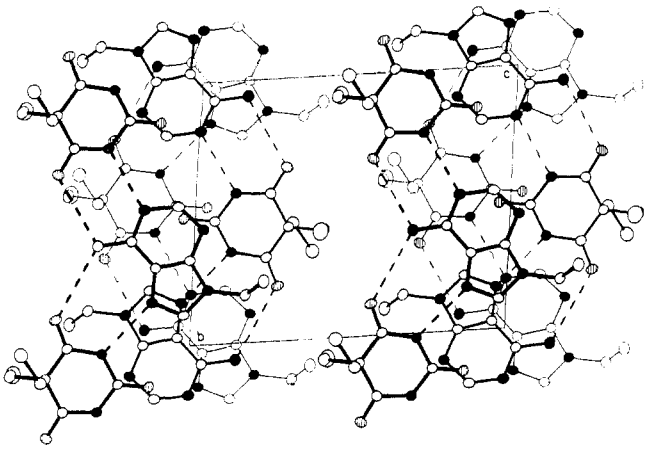

Figure 3. A projection of three consecutive hydrogen-bonded layers of the crystal structure onto the (1, 0, 0) plane of the crystal. This illustrates the stacking relationships in the structure. Hydrogen bonds are represented as dashed lines. Carbon atoms are depicted as open ellipsoids, nitrogen atoms are filled ellipsoids, and oxygen atoms are shaded ellipsoids. Hydrogen atoms have been omitted for the sake of clarity.

Table V. Deviations, in Ångstroms, of Nonhydrogen Atoms from the Least-Squares Planes through the Adenine Atoms (Plane 1), the Barbiturate Atoms (Plane 2), and the Adenine–Barbiturate Complex (Plane 3)

Atom	Plane 1[b]	Plane 2[c]	Plane 3[d]
	Adenine		
N-1	0.001		0.284
C-2	−0.003		0.299
N-3	−0.005		0.181
C-4	−0.009		0.028
C-5	−0.008		−0.007
C-6	−0.003		0.131
N-7	−0.009		−0.176
C-8	−0.005		−0.233
N-9	−0.009		−0.121
N-6	0.023		0.139
C-1′	0.028		−0.111
	Barbiturate		
N-1		−0.006	−0.141
C-2		0.000	−0.063
N-3		0.037	0.026
C-4		−0.038	−0.062
C-5		−0.266[a]	−0.370[a]
C-6		0.012	−0.148
O-2		−0.012	−0.057
O-4		0.006	0.032
O-6		0.188[a]	−0.039[a]
rms deviation	0.012	0.021	0.150

[a] Atoms not included in the least-squares fit. [b] The equation of plane 1 is: $10.2183x - 1.0118y + 0.6551z = 1.6989$. [c] The equation of plane 2 is: $6.0830x + 0.8305y + 0.7024z = 1.9049$. [d] The equation of plane 3 is: $6.3054x + 0.2671y + 0.6161z = 1.6663$.

However, there are also many crystal structures reported in which the barbiturate ring assumes some other conformation such as that of coplanarity.[18] As has been pointed out by Voet and Rich[18] and also by Gatehouse and Craven,[19] there seems to be no reliable correlation between the mode of barbiturate ring puckering and the nature of the substituents at atom C-5. Indeed, the mode of barbiturate ring puckering varies quite significantly among the six crystal structures containing 5,5-diethylbarbituric acid that have been reported.[20-23] This suggests that little energy is required to cause small distortions of the barbiturate ring from its equilibrium conformation. Therefore, in the solid state the mode of barbiturate ring puckering must be largely directed by crystal packing forces.

The two ethyl groups substituent to the barbiturate have quite different conformations relative to the barbiturate ring as can be seen in Figures 2–4. Atom C-1′ is in a nearly equatorial position with respect to the barbiturate ring whereas atom C-3′ is almost axial.

(19) B. M. Gatehouse and B. M. Craven, *Acta Crystallogr., Sect. B*, 27, 1337 (1971).
(20) B. M. Craven, E. A. Vizzini, and M. M. Rodrigues, *ibid., Sect. B*, 25, 1978 (1969).
(21) B. M. Craven and E. A. Vizzini, *ibid., Sect. B*, 27, 1917 (1971).
(22) B. M. Craven and G. L. Gartland, *J. Pharm. Sci.* 59, 1666 (1970).
(23) S. Kiryu, *ibid.*, 60, 699 (1971).

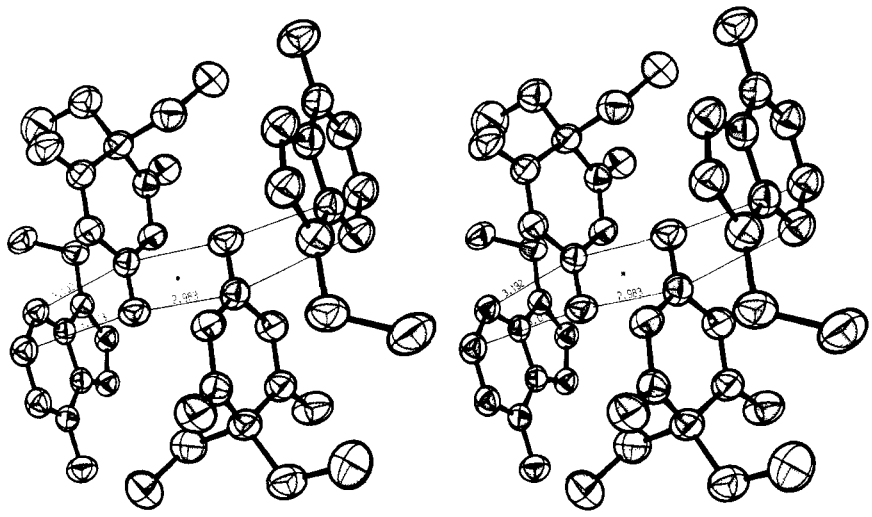

Figure 4. A stereodrawing illustrating the dipole–dipole interactions among the adenine and the barbiturate rings in four consecutive layers of the crystal structure. The atoms are represented as thermal ellipsoids of such a size that the vibrating atoms have a 50% probability of being found within them. Hydrogen atoms have been omitted for the sake of clarity.

The C-1′–C-2′ bond has a trans configuration with respect to the bond sequence C-2′–C-1′–C-5–C-3′. Thus the C-1′–C-2′ ethyl group is pointed back over the barbiturate ring in a manner that is quite common among 5-substituent ethyl groups in barbiturates. However, the C-3′–C-4′ bond assumes a gauche configuration with respect to the C-4′–C-3′–C-5–C-1′ bond sequence and thus is pointed away from the ring. This latter conformation is quite unusual among 5-substituent ethyl groups in barbiturates.

The Intermolecular Associations

The most striking structural feature of the crystalline adenine–barbiturate complex (1) is that it forms extended planar sequences of alternating adenine and barbiturate rings. These are held together by cyclic dimers of hydrogen bonds as is shown in Figure 2.[24,25] The hydrogen-bonded ribbons are organized side by side to form planar sheets. These in turn stack to form a layered structure. This is illustrated in Figure 3.[24] Alternate layers in this arrangement are related to each other by centers of symmetry located between the layers.

If barbiturates are considered to be derivatives of uracil, then it can be seen in Figure 2 that one of the two types of hydrogen-bonded cyclic dimers present in the structure has the Watson–Crick base pairing configuration and the other has the Hoogsteen (imidazole) configuration.[18] The bond lengths and the bond angles of these hydrogen bonds are given in Table IV. It can be seen that the two N–H···N hydrogen bonds have parameters within the normal ranges for these quantities.[18,26] However, the two N–H···O hydrogen bonds are extremely long. Indeed, the one involving barbiturate atom O-6 has an O···H distance of 2.47 Å. This is just slightly shorter than the O···H van der Waals contact distance of 2.6 Å[27] and hence the interaction energy of this hydrogen bond must be extremely weak.[28]

The best planes through the adenine ring and through the barbiturate ring (planes 1 and 2 in Table V) are related by a dihedral angle of 10.2°. This is a rather large dihedral angle relating planar hydrogen-bonded base pairs.[18] However, there are considerably less degrees of freedom for efficiently packing extended hydrogen-bonded sequences of rigidly coplanar bases into a crystalline lattice than there are for the more usual complexes consisting of two coplanar hydrogen-bonded molecules. Thus it seems reasonable to attribute the large dihedral angle between the best planes through the adenine and the barbiturate rings to crystal packing forces.

An extremely interesting feature of the crystalline complex is the close contact made between two symmetry related barbiturate carbonyl groups, C-2–O-2. These groups lie in neighboring planes of hydrogen-bonded rings as is shown in Figures 3 and 4.[24,25] The noncovalent C-2···(O-2)′ contact is 2.983 Å which is somewhat less than the C···O van der Waals contact distant of 3.1 Å.[27] Such short intermolecular C···O contacts are not uncommon in crystal structures of conjugated ring molecules that have several substituent carbonyl groups.[29]

Each barbiturate C-2–O-2 carbonyl group is also in very close contact with atoms C-2 and N-3 of an adenine ring located in a neighboring layer but on the side of the barbiturate ring opposite the close carbonyl–carbonyl contact. This interaction, which can also be seen in Figures 3 and 4, has two intermolecular contacts that are slightly shorter than generally accepted van der Waals contact distances. These are the BC-2–AN-3 distance which is 3.192 Å and the BO-2–AC-2 distance which is 3.073 Å. The minimum van der Waals distances for C···N and C···O contacts are 3.2 and 3.1 Å, respectively.[27]

(24) C. K. Johnson, "ORTEP: A FORTRAN Thermal Ellipsoid Plot Program for Crystal Structure Illustrations," Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965, ORNL-3794.

(25) Inexpensive glasses that give the stereo effect with this figure may be purchased from Taylor Merchant Corp., New York, N. Y. 10036, or from Hubbard Scientific Co., Northbrook, Ill. 60062.

(26) J. Donohue in "Structural Chemistry and Molecular Biology," A. Rich and N. Davidson, Ed., W. H. Freeman, San Francisco, Calif., 1968, p 443.

(27) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960.

(28) W. C. Hamilton and J. A. Ibers, "Hydrogen Bonding in Solids," W. A. Benjamin, New York, N. Y., 1968, p 182.

(29) W. Bolton, *Nature (London)*, 201, 987 (1964).

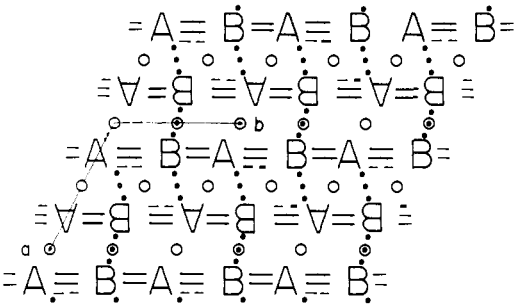

Figure 5. A schematic representation of the hydrogen bonding and the dipole–dipole interactions found in the structure of the complex 9-ethyladenine–5,5-diethylbarbituric acid: A, 9-ethyladenine; B, 5,5-diethylbarbituric acid; solid line, N–H···N or N–H···O hydrogen bond; dashed line, C–H···O hydrogen bond-like interaction; dotted line, dipole–dipole interaction; open circle, center of symmetry.

Bolton[29] has attributed close carbonyl–carbonyl contacts to electrostatic attractions between activated dipoles on the interacting carbonyl groups. This hypothesis was tested by a CNDO/2 molecular orbital calculation[30,31] on 5,5-diethylbarbituric acid using the atomic coordinates found in Table III. The total atomic charges calculated for the barbiturate molecule are given in Table VI. This table shows that the two-fold symmetry of the barbiturate molecule is maintained to within 0.01 electron unit with the exception of the disordered, and therefore distorted, methyl group. It can be seen that the charge separation on the C-2–O-2 carbonyl group is 15% greater than those on the other carbonyl groups.

Table VI. Total Atomic Charges, in Electron Units, of the 5,5-Diethylbarbituric Acid Molecule as Determined Using the CNDO/2 Method of Calculating Molecular Orbitals[a]

Atom	Charge	Atom	Charge
N-1	−0.24	H-1	0.14
C-2	0.47	H-2	0.14
N-3	−0.24	H-3	0.01
C-4	0.39	H-4	0.01
C-5	−0.08	H-5	0.04
C-6	0.38	H-6	0.04
O-2	−0.37	H-7	0.03
O-4	−0.34	H-8	0.01
O-6	−0.33	H-9	0.01
C-1′	−0.03	H-10	0.03
C-2′	−0.10	H-11	0.02
C-3′	−0.03	H-12	0.03
C-4′	−0.05		

[a] The calculations were based on the atomic coordinates found in Table III.

A CNDO/2 calculation on adenine that was calculated by Geissner-Prettre and Pullman[32] predicts that ring atoms N-1 and N-3 are the most negatively charged positions of the adenine molecule. They have total net charges of −0.26 electron unit each. In addition, atom C-2, with a total net charge of 0.21 electron unit, is second to atom C-6 (with 0.27 electron unit) as the most positively charged atom of the adenine molecule. Thus, the close contact between the barbiturate carbonyl group C-2–O-2 and the adenine ring atoms C-2–N-3 can also be attributed to a strongly attractive dipole–dipole interaction.

Barbiturate atom O-2 appears to take part in a hydrogen bond-like interaction with the C–H group at atom C-8 of the adenine ring making the Hoogsteen pair with the barbiturate. The C···O contact for this interaction is 3.180 Å and the H···O contact is 2.47 Å. These distances are significantly less than the normal van der Waals contacts for these quantities of 3.6 and 2.6 Å, respectively.[27] Such close C–H···O contacts are commonly observed between oxygen atoms and the C-8 position of purines.[18]

The short C–H···O contact involves the carbonyl group that takes part in the dipole–dipole interaction. Through the center of symmetry, there are two short C–H···O contacts surrounding the interacting carbonyl groups. Considering the supposed electrostatic nature of C–H···O interactions, it seems likely that the C–H···O and the dipole–dipole interactions found in the structure mutually stabilize each other. Hence, a second feature that has major responsibility in maintaining the stereochemistry of the crystal structure is the sequence of four stacked dipoles, flanked by two C–H···O hydrogen bond-like interactions. The entire assembly of molecules that are associated through hydrogen bonds and dipole–dipole interactions is schematically depicted in Figure 5.

Each adenine ring contacts two other adenine rings. As can be seen in Figure 3, these contacting adenine rings are in adjoining layers and are related by centers of symmetry. The data in Table IV show that the closest of these adenine–adenine interatomic distances are greater than 3.35 Å. Hence, these are normal stacking interactions.[18] As can be seen in Figure 3, there is remarkably little overlap of rings in neighboring layers. This manner of packing parallel rings is not uncommon in crystal structures of purines and pyrimidines.[33]

The ethyl groups of the adenine and the barbiturate molecules are gathered together above and below the assembly represented in Figure 5 so as to form continuous bands of closely associated ethyl groups. Thus, as can be seen in Figure 3, the crystal structure consists of these bands interspersed with the regions containing the stacks of associated rings. This type of structural feature, in which groups of atoms with similar polarities are closely associated, is often found in crystal structures of organic molecules.

Discussion

The basic structural features of I closely resemble those of the crystalline complex 9-ethyladenine–5-isopropyl-5-bromoallylbarbituric acid[6] (II). The hydrogen bonding patterns of the two complexes are almost identical. Both have two N–H···N hydrogen bonds of normal length, two abnormally long N–H···O hydrogen bonds and a short AC-8···BO-2 contact. However, in II the N–H···O hydrogen bonds are about 0.2 Å shorter and the AC-8···BO-2 contact is about 0.1 Å longer than the corresponding contacts in I. In both crystalline complexes the barbiturate C-2–O-2

(30) J. A. Pople and G. A. Segal, *J. Chem. Phys.*, **43**, S136 (1965).
(31) G. A. Segal, A CNDO/2 Program, Carnegie Institute of Technology, Pittsburgh, Pa., 1966.
(32) C. Geissner-Prettre and A. Pullman, *Theor. Chim. Acta*, **9**, 279 (1968).
(33) C. E. Bugg, J. M. Thomas, M. Sundaralingham, and S. T. Rao, *Biopolymers*, 10, 175 (1971).

carbonyl group has a close contact with a centrosymmetrically related C-2–O-2 group, but in II the intermolecular C-2···(O-2)′ distance of 3.165 Å is 0.182 Å longer than in I.

In the structure of the crystalline complex phenobarbital–(8-bromo-9-ethyladenine)$_2$ (III), the phenobarbital molecule forms a separate Watson–Crick type base pair with each of two crystallographically independent adenine rings.[5] The N–H···O distance for the hydrogen bond involving the barbiturate atom O-2 is 2.97 Å, whereas the analogous N–H···O distance involving barbiturate atom O-4 is 3.19 Å. This latter N–H···O contact is also considerably longer than usual.

There are eight reported crystal structures of adenine–uracil complexes that contain N–H···O hydrogen bonds involving atom N-6 of the adenine derivative and atom O-4 of the uracil derivative.[18] None of these N–H···O hydrogen bonds have lengths outside the normal range for such interactions. Yet in the three reported adenine–barbiturate complexes (I–III), all five N–H···O bonds involving barbiturate atom O-4 (or its chemical equivalent, O-6) are anomalously long. The forces stabilizing hydrogen bonds are believed to be largely electrostatic in character.[27] Yet Table VI shows that the net atomic charges on all three barbiturate carbonyl oxygen atoms should be approximately equal in the isolated barbiturate molecule. In addition a comparison of the values in Table VI with the net atomic charges on thymine, as calculated by Geissner-Prettre and Pullman[32] using the CNDO/2 method, reveals that analogous positions in 5,5-diethylbarbituric acid and thymine should have almost identical net atomic charges. This suggests that the interaction between adenine and barbiturate derivatives somehow polarizes the barbiturate ring so as to reduce the charges on atoms O-4 and O-6.

The data in Table VI and that of Geissner-Prettre and Pullman[32] suggest that the C-2–O-2 carbonyl groups in both barbiturates and uracil derivatives have strong dipole moments. Nevertheless, dipole–dipole interactions between carbonyl groups are rather uncommon phenomena in the crystal structures of dialkylbarbiturates and have not been observed in crystal structures of uracil derivatives.[18] Thus it appears that such dipole–dipole interactions occur only when the dipoles are "activated"[29] in some manner.

It has been observed that adenine and barbiturate derivatives form highly specific hydrogen-bonded complexes which, in chloroform solutions, have association constants that are an order of magnitude greater than those of adenine–uracil complexes.[3] The nature of this hydrogen bonding specificity, which has been termed "electronic complementarity,"[34] is not understood. However, the foregoing discussion suggests that the immediate result of the "electronically complementarity" adenine–barbiturate association is a redistribution of the bonding electron density on the barbiturate ring so as to reduce the electrostatic charge on atoms O-4 and O-6 and to enhance the dipole moment on the C-2–O-2 carbonyl group.

In light of its apparently greater charge, it may appear surprising that barbiturate atom O-2 is not a member of one of the N–H···O hydrogen bonds in I and II. However, in the crystal structure of alloxan[35] (5-oxobarbituric acid), each molecule has the potential to participate in four intermolecular hydrogen bonds. It should therefore be expected that this number of hydrogen bonds will form.[26] Yet none are observed. Rather the structure is held together by a number of carbonyl–carbonyl dipolar interactions. This demonstrates that if dipolar interactions are sufficiently strong, they can form at the expense of hydrogen bonding interactions.

In II, the requirement of efficiently packing the barbiturate's bulky bromoallyl and isopropyl side groups into the crystalline lattice probably prevents the adenine rings from closely approaching the C-2–O-2 carbonyl groups as they do in I. It is quite likely that the additional dipole–dipole interactions in I provided by the proximity of the adenine C-2–N-3 bonds to the barbiturate C-2–O-2 carbonyl groups enhance the charge polarization in the barbiturate ring. Thus it is not surprising that anomalies in N–H···O hydrogen bond lengths and carbonyl–carbonyl contacts are more extreme in I than in II.

Voet and Rich[6] explained the long N–H···O hydrogen bonds in II as being due to the packing forces in the crystal that maintain the translational equivalence of all adenine (and barbiturate) molecules in the same layer. This would force the N–H···O hydrogen bonds to lengthen because if they were all of normal length, alternate molecules in the hydrogen-bonded sequence could not be parallel. The present study sheds more light on the molecular forces underlying these distortions and suggests why the dipole–dipole interactions appear to form at the expense of the N–H···O hydrogen bonding strength.

In the solid state, the C–H bonds at the C-8 position of purines are commonly observed to participate in close C–H···O contacts. It is known that the C–H groups at these positions are considerably more acidic than is usually the case for C–H groups.[36,37] Therefore, a close C–H···O contact may be symptomatic of an unusually large electrostatic charge difference between the oxygen atom and the C–H hydrogen atom. If this is the basis of close C–H···O contacts, it follows that if the charge on the oxygen atom were increased, the C–H···O contact distance should decrease. As was explained above, the close approach of the adenine C-2–N-3 bond to the barbiturate C-2–O-2 carbonyl group in I appears to induce a greater negative charge on atom BO-2 than would otherwise be the case. Thus the AC-8···BO-2 contact in I might be expected to be significantly shorter than the analogous contact in II. This is what is observed.

There has been some controversy concerning the nature of close C–H···O contacts.[26,28,38] Their C–H–O angles appear to have much greater departures from linearity[26,38] than has been found for the analogous angles in normal N–H···O, N–H···N, and O–H···O hydrogen bonds.[18,26] This suggests that C–H···O interactions have a lesser covalent character

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than is true of normal hydrogen bonds. Normal hydrogen bonds are directly observable by a number of physical-chemical techniques such as infrared and nmr spectroscopy. So far, C–H···O interactions in molecules such as purines and pyrimidines have not been observed using these techniques.[39] Therefore, although the reality of C–H···O interactions in the solid state can no longer be denied,[18,22,40] they must be placed in a class apart from normal hydrogen-bonding interactions until it can be shown that they exhibit similar physical characteristics. Hence in this report short C–H···O contacts are referred to as hydrogen bond-*like* interactions.

There is no direct evidence to support the hypothesis that adenine–barbiturate base pairing has biological significance. Nevertheless, the great specificity and binding strength of this interaction[3] makes this hypothesis seem extremely plausible. The biological significance, if any, of the stacked dipoles found in I and II is less clear. In aqueous media, the free energies of such interactions are insignificant as are those of hydrogen bonds between bases. However, as was previously explained, it is quite likely that the barbiturate receptor site is in a nonpolar environment. The low dielectric constant of such a medium would stabilize any dipole–dipole interactions present. Hence, it may be that the barbiturate receptor site contains a group of atoms forming a strong dipole. This could be aligned so as to form an attractive interaction with the C-2–O-2 dipole of the barbiturate when it forms a hydrogen-bonded base pair with the adenine residue supposed to be at the receptor site. Such an interaction would enhance the strength of the adenine–barbiturate base pair and would therefore increase the already large specificity and binding strength of the barbiturate with its receptor site.

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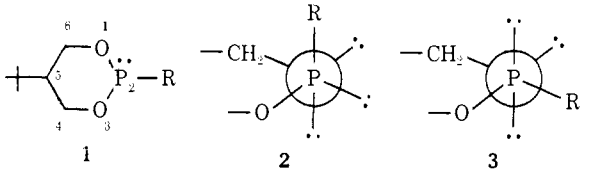
Communications to the Editor

Conformations of Saturated Phosphorus Heterocycles. Possible p_π–d_π Overlap Effects on the Apparent Conformational Energies of the Dimethylamino Group and the Influence of Phosphorus Lone-Pair Orientation on $^3J_{H_{eq}P}$

Sir:

Earlier work[1] has demonstrated that 2-R-5-*tert*-butyl-1,3,2-dioxaphosphorinanes **1** prefer to be in chair con-

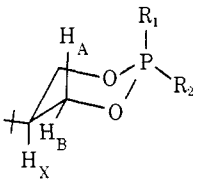


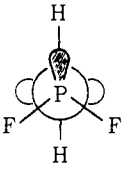
1 2 3

formations with the substituent on phosphorus *axial* rather than *equatorial* (for R = Cl,[1b] MeO,[1b] Me,[1a] *i*-Pr,[2] Ph[1c]). Consequently, the cis isomers (*t*-Bu equatorial, R axial) have been found to be more stable than the trans species. Thus, conformation about phosphorus is not determined primarily by 1,3-steric interactions but rather by the balance of vicinal interactions[3] between adjacent phosphorus and oxygen ring atoms and the substituent R (compare sturctures **2** and **3**).

We now report evidence that the dimethylamino group on phosphorus is more stable in the equatorial position with the consequence that *trans-2-dimethylamino-5-tert-butyl-1,3,2-dioxaphosphorinane* (**4a**) *is more stable than its cis isomer* **4b**.[4] This finding is quite surprising in that the Me_2N should have similar steric requirements to those of the isopropyl group[5] and also could impart to the system with axial Me_2N the stabilization usually ascribed to the anomeric effect.[6] In addition, results are presented that very strongly suggest that *the size of* $^3J_{H_{eq}P}$ *is greatly dependent on the axial or equatorial orientation of the lone pair on phosphorus.*

Compound **4** was synthesized by reaction of 2-*tert*-





6

4a, R_1 = e⁻ pair; R_2 = Me_2N
b, R_1 = Me_2N; R_2 = e⁻ pair
5a, R_1 = O; R_2 = Me_2N
b, R_1 = Me_2N; R_2 = O

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(3) The so-called *gauche effect* may be operative: S. Wolfe, *Accounts Chem. Res.*, **5**, 102 (1972).
(4) This conclusion has been reached on the basis of independent evidence from a study of the *meso*-2-dimethylamino-4,6-dimethyl-1,3,2-dioxaphosphorinane system: J. A. Mosbo and J. G. Verkade, *J. Amer. Chem. Soc.*, **94**, 8224 (1972).
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