

- IWASAKI, F. & KAWANO, Y. (1977). *Acta Cryst.* B33, 2455–2459.
- IWASAKI, F., SATO, M. & AIHARA, A. (1976). *Acta Cryst.* B32, 102–106.
- IWASAKI, F., TANAKA, I. & AIHARA, A. (1976). *Acta Cryst.* B32, 1264–1266.
- Kagakubinran* (1966). Vol. II, edited by The Chemical Society of Japan, pp. 1054–1058. Tokyo: Maruzen.
- KAGAWA, T., KAWAI, R., KASHINO, S. & HAISA, M. (1976). *Acta Cryst.* B32, 3171–3175.
- KAWAI, R., KASHINO, S. & HAISA, M. (1976). *Acta Cryst.* B32, 1972–1975.
- KUMAKURA, S., IWASAKI, F. & SAITO, Y. (1967). *Bull. Chem. Soc. Jpn.*, 40, 1826–1833.
- NAKAMOTO, K., MARGOSHES, M. & RUNDLE, R. E. (1955). *J. Am. Chem. Soc.* 77, 6480–6486.
- NEUSTADT, R. J. & CAGLE, F. W. JR (1975). *Acta Cryst.* B31, 2727–2729.
- SAKURAI, T., ITO, T., IWASAKI, H., WATANABE, Y. & FUKUHARA, M. (1967). *Rikagaku Kenkyusho Hokoku*, 43, 62–69.
- SCHOMAKER, V. & TRUEBLOOD, K. N. (1968). *Acta Cryst.* B24, 63–76.
- WILLIAMS, D. E. (1969). *Acta Cryst.* A25, 464–470.

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Preparation and X-ray Analysis of a 1:2 Adduct of Hexamethylenetetramine and Thiourea

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A 1:2 molecular compound of hexamethylenetetramine and thiourea has been prepared and subjected to crystal-structure analysis. The crystals are monoclinic, space group $C2/c$, with $a = 18.391(6)$, $b = 8.380(4)$, $c = 9.469(4)$ Å, $\beta = 109.84(5)^\circ$ and $Z = 4$. The structure was solved by direct methods and refined by full-matrix least squares with 1193 observed $Cu K\alpha$ diffractometer data to a final R index of 0.079. The hexamethylenetetramine molecule occupies a site of symmetry 2, with all four tertiary N atoms serving as proton acceptors in hydrogen bonding. In the crystal lattice the two types of molecular components are linked by $N \cdots H-N$ and $S \cdots H-N$ hydrogen bonds to form corrugated layers normal to the b axis. Neighboring layers, being related by the c glide, pack with protuberances fitting snugly into recesses.

Introduction

Thiourea forms channel inclusion complexes (Lenné, 1954; Fetterly, 1964) with carbon tetrachloride, branched-chain and alicyclic hydrocarbons, halo-paraffins, and other organic molecules with cross-sectional diameters in the range 5.8–6.8 Å (Schuessler & Flitter, 1952). Since hexamethylenetetramine [(CH_2) $_6$ N $_4$, hereafter abbreviated to HMT] appears to meet the spatial requirements for an enclosed guest species, we set out to prepare its thiourea channel complex, but succeeded instead in obtaining a hitherto unreported compound of stoichiometry HMT·2(NH $_2$) $_2$ CS. To elucidate the nature of molecular association in this 1:2 adduct, we have accordingly undertaken an X-ray analysis. It constitutes part of our current structural investigation on hydrogen-

bonded molecular compounds of HMT (Tse, Wong & Mak, 1977; Mak, Tse, Chong & Mok, 1977).

Experimental

Preparation of hexamethylenetetramine–thiourea 1:2 adduct

Hexamethylenetetramine (I) and thiourea (II) were recrystallized from ethanol. Compounds (I) (0.6 g, 4 mmol) and (II) (0.6 g, 8 mmol) were dissolved separately in the minimum amount of ethanol. The solutions were mixed, heated to below boiling ($\sim 70^\circ C$) for 1 h, and then set aside for crystallization. The reaction mixture, after standing in the dark for several days, deposited colorless, needle-shaped crystals (III)

of stoichiometry $C_8H_{20}N_8S_2$,* m.p. 161–163°C (in sealed tube). The IR spectrum of (III) consisted essentially of a superposition of the spectra of (I) and (II), except that the N–H stretching bands from (II) at 3380 and 3260 cm^{-1} were shifted to 3350 and 3290 cm^{-1} respectively, the bands at 1435 and 1395 cm^{-1} from (II) merged into partially overlapping bands centered at 1420 and 1400 cm^{-1} , the strong band at 1595 cm^{-1} from (II) was shifted to 1625 cm^{-1} , and additional peaks at 680 cm^{-1} (sharp) and 580 cm^{-1} (broad) appeared in the spectrum of the adduct. The NMR spectrum in DMSO- d_6 gave δ 4.58 and δ 7.1 (broad) in the ratio of 3:2. [Compounds (I) and (II) each show a single peak at δ 4.58 and δ 7.1 respectively in the same solvent.]

Samples suitable for X-ray study were crystallized from aqueous ethanol in the form of colorless prisms elongated parallel to **b**. Unit-cell and space-group information were obtained from Weissenberg photographs and intensity statistics. Accurate unit-cell parameters were obtained by a weighted ($w = \tan \theta$) least-squares fit to the θ values of 14 reflections measured at the University of Surrey on a Siemens four-circle diffractometer (AED) with Cu $K\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$).

Crystal data

$(CH_2)_6N_4 \cdot 2(NH_2)_2CS$, $M_r = 292.4$, m.p. 162°C; monoclinic, $a = 18.391(6)$, $b = 8.380(4)$, $c = 9.469(4) \text{ \AA}$, $\beta = 109.84(5)^\circ$, $V = 1372.7 \text{ \AA}^3$, $Z = 4$, D_m (by flotation in CCl_4 /hexane) = 1.4147(5), $D_c = 1.415 \text{ g cm}^{-3}$; space group $C2/c$, $\mu(Cu K\alpha) = 33.9 \text{ cm}^{-1}$.

For the collection of intensity data a roughly spherical crystal of diameter 0.5 mm was used. The intensities of 1243 symmetry-independent reflections with $\sin \theta/\lambda \leq 0.60 \text{ \AA}^{-1}$ were measured on the diffractometer equipped with a scintillation counter and pulse-height analyser. There was no evidence of crystal decomposition from the monitoring of a reference reflection during the period of data collection.

* Elemental analysis performed by the Australian Micro-analytical Service, CSIRO, Parkville, Victoria, Australia.

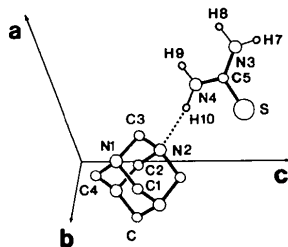


Fig. 1. Atom numbering of the asymmetric unit. Methylene H atoms have been omitted for the sake of clarity.

Each net intensity was assigned a variance, $\sigma^2(I)$, based upon the counting statistics. 50 reflections were classified as unobserved based on the criterion $I/\sigma(I) \leq 2.58$, and omitted from the analysis. The intensities were corrected for Lorentz and polarization factors but not for absorption.

Structure determination and refinement

The structure was solved by direct phase determination using the multisolution program *MULTAN* (Germain, Main & Woolfson, 1971). Successive cycles of isotropic and anisotropic least-squares refinement of non-hydrogen atoms yielded a conventional R factor of 0.088 for 1193 observed reflections. Further refinement including methylene H atoms deduced from reasonable structural assumptions [*viz* C–H bond lengths of 1.09 Å ; angles N–C–N(α), H–C–H(β) and H–C–N(γ) related by the equations: $\cot^2(\alpha/2) + \cot^2(\beta/2) = 1$ and $\cos \gamma = -\cos(\alpha/2) \cos(\beta/2)$], each with the same isotropic temperature factor $B = 5.0 \text{ \AA}^2$, gave a final R value of 0.079. Three of the strongest reflections (002, 31 $\bar{1}$, and 42 $\bar{2}$), which required the sixth attenuator during intensity measurement, appeared to suffer from large extinction effects and were given zero weight in the calculation.

A Fourier-difference map calculated using reflections with $\sin \theta/\lambda < 0.50 \text{ \AA}^{-1}$ gave well resolved peaks of 0.41, 0.59 and 0.53 $e \text{ \AA}^{-3}$ in the expected positions for

Table 1. Fractional coordinates ($\times 10^4$ for S, C and N; $\times 10^3$ for H) with *e.s.d.*'s in parentheses

H(7), H(8) and H(9) were located from a difference map; other H positions were deduced on the basis of reasonable structural assumptions.

| | Bonded to | x | y | z |
|-------|-----------|----------|----------|---------------|
| C(1) | | 0 | 4622 (7) | $\frac{1}{4}$ |
| C(2) | | 0 | 621 (6) | $\frac{1}{4}$ |
| C(3) | | 972 (2) | 2624 (4) | 3198 (5) |
| C(4) | | 29 (2) | 2624 (4) | 735 (4) |
| N(1) | | 514 (2) | 3666 (4) | 1946 (3) |
| N(2) | | 486 (2) | 1590 (4) | 3768 (3) |
| S | | 1549 (1) | 2531 (1) | 7973 (1) |
| C(5) | | 2135 (2) | 1159 (4) | 7565 (4) |
| N(3) | | 2840 (2) | 851 (4) | 8549 (3) |
| N(4) | | 1904 (2) | 389 (4) | 6253 (4) |
| H(1) | C(1) | 36 | 536 | 342 |
| H(2) | C(2) | 38 | -12 | 210 |
| H(3) | C(3) | 132 | 338 | 412 |
| H(4) | C(3) | 134 | 187 | 279 |
| H(5) | C(4) | 41 | 187 | 36 |
| H(6) | C(4) | -33 | 338 | -18 |
| H(7) | N(3) | 305 | 150 | 955 |
| H(8) | N(3) | 330 | 60 | 820 |
| H(9) | N(4) | 230 | -20 | 595 |
| H(10) | N(4) | 138 | 63 | 550 |

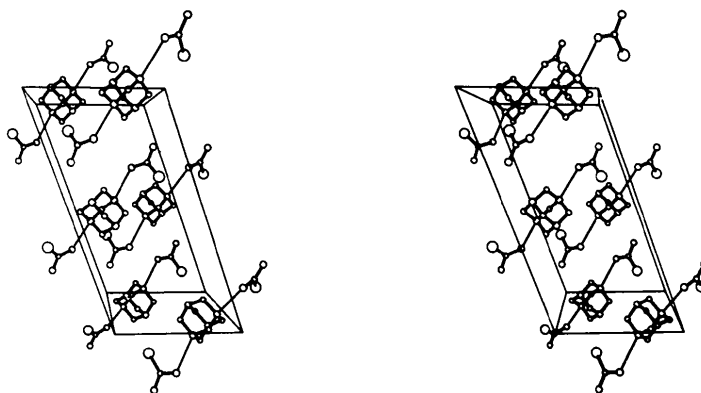


Fig. 2. Stereodrawing showing the packing of 1:2 molecular aggregates viewed approximately along *b* toward the origin of the unit cell at the lower left corner. Other hydrogen bonds which give rise to the corrugated layer structure are not included.

the amido H atoms H(7), H(8) and H(9); all other peaks in the map were less than $0.27 \text{ e } \text{Å}^{-3}$.

Scattering factors for non-hydrogen atoms were taken from *International Tables for X-ray Crystallography* (1974), whereas for H atoms the form factors for a terminal H atom were used (Stewart, Davidson & Simpson, 1965). Structure factor and least-squares refinement were carried out using a local adaptation of

ORFLS (Busing, Martin & Levy, 1962). The weighting scheme used was of the form $w = (2A + |F_o| + 2|F_o|^2/B)^{-1/2}$ with *A* and *B* taken as 4.0 and 200.0 respectively. All computations were performed on an ICL-1904A system in the Hong Kong Universities and Polytechnic Computing Centre.

The atoms are numbered as shown in Fig. 1. The final atomic positional parameters are given in Table 1.* A *PLUTO* (W. D. S. Motherwell, private communication) stereoplot of the crystal structure viewed along *b* is shown in Fig. 2. Bond lengths and angles are listed in Table 2.

Table 2. Bond lengths (Å) and bond angles (°) with *e.s.d.*'s in parentheses

(a) Hexamethylenetetramine

| | | | |
|------------------------|-----------|-----------------------------|-----------|
| C(1)—N(1) | 1.465 (4) | C(1)—N(1)—C(3) | 107.2 (3) |
| C(2)—N(2) | 1.473 (4) | C(1)—N(1)—C(4) | 108.0 (3) |
| C(3)—N(1) | 1.483 (5) | C(3)—N(1)—C(4) | 107.6 (3) |
| C(3)—N(2) | 1.472 (5) | C(2)—N(2)—C(3) | 107.6 (2) |
| C(4)—N(1) | 1.476 (5) | C(2)—N(2)—C(4) ⁱ | 107.9 (2) |
| C(4)—N(2) ^j | 1.474 (5) | C(3)—N(2)—C(4) ⁱ | 107.9 (3) |
| | | N(1)—C(1)—N(1) ⁱ | 113.7 (4) |
| | | N(2)—C(2)—N(2) ^j | 113.1 (4) |
| | | N(1)—C(3)—N(2) | 112.9 (3) |
| | | N(1)—C(4)—N(2) ^j | 112.6 (3) |

(b) Thiourea

| | | | |
|-----------|-----------|----------------|-----------|
| C(5)—S | 1.708 (3) | S—C(5)—N(3) | 120.6 (3) |
| C(5)—N(3) | 1.339 (5) | S—C(5)—N(4) | 120.6 (3) |
| C(5)—N(4) | 1.335 (5) | N(3)—C(5)—N(4) | 118.8 (3) |

(c) Hydrogen bonds

| | | | |
|--------------------------------|-----------|-------------------|-----------|
| N(3)···N(1) ⁱⁱ | 3.243 (7) | N(4)···N(2) | 3.031 (8) |
| H(8)···N(1) ⁱⁱ | 2.32 (3) | H(10)···N(2) | 2.05 (3) |
| N(3)—H(8)···N(1) ⁱⁱ | 149 (2) | N(4)—H(10)···N(2) | 164 (2) |
| N(3)···S ⁱⁱⁱ | 3.381 (7) | | |
| H(7)···S ⁱⁱⁱ | 2.35 (2) | | |
| N(3)—H(7)···S ⁱⁱⁱ | 168 (2) | | |

Roman numerals refer to the following equivalent positions relative to the atom at *x,y,z*: (i) $-x, y, \frac{1}{2}-z$; (ii) $\frac{1}{2}-x, \frac{1}{2}-y, 1-z$; (iii) $\frac{1}{2}-x, \frac{1}{2}-y, 2-z$.

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33207 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

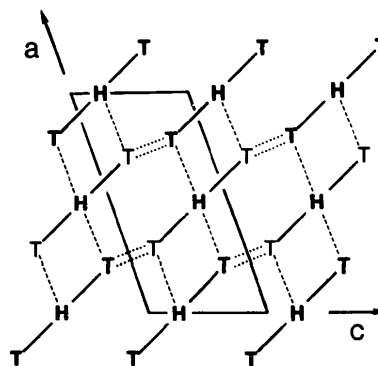


Fig. 3. Schematic representation of a corrugated layer of hexamethylenetetramine (H) and thiourea (T) molecules. Relative to H molecules in the plane of the paper, T molecules lying above and below are denoted respectively by letters of heavier and lighter types. Full, broken, and dotted lines indicate hydrogen-bond types N(4)—H(10)···N(2), N(3)—H(8)···N(1), and N(3)—H(7)···S respectively. An outline of the unit cell projected along *b* is inset.

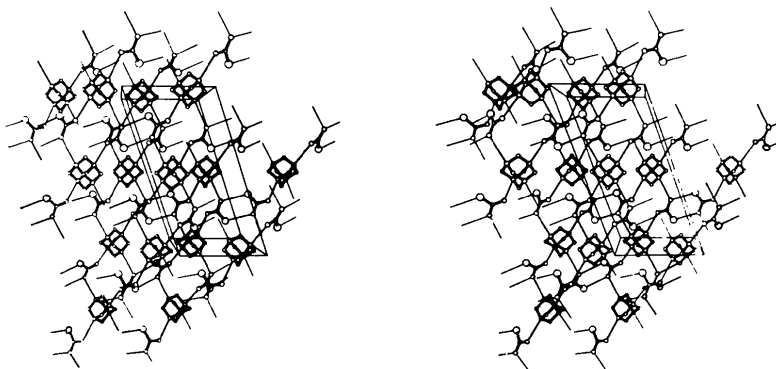


Fig. 4. Stereodrawing showing the details of hydrogen bonding and the packing of corrugated layers.

Discussion

The HMT molecule occupies a site of symmetry 2 in the crystal, with the crystallographic diad axis passing through C(1) and C(2). It is linked to four thiourea molecules by $N(sp^3)\cdots H-N(sp^2)$ hydrogen bonds. This mode of hydrogen bonding differs from those found for $HMT \cdot 3C_6H_5OH$ (Jordan & Mak, 1970) and $HMT \cdot p-C_6H_4(OH)_2$ (Mak *et al.*, 1977), in which the HMT groups form three and two hydrogen bonds respectively. The two symmetry-independent $N\cdots H-N$ hydrogen bonds are significantly different in length (Table 2), so that a 1:2 molecular aggregate corresponding to the stoichiometric formula can be readily picked out in the crystal structure (Fig. 2).

The thiourea molecules are held together in pairs by two equivalent $N(3)-H(7)\cdots S$ interactions (Table 2) which meet the accepted geometrical criteria for hydrogen bonding involving N and S (Donohue, 1969). Thus each thiourea molecule, besides being hydrogen-bonded to two HMT molecules, couples with another thiourea molecule across a center of symmetry in a configuration somewhat analogous to that in the acetic acid dimer. Because of the inversion center, the planes of the two symmetry-related thiourea molecules must be parallel, though not necessarily coplanar. The separation of 0.267 (5) Å between these two planes indicates that the 'thiourea dimer' departs from planarity as a result of steric packing requirements. Similar situations have been found in a number of carboxylic acids which dimerize across a center of symmetry in the crystalline state (Jeffrey & Sax, 1963). Of the four amido H atoms, only H(9) is precluded on geometrical and structural grounds from participation in hydrogen bonding. By contrast, in orthorhombic thiourea all H atoms take part in hydrogen bonding, each thiourea molecule (site symmetry m) being linked to the S atoms of four others by non-equivalent bonds of lengths 3.24 and 3.54 Å (Truter, 1967).

The network of $N-H\cdots N$ and $N-H\cdots S$ hydrogen bonds connects the two molecular components of the

adduct to form corrugated layers packed normal to the b axis. Each layer consists of infinite zigzag chains of 1:2 molecular aggregates running parallel to [103], adjacent chains being cross-linked by weaker hydrogen bonds of the type $N(3)-H(8)\cdots N(1)^{ii}$ (Fig. 3). Neighboring layers, being related by the c glide, pack with protuberances fitting snugly into recesses. Details of the hydrogen bonding and the packing of corrugated layers are shown in Fig. 4.

The measured dimensions of HMT are in excellent agreement with those determined for crystalline cubic HMT (Becka & Cruickshank, 1963). The thiourea molecule, excluding the amido H atoms, is planar within experimental error. The equation to the least-squares plane containing S, C(5), N(3) and N(4) is $-0.5598X - 0.7224Y + 0.4059Z = 1.1918$, where X , Y and Z are Cartesian coordinates in Å referred to a set of axes directed along a , b and c^* . The estimated standard deviation of the non-hydrogen atoms from this plane is 0.005 Å. The measured dimensions of thiourea in the present adduct are also in accord with corresponding values in orthorhombic thiourea (Kunchur & Truter, 1958; Truter, 1967; Elcombe & Taylor, 1968).

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References

- BECKA, L. N. & CRUICKSHANK, D. W. J. (1963). *Proc. R. Soc. London Ser. A*, **273**, 435-454.
 BUSING, W. R., MARTIN, K. O. & LEVY, H. A. (1962). *ORFLS*. Report ORNL-TM-305. Oak Ridge National Laboratory, Tennessee.
 DONOHUE, J. (1969). *J. Mol. Biol.* **45**, 231-235.
 ELCOMBE, M. M. & TAYLOR, J. C. (1968). *Acta Cryst.* **A24**, 410-420.
 FETTERLY, L. C. (1964). *Non-Stoichiometric Compounds*, edited by L. MANDELICORN, pp. 530-538. New York: Academic Press.

- GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* **A27**, 368–376.
- International Tables for X-ray Crystallography* (1974). Vol. IV. Birmingham: Kynoch Press.
- JEFFREY, G. A. & SAX, M. (1963). *Acta Cryst.* **16**, 430.
- JORDAN, T. J. & MAK, T. C. W. (1970). *J. Chem. Phys.* **52**, 3790–3794.
- KUNCHUR, N. R. & TRUTER, M. R. (1958). *J. Chem. Soc.* pp. 2551–2557.
- LENNÉ, H. U. (1954). *Acta Cryst.* **7**, 1–15.
- MAK, T. C. W., TSE, C.-S., CHONG, Y.-H. & MOK, F.-C. (1977). *Acta Cryst.* **B33**, 2980–2982.
- SCHIESSLER, R. W. & FLITTER, D. (1952). *J. Am. Chem. Soc.* **74**, 1720–1723.
- STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.
- TRUTER, M. R. (1967). *Acta Cryst.* **22**, 556–559.
- TSE, C.-S., WONG, Y.-S. & MAK, T. C. W. (1977). *J. Appl. Cryst.* **10**, 68–69.

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Molecular and Crystal Structure of 6-Azathymidine: Similarities with Azaribonucleosides

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The crystal and molecular structure of the carcinostatic agent 6-azathymidine has been determined from X-ray counter data. The nucleoside crystallizes in the orthorhombic space group $P2_12_12_1$ with four molecules per unit cell of dimensions $a = 8.169$ (4), $b = 7.412$ (4), $c = 18.287$ (9) Å. The structure was solved by direct methods and adjusted by full-matrix least-squares refinement to the 1014 data, yielding a final R factor of 4.3%. Similarly to other nucleosides with an aza group *ortho* to the glycosidic bond, 6-azathymidine occurs in an extreme *anti* conformation with O(1')–C(1')–N(1)–N(6) at 88°. The ribose conformation is C(2')-*exo*, C(3')-*endo* and the orientation of the C(5')–O(5') bond is *gauche, gauche*. This X-ray study suggests that the biochemical properties of 6-azathymidine can be explained similarly to those of 6-azauridine and its 5'-phosphate.

Introduction

Nucleosides with aza groups *ortho* to the glycosidic linkage were first discovered in sponges and later obtained synthetically (Suhadolnik, 1970). They are of biochemical interest owing to their pronounced cytostatic activity and have been tested for clinical use against human leukaemia (Skoda, 1963; Hernandez, Pinkel, Lee & Leone, 1969; Sorm & Veseley, 1961). In order to study structure–function relationships for this class of nucleosides, NMR studies were carried out for 6-azauridine (Hruska, 1973) and X-ray crystal structures were determined for this molecule (Schwalbe & Saenger, 1973), for 6-azauridine 5'-phosphate (Saenger & Suck, 1973), for 6-azacytidine (Singh & Hodgson, 1974*a*), for 8-azaadenosine (Singh & Hodgson, 1974*b*), and for formycin (Prusiner, Brennan & Sundaralingam, 1973; Prusiner & Sundaralingam, 1973). All these investigations yielded a consistent picture: while in

normal nucleosides the preferred orientation about the glycosidic linkage is *anti* with the torsion angle O(1')–C(1')–N(1)–N(6) nearly *cis*-planar ($\sim 20^\circ$), in the azanucleosides this angle is about 90° , rendering the torsion angle C(2')–C(1')–N(1)–N(6) nearly *cis*-planar (extreme *anti* or high *anti* conformation). On the other hand, the preferred orientation about C(4')–C(5') is *gauche, gauche* for normal nucleosides but *gauche, trans* or *trans, gauche* in the aza series. Most striking is the *gauche, trans* conformation for 6-azauridine 5'-phosphate which is in contrast to the *gauche, gauche* observed thus far in all the 5'-ribonucleotides. This finding led to a proposal for the anti-metabolic activity of 6-azauridine 5'-phosphate (Saenger & Suck, 1973; Saenger, Suck, Knappenberg & Dirx, 1978).

The question arises as to whether the unusual conformational properties of the azanucleotides are limited to the ribo series or whether they are found in deoxyriboazanucleosides as well. In this contribution the X-ray analysis of 6-azathymidine is reported.

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