# The Crystal and Molecular Structure of the Antifolate Drug Trimethoprim (2,4-Diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine). A Neutron Diffraction Study

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**Abstract:** Neutron diffraction data from a colorless 58 mg single crystal of trimethoprim (2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine ($C_{14}H_{18}N_4O_3$) were used to obtain a high-precision description of the structure. Crystallographic data: space group $P\bar{1}$, $a$ = 10.523 (4) Å, $b$ = 11.222 (4) Å, $c$ = 8.068 (3) Å, $\alpha$ = 101.22 (1)°, $\beta$ = 112.15 (1)°, $\gamma$ = 112.65 (2)°, $Z$ = 2. A multisolution method was used to solve the phase problem and the structure was refined by least-squares techniques on $F_o^2$ (all 4039 reflections) with parameters grouped in two blocks to yield $R$ = 0.045 and $R_w$ = 0.071. The 2,4-diaminopyrimidine tautomer is confirmed. The bases form an extended hydrogen-bonded ribbon with N(1) and N(2) acting as acceptor and donor respectively across one center of symmetry. Atoms N(3) and N(4) interact similarly across another inversion center. This hydrogen-bonding pattern supports a previously postulated model for binding of the drug to the receptor. No base-stacking interactions of the pyrimidine rings were observed and so no conclusions could be reached regarding the role of this associative mode in the receptor binding. A conformational energy calculation indicates considerable rotational freedom about the two bonds linking the aryl groups. The trimethoxy benzyl systems do not participate in any specific nonbonded interactions.

Substituted 2,4-diaminopyrimidines are widely employed as metabolic inhibitors of pathways leading to the synthesis of proteins and nucleic acids in the chemotherapy of malaria and neoplastic diseases.[1] The active locus of these drugs is the enzyme dihydrofolate reductase (EC 1.5.1.3) to which the inhibitors bind much more tenaciously than does the substrate (folic acid). Trimethoprim (2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine) (I) is a popular member of this class of antifolates and has the unusual property of being bound some 5000 times more strongly to the bacterial (*Escherichia coli*) reductase than to the equivalent protein from mammalian sources.[2]

A crystallographic study of trimethoprim was initiated to provide data related to the following questions. (i) Is the tautomeric form really that of a 2,4-diaminopyrimidine? (ii) Of the various hydrogen-bonding acceptors and donors in this molecule which are those that participate in such interactions? (iii) Do base-stacking interactions occur and contribute to the packing forces as has been shown for many other aromatic bases? (iv) Could any evidence be found for a strongly preferred conformation which would be indicative of the nature of the receptor site on the enzyme?

As will be seen, answers to these questions lend support to a postulated binding mode for the drug class of which trimethoprim is a member.

## Experimental Section

Large colorless single crystals were grown by cooling a solution of the title compound in EtOH–MeOH–$H_2O$ (4:1:1). An approximately equidimensional specimen weighting 58 mg ($V$ = 44 mm$^3$) was selected for data collection and placed on a four-circle diffractometer at the Brookhaven National Laboratory High Flux Beam Reactor, operating under the Multiple Spectrometer Control System.[3] Unit cell dimensions were determined by least-squares refinement against the setting angles of 31 reflections carefully centered on the diffractometer. These dimensions and other crystallographic data are given in Table I.

A total of 4637 reflections inside the mechanical scattering angle limit ($2\theta_{max}$ = 90°) were collected using a beam of neutrons with wavelength 1.021 Å and a $\theta/2\theta$ step-scan procedure in which the total scan width was varied according to the formulas: $\Delta 2\theta$ = 3.6°(1 − 1.9 tan $\theta$) for 0.05 ≤ $d^*$ ≤ 0.52 Å$^{-1}$ and $\Delta 2\theta$ = 1.04°(1 + 5.0 tan $\theta$) for 0.50 ≤ $d^*$ ≤ 1.4 Å$^{-1}$. The peak profiles were divided into peak and background by the method of Lehmann and Larsen[4] and absorption corrections, calculated by the Gaussian integration method,[5] applied. Contributions to the linear absorption coefficient ($\mu$) from oxygen and carbon atoms were assumed negligible and mass absorption coefficients ($\mu/\rho$) of 0.048 and 23.9 cm$^2$/g for nitrogen and hydrogen, respectively, were used to obtain $\mu$ = 1.926 cm$^{-1}$. The range of absorption correction terms applied was 0.494 to 0.669. Non-Poisson contributions were added to the counting statistics variance for each reflection: these terms were the squares of 2% of the total intensity to allow for experimental instability and 2% of the difference between the uncorrected and absorption-corrected intensity. Equivalent and remeasured reflections were merged to yield 4039 unique data points with a discrepancy index $R_m = (\Sigma 1/n(|F^2 - \bar{F}^2|))/\Sigma\bar{F}^2$, where $n$ is the number of contributors to a form, of 0.013 for the 319 reflections possessing more than one contributor.

Solution of the phase problem was achieved in a straightforward manner by means of an automated multi-solution tangent-formula procedure.[6] The initial model (20 of 21 nonhydrogen atoms) was expanded by Fourier methods and refined by full-matrix least-squares techniques against $F_o^2$. The final model allowed anisotropic thermal vibration tensors for all atoms which, together with the scale factor, isotropic extinction coefficient, and atomic coordinates, comprised 353 variable parameters. These parameters were refined in two blocks using the neutron scattering lengths $b_C$ = 0.6626 × 10$^{-12}$ cm, $b_H$ = −0.3723 × 10$^{-12}$ cm, $b_O$ = 0.575 × 10$^{-12}$ cm,[7] and $b_N$ = 0.920 × 10$^{-12}$ cm.[8] All reflections, except 4,1,$\bar{2}$ which was mismeasured, were used in the refinements, which led to agreement factors

$$R = \Sigma|F_o^2 - k^2F_c^2|/\Sigma|F_o^2| = 0.045$$

$$R_w = (\Sigma w|F_o^2 - k^2F_c^2|^2/\Sigma wF_o^4)^{1/2} = 0.071$$

and

$$S = (\Sigma w|F_o^2 - k^2F_c^2|^2/(m - n))^{1/2} = 2.02$$

The observed and calculated squared structure factors are presented in Table II (see note regarding supplementary material at the end of this article).

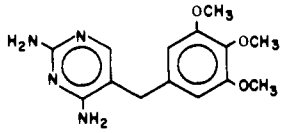
## Discussion

Final positional and thermal vibration parameters are given in Table III. Bond distances and angles are given in Figures 1A and 1B which also give the atomic nomenclature and indicate that the tautomeric form I is correct. Se-

**Table I.** Some Crystallographic Quantities for Trimethoprim[a]

| | | | |
|---|---|---|---|
| Formula | $C_{14}H_{18}N_4O_3$ | Space group | $P\bar{1}$ |
| $a$ | 10.523 (4) Å | $\rho_{obsd}$(Kl/$H_2O$) | 1.288 g/cm$^3$ |
| $b$ | 11.222 (4) Å | $\rho_{calcd}$($Z$ = 2) | 1.292 g/cm$^3$ |
| $c$ | 8.068 (3) Å | | |
| $\gamma$ | 101.22 (1)° | | |
| $\beta$ | 112.15 (1)° | | |
| $\gamma$ | 112.65 (1)° | | |

[a] Cell parameters were obtained at 24 °C from reflections centered with a tightly collimated neutron beam, of wavelength 1.021 Å, calibrated with a KBr single crystal (fcc, $a$ = 6.600 Å).




molecular diagram I

lected torsion angles are given in Table IV, while Table V presents the deviations from planarity of the two aryl moieties and their substituents. Because of the very low standard deviation of this analysis (average $\sigma$ = 0.0008 Å for the displacement of an atom from the plane) these rings may be considered nonplanar in a statistical sense. The largest out-of-plane displacement of a ring atom is only 0.043 Å, however, and essentially the rings are planar. Of greater significance is the fact that the ring substituents de-

**Table IV.** Torsion Angles[19] Describing the Conformation Adopted by the Trimethoprim Molecule[a]

| | |
|---|---|
| $\tau_1$ | C(4)–C(5)–C(7)–C(1′) = −89.4 (1)° |
| $\tau_2$ | C(5)–C(7)–C(1′)–C(2′) = 153.3 (1)° |
| | C(8)–O(3′)–C(3′)–C(2′) = −4.9 (1)° |
| | C(9)–O(4′)–C(4′)–C(3′) = −101.0 (1)° |
| | C(10)–O(5′)–C(5′)–C(4′) = −172.3 (2)° |

[a] Standard deviations for these, and all other, molecular parameters were derived from the complete variance–covariance matrix by the methods of Busing, Martin, and Levy.[20]

**Table V.** Displacements of Atoms from Least-Squares Planes[a]

| Pyrimidine ring | | Phenyl ring | |
|---|---|---|---|
| Atom | Displacement, Å | Atom | Displacement, Å |
| N(1)* | 0.030 | C(1′)* | 0.004 |
| C(2)* | −0.043 | C(2′)* | 0.003 |
| N(3)* | −0.002 | C(3′)* | −0.007 |
| C(4)* | 0.037 | C(4′)* | 0.004 |
| C(5)* | −0.033 | C(5′)* | 0.004 |
| C(6)* | −0.000 | C(6′)* | −0.007 |
| N(2) | −0.194 | C(7) | 0.134 |
| N(4) | 0.117 | H(2′) | 0.035 |
| C(7) | 0.228 | O(3′) | −0.019 |
| H(6) | 0.024 | O(4′) | 0.053 |
| | | O(5′) | 0.030 |
| | | H(6′) | 0.000 |

[a] In each case the asterisks denote the atoms used to define the planes.

**Table III.** Final Fractional Coordinates (×10$^4$) and Thermal Vibration Parameters (×10$^4$) for One Molecule of Trimethoprim[a]

| Atom | $X$ | $Y$ | $Z$ | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{12}$ | $U_{13}$ | $U_{23}$ |
|---|---|---|---|---|---|---|---|---|---|
| N(1) | 3641 (1) | 599 (1) | 5333 (1) | 462 (3) | 511 (4) | 290 (2) | 373 (3) | 93 (2) | 82 (2) |
| C(2) | 2755 (1) | −19 (1) | 3379 (1) | 358 (4) | 382 (4) | 284 (3) | 262 (3) | 120 (3) | 96 (3) |
| N(3) | 1535 (1) | 125 (1) | 2288 (1) | 338 (3) | 382 (3) | 265 (2) | 246 (2) | 118 (2) | 102 (2) |
| C(4) | 1105 (1) | 880 (1) | 3229 (1) | 309 (4) | 312 (4) | 294 (3) | 200 (3) | 128 (3) | 104 (3) |
| C(5) | 1847 (1) | 1447 (1) | 5292 (1) | 352 (4) | 268 (3) | 296 (3) | 190 (3) | 145 (3) | 85 (3) |
| C(6) | 3131 (1) | 1286 (1) | 6232 (1) | 452 (5) | 411 (4) | 274 (3) | 305 (4) | 107 (3) | 75 (3) |
| N(2) | 3111 (1) | −870 (1) | 2452 (1) | 532 (4) | 678 (5) | 334 (3) | 473 (4) | 139 (3) | 70 (3) |
| N(4) | −91 (1) | 1048 (1) | 2113 (1) | 485 (4) | 635 (4) | 359 (3) | 439 (3) | 153 (3) | 154 (3) |
| C(7) | 1223 (1) | 2080 (1) | 6380 (1) | 418 (4) | 274 (4) | 394 (4) | 186 (3) | 244 (3) | 105 (3) |
| C(1′) | 1805 (1) | 3640 (1) | 6947 (1) | 316 (4) | 261 (3) | 328 (3) | 162 (3) | 168 (3) | 72 (3) |
| C(2′) | 831 (1) | 4138 (1) | 7183 (1) | 334 (4) | 323 (4) | 415 (4) | 189 (3) | 201 (3) | 80 (3) |
| C(3′) | 1387 (1) | 5585 (1) | 7856 (1) | 420 (4) | 348 (4) | 414 (4) | 253 (4) | 230 (3) | 90 (3) |
| C(4′) | 2927 (1) | 6535 (1) | 8320 (1) | 448 (4) | 286 (4) | 382 (4) | 202 (3) | 229 (3) | 69 (3) |
| C(5′) | 3895 (1) | 6027 (1) | 8077 (1) | 359 (4) | 274 (4) | 389 (4) | 145 (3) | 197 (3) | 68 (3) |
| C(6′) | 3331 (1) | 4581 (1) | 7378 (1) | 337 (4) | 291 (4) | 408 (4) | 175 (3) | 206 (3) | 89 (3) |
| O(3′) | 534 (1) | 6180 (1) | 8122 (2) | 585 (7) | 517 (6) | 732 (7) | 399 (6) | 387 (6) | 150 (6) |
| O(4′) | 3486 (1) | 7953 (1) | 9058 (2) | 678 (7) | 289 (5) | 482 (5) | 245 (5) | 308 (5) | 70 (4) |
| O(5′) | 5378 (1) | 7033 (1) | 8589 (2) | 418 (5) | 348 (5) | 646 (7) | 118 (4) | 286 (5) | 91 (5) |
| C(8) | −1064 (1) | 5273 (1) | 7548 (2) | 573 (7) | 783 (8) | 839 (8) | 499 (7) | 406 (6) | 271 (7) |
| C(9) | 3450 (1) | 8575 (1) | 7676 (2) | 630 (6) | 375 (5) | 577 (6) | 260 (5) | 241 (5) | 177 (4) |
| C(10) | 6350 (1) | 6597 (1) | 8158 (2) | 445 (5) | 559 (6) | 670 (6) | 170 (5) | 346 (5) | 145 (5) |
| H(6) | 3792 (3) | 1718 (2) | 7825 (2) | 807 (14) | 814 (14) | 332 (8) | 576 (12) | 124 (8) | 89 (8) |
| H(1N2) | 4163 (2) | −828 (2) | 3210 (2) | 592 (11) | 747 (12) | 504 (9) | 523 (10) | 201 (8) | 163 (9) |
| H(2N2) | 2558 (3) | −1305 (3) | 1006 (2) | 776 (14) | 875 (15) | 374 (8) | 590 (12) | 205 (9) | 96 (9) |
| H(1N4) | −566 (2) | 647 (2) | 636 (2) | 536 (10) | 706 (12) | 426 (8) | 436 (9) | 169 (7) | 188 (8) |
| H(2N4) | −344 (3) | 1723 (3) | 2702 (3) | 777 (14) | 935 (16) | 594 (11) | 699 (13) | 282 (10) | 230 (11) |
| H(71) | 1531 (3) | 1889 (2) | 7723 (3) | 945 (15) | 548 (11) | 575 (10) | 441 (11) | 489 (10) | 296 (9) |
| H(72) | −74 (2) | 1500 (2) | 5555 (3) | 480 (10) | 429 (9) | 759 (12) | 183 (8) | 350 (9) | 112 (8) |
| H(2′) | −344 (2) | 3391 (2) | 6872 (3) | 406 (9) | 512 (10) | 808 (13) | 201 (8) | 330 (9) | 141 (9) |
| H(6′) | 4079 (2) | 4180 (2) | 7196 (3) | 521 (10) | 503 (10) | 850 (13) | 325 (8) | 417 (9) | 211 (9) |
| H(81) | −1736 (3) | 4607 (4) | 6013 (5) | 686 (16) | 1299 (27) | 895 (17) | 506 (17) | 209 (14) | 243 (18) |
| H(82) | −1505 (4) | 5947 (4) | 7858 (7) | 1039 (22) | 1227 (26) | 2239 (43) | 861 (21) | 1013 (27) | 512 (28) |
| H(83) | −1182 (4) | 4603 (4) | 8337 (5) | 1006 (22) | 1378 (30) | 1255 (26) | 657 (22) | 793 (21) | 725 (24) |
| H(91) | 2280 (4) | 8073 (4) | 6475 (5) | 995 (21) | 1012 (23) | 915 (19) | 433 (18) | 107 (17) | 405 (17) |
| H(92) | 4173 (5) | 8493 (5) | 7126 (6) | 1799 (37) | 1613 (35) | 1781 (35) | 1227 (32) | 1458 (33) | 1284 (32) |
| H(93) | 3820 (5) | 9642 (3) | 8360 (5) | 1769 (34) | 506 (14) | 1000 (21) | 557 (19) | 513 (22) | 308 (14) |
| H(101) | 6604 (3) | 5966 (3) | 8921 (4) | 694 (16) | 1050 (21) | 1140 (21) | 526 (16) | 488 (15) | 484 (18) |
| H(102) | 5812 (4) | 5990 (4) | 6639 (4) | 956 (20) | 1177 (24) | 829 (17) | 465 (18) | 563 (16) | 75 (16) |
| H(103) | 7437 (3) | 7543 (3) | 8633 (5) | 622 (13) | 806 (18) | 1383 (24) | 196 (13) | 640 (15) | 344 (17) |

[a] Here and throughout this paper the bracketted quantities are the standard deviation in units of the least significant digit quoted. The $U_{ij}$ coefficients are terms in the expression $\exp(-2\pi^2(U_{11}h^2a^{*2} \ldots 2U_{12}hka^*b^* \ldots))$.

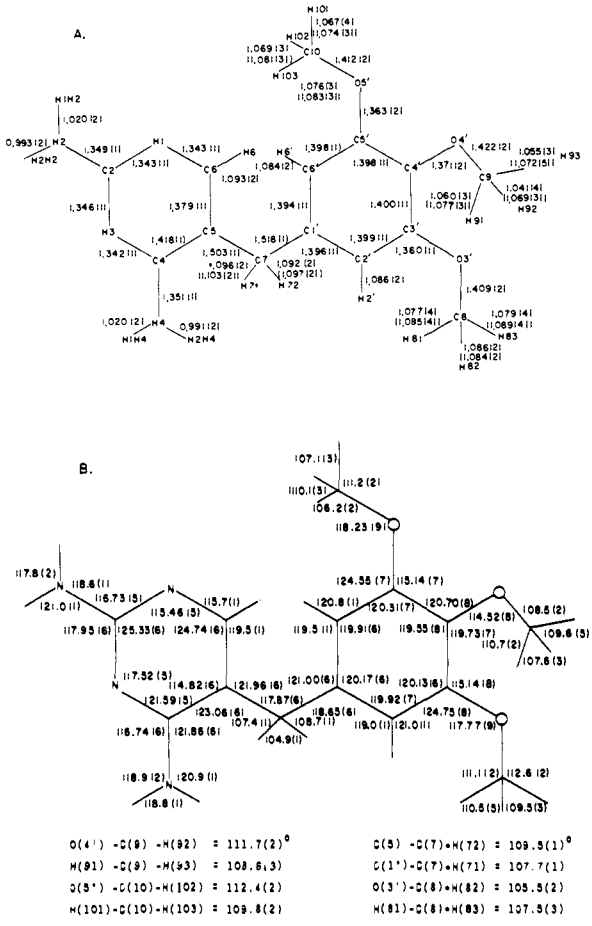


**Figure 1.** Atomic nomenclature and bond distances (part A) and interbond angles (part B). Bracketted distances involving alkyl hydrogen atoms are the C–H bond distances corrected for thermal motion by the lower bound algorithm.[21]

viate from these planes. The pyrimidine ring is bowed with both C(7) and N(4) on the side of the ring away from the phenyl system. Smaller distortions are observed for the phenyl ring substituents but here too strain is evidenced by the displacement of C(7) to the side of the phenyl system remote from the pyrimidine ring.

In general, good agreement between the chemically equivalent molecular parameters is observed. None of the four intra-ring C⋯N distances deviates by more than $1.5\sigma$ from the mean, and the two exocyclic C–N linkages are insignificantly different as are the three Ar–H bonds. The six C⋯C bonds of the phenyl ring are in accord and only minor deviations from ideality are observed in the internal bond angles of the ring. Oxygen atoms O(3′) and O(5′) which have the carbon atoms of their methyl substituents in the plane of the ring have equivalent environments and exhibit very similar distances and angles. The Ph–O and $H_3C$–O distances for O(4′) are both greater than those for the other two oxygen atoms and the angle between these bonds is about 3.5° less for this central oxygen atom, implying that O(3′) and O(5′) have assumed greater $sp^2$ character than has O(4′). The close approaches involving the meta methoxy groups and the ortho hydrogen atoms have forced the angles C2′–C3′–O3′ and C6′–C5′–O5′ to be larger than 120°, and the angles C4′–C3′–O3′ and C4′–C5′–O5′ to be correspondingly less.

Of the two C⋯C bonds in the pyrimidine ring, C(4)–C(5), which involves the carbon atom with two nitrogen substituents, is significantly longer than C(5)–C(6). This pattern has been observed in other substituted pyrimidines[9] and has been interpreted in terms of valence bond structures.[11]

The trimethoprim molecule has only two important degrees of conformational freedom. These are described by the torsion angles around the two bonds C(5)–C(7) and C(1′)–C(7). In this structure these torsion angles have the values $\tau_1 = -89.4°$ and $\tau_2 = 153.3°$, respectively (Table IV). The observed conformation is depicted in Figure 2 which also portrays the ellipsoids of thermal vibration.[12] The acetate salt of trimethoprim[9] adopts a solid-state conformation ($\tau_1 = -77.9$, $\tau_2 = 155.1°$) which is very similar to that found here. Torsion angles for the hydrobromide salt were estimated from a drawing[9] at $\tau_1 \sim 155°$ and $\tau_2 = \sim 90°$ (no atomic coordinates were published for this structure). The different conformations observed for trimethoprim in the solid state imply that the enzyme/drug interaction may occur with the drug in any one of a variety of conformations. In order better to define the conformational energy surface for rotations $\tau_1$ and $\tau_2$, a plot of potential energy against the two torsion angles was prepared.[13] This plot, which is presented as Figure 3, indicates that the free molecule may assume a variety of conformations in agreement with the earlier conclusions of Haltiwanger.[9] It is possible that the energy of binding the drug to its receptor is sufficient to stabilize an improbable conformation for the free molecule and so the conformation of minimum energy should only be regarded as likely for the way in which the antimetabolite is presented to the enzyme.

An infinite ribbon of base triples is formed in which each 2,4-diaminopyrimidine ring is hydrogen bonded to two others. The ribbon-generating inversion centers at 0, 0, 0 and ½, 0, ½ are indicated in Figure 4 which shows the hydrogen bonding. Parameters for the two distinct hydrogen bonds in the ribbon are: N(1)⋯N(2) = 3.059 (2) Å, N(3)⋯N(4) = 3.036 (2) Å, N(1)⋯H(1N2) = 2.041 Å, N(3)⋯H(1N4) = 2.017 (2) Å, N(2)–H(1N2)⋯N(1) = 175.1 (2)°, and N(4)–H(1N4)⋯N(3) = 178.7 (2)°. The two N–H covalencies involved in the bonds are each 1.020 (2) Å while the other two N–H linkages differ by less than $1\sigma$ from their mean of 0.992 (2) Å. This difference in N–H bond distances for aryl amino groups which form only one hydrogen bond appears to be a general property of such systems.[14]

The hydrogen-bonding pattern adopted here is the same as that observed in two crystalline salts of trimethoprim[9,10] and is also identical with that found in the only other crystal structure of an antifolate (2,4-diamino-5-methyl-6-benzylpyrido[2,3-*d*]pyrimidine hydrobromide)[15] completed to date. This consistent mode of intermolecular hydrogen bonding agrees with that postulated from studies of binding constants to dihydrofolate reductase for a variety of compounds.[16] Figure 5 illustrates the hydrogen-bonding schemes observed and the tautomeric shift that a folate ion must undergo in order to conform to this pattern with four hydrogen bonds. That the keto-to-hydroxy equilibrium in folic acid is strongly in favor of the keto form has been shown from theoretical calculations[17] and on experimental grounds.[18] Therefore at any instant very few folate ions are tautomerically prepared for optimal binding to the receptor, which is a plausible explanation for the fact that trimethoprim (for example) so easily displaces the natural substrate.

Other possible molecular associations are (i) aryl stacking involving either of the two delocalized systems and (ii) hydrogen bonding with one or more of the ether oxygen atoms as acceptors. There is an N–H⋯O contact of this latter type with parameters N(2)⋯O(4′) = 3.035 (1) Å, H(2N2)⋯O(4′) = 2.322 (2) Å, and N(2)–H(2N2)⋯O(4′) = 127.9 (1)°, cross-linking the ribbons but because of the long H⋯O distance, the large departure from linearity (52°), and the absence of any lengthening of the N–H

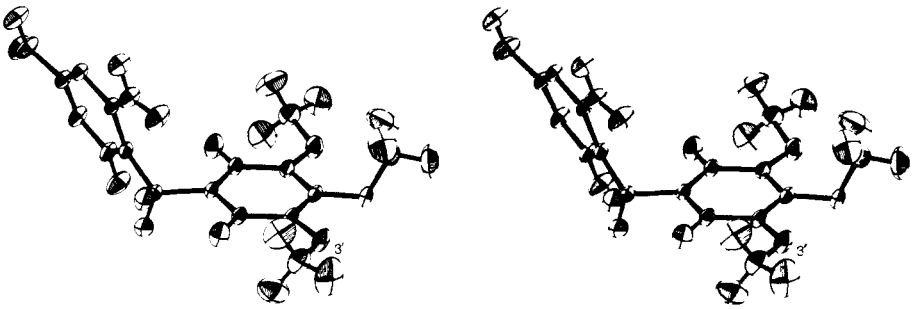


Figure 2. A computer-generated stereoscopic-pair drawing[12] showing the molecular conformation and the ellipsoids of thermal vibration. The ellipsoid surfaces are drawn at the 30% probability level.

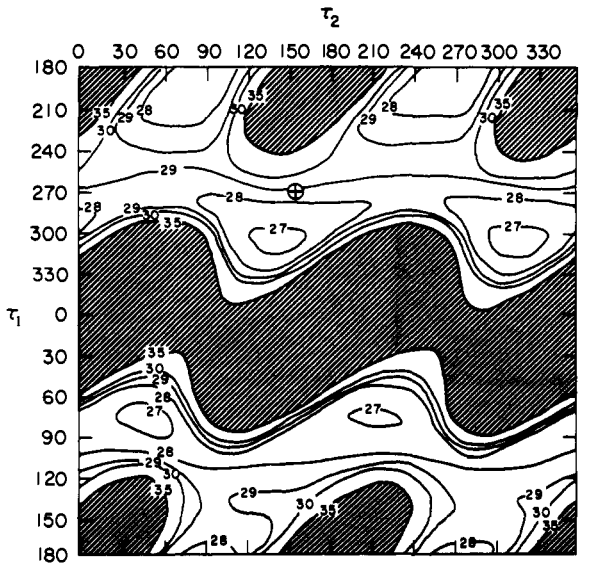



Figure 3. The conformational potential energy for trimethoprim as a function of rotations about the C–C bonds to C(7). The contour levels are quantified in nominal units of kcal/mol. The conformation observed here is marked with a cross.

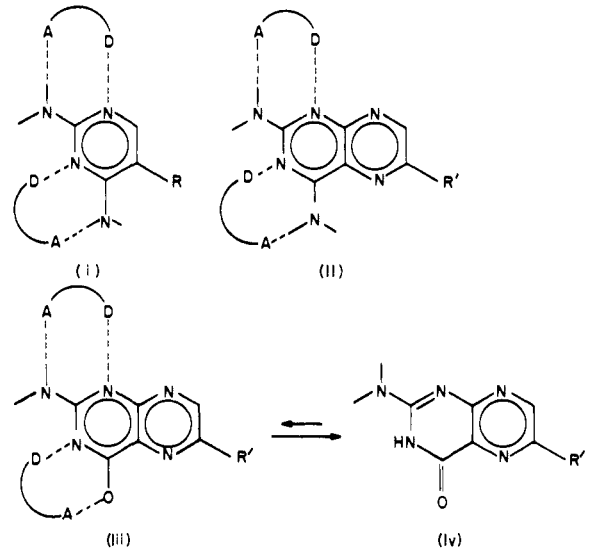



Figure 5. Hydrogen bonding schemes for inhibitors and a substrate of dihydrofolate reductase: (i) pattern observed in crystallographic studies, (ii) proposed hydrogen bonding mode for aminopterin, (iii) analogous binding for enol tautomer of folate, (iv) stable tautomer of folate.

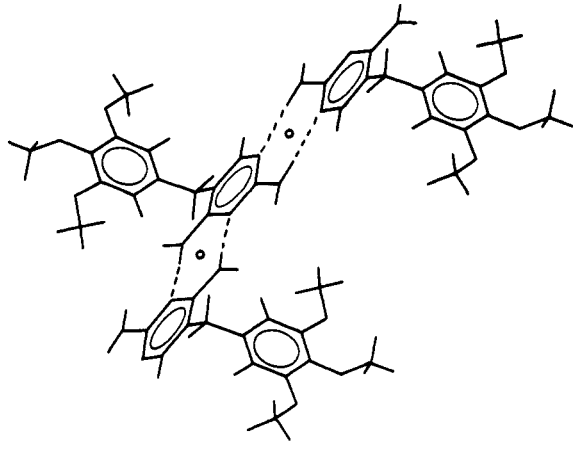


Figure 4. An illustration of a segment of the trimethoprim structure showing the base-base interactions.

bond, this interaction is considered to be very weak. Neither the pyrimidine nor the trimethoxyphenyl system participate in any stacking interactions here although the existence of both delocalized $\pi$-electron systems and polar exocyclic groups implies that these might be expected to occur.

Definitive information on which of the above modes of molecular association may be operative at the receptor site will probably be supplied only by a high resolution crystallographic study of an enzyme–inhibitor–cofactor ternary complex.

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**Supplementary Material Available:** Table II, a listing of squared structure factors (23 pages). Ordering information is given on any current masthead page.

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# Application of Photoelectron Spectroscopy to Conformational Analysis of *S*-Tetrathianes[1]

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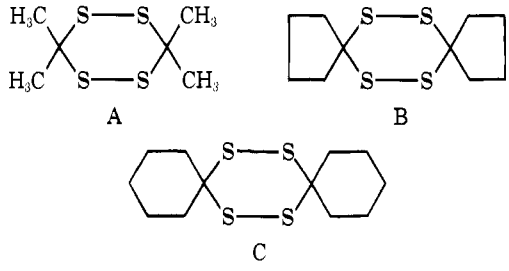
**Abstract:** The conformational study of three *S*-tetrathianes has been accomplished by photoelectron spectroscopy. After evaluation of the magnitudes of the interactions between the sulfur lone pairs in the two probable forms of *S*-tetrathianes (chair and twist forms), we conclude that the preferential forms in the vapor phase are twist for 3,3,6,6-tetramethyl-*S*-tetrathiane, and chair for the 3,3:6,6-bis(tetramethylene) and 3,3:6,6-bis(pentamethylene) derivatives.

Many $^1$H NMR studies have been reported concerning the three *S*-tetrathiane derivatives:[2] 3,3,6,6-tetramethyl-*S*-tetrathiane (A), 3,3:6,6-bis(tetramethylene)-*S*-tetrathiane (B), and 3,3:6,6-bis(pentamethylene)-*S*-tetrathiane (C).




A

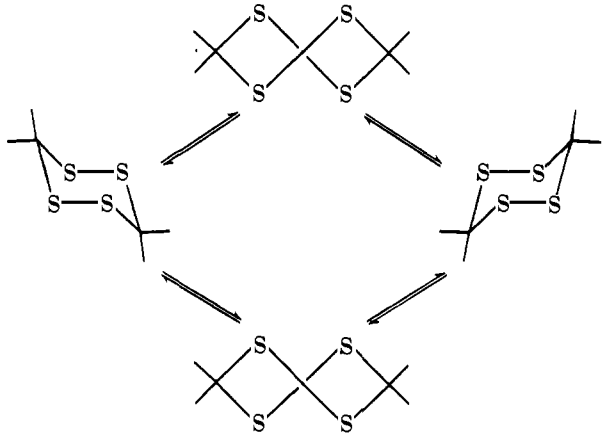



B




C

For these three compounds, in solution in carbon disulfide, Bushweller et al.[2] concluded the existence of a chair to twist equilibration, the equilibrium ratio for each form being dependent on its substituents. However, recent x-ray crystallographic studies on tetrathianes have shown that 3,3,6,6-tetramethyl-*S*-tetrathiane[3] exists in the twist con-




formation and that 3,3:6,6-bis(pentamethylene)-*S*-tetrathiane[2i] exists in the chair conformation in the crystal.

The purpose of our study has been to determine the preferential conformation of these compounds in the vapor phase. We have already used photoelectron spectroscopy for a study of 1,2,4-trithiolane derivatives[4,5] and shown that this technique allowed us to determine directly the interactions between the lone pairs of heteroatoms. These interactions are dependent upon the conformations of the compounds studied.

The four highest occupied molecular orbitals of *S*-tetrathianes correspond to the lone pairs of sulfur atoms. The positions of the MO's of different symmetry are determined solely by the interactions between the lone pairs.[6] Therefore, we found it useful to make an initial estimate of the importance of these interactions for each conformer considered, before proceeding to analyze the experimental spectra.

## Analysis of the Interactions Involved

A priori, we can consider individually three kinds of interactions for each of the two conformers (chair and twist forms): 1-2, 1-3, 1-4 interactions (Figure 1).

**1-2 Interaction.** This "through-space" interaction has a clear dependence on the dihedral angle $\theta$ defined by the directions of the lone pairs. The splitting into bonding ($n_1 + n_2$) and antibonding ($n_1 - n_2$) combinations ($\Delta E_{1,2}$) that results from this interaction reaches a maximum for a $\theta = 0°$ and a minimum for $\theta \sim 90°$.[7-14] For the chair form of 3,3:6,6-bis(pentamethylene)-*S*-tetrathiane, the angle $\theta$ was reported to be 66° in the crystalline form.[2i] This value corresponds [4]to a $\Delta E_{1,2}$ splitting of about 0.6–0.7 eV. For the twist form, we can expect a slightly larger $\theta$ (≈80°) thus a slightly smaller splitting.

**1-3 Interaction.** When the molecule exists in a conformation with two nonparallel lone pairs separated by a tetragonal carbon (which occurs in the chair and twist conformers of *S*-tetrathiane) "through space" interaction (direct overlap) causes splitting into destabilized minus ($n_1 - n_3$) and stabilized plus ($n_1 + n_3$) combinations. The $\Delta E_{1,3}$ splitting had been estimated to be 0.45 eV for 1,3-dithiane[15] and to be 1.07 eV for dimercaptomethane.[16] For *S*-tetrathiane, this interaction, which is very similar in both the chair and twist form, should produce a splitting between 0.5 and 1 eV.

**1-4 Interaction.** The nature and the importance of this interaction will, in contrast, be very different according to the conformer.