Aza Analogues of Nucleic Acid Constituents: the Crystal Structures of 6-Azauracil and 6-Azathymine

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Summary 6-Azauracil and 6-azathymine have different hydrogen bonding schemes, but in both cases every available atom except N(6) is involved in the hydrogen bonding.

Aza analogues of pyrimidines, purines, and their nucleosides are of great importance as antibacterial and anti-neoplastic agents; thus, for example, 6-azauracil effectively inhibits animal tumours[1] and 6-azathymine inhibits the growth of *S. faecalis*.[2]

While the structures of azapyrimidines would be expected to be quite similar to those of the corresponding pyrimidines, it has been shown[3] that replacement of any pyrimidine ribonucleoside in the valine codon GpUpU or GpUpC by 6-azauridine or 6-azacytidine results in a non-functional unit. These azapyrimidines differ from their normal counterparts only in having N or NH instead of CH adjacent to the glycosidic bond. It has been suggested[4] that the presence of a hydrogen atom on the C(6) atom in pyrimidine nucleosides may restrict rotation around the glycosidic bond. The absence of a hydrogen atom on this atom would reduce the barrier to rotation around the glycosidic bond and might allow interconversion between the *anti* and *syn* conformations; hydrogen bond formation to N(6) of the azapyrimidine, however, would again hinder this rotation. Since it is clear that these conformational differences are of biological significance,[4] the hydrogen bonding scheme of azapyrimidines and azapurines is of great importance. The crystal structures of only two azapurines (8-azaguanine[5,6] and 8-azaxanthine[7,8]) have been reported, and we are aware of no structural data on azapyrimidines. Hence, we have investigated the structures of the azapyrimidines 6-azauracil and 6-azathymine.

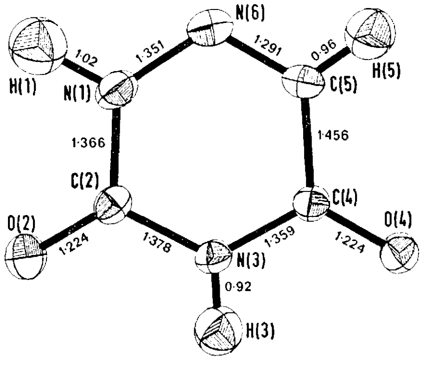

Figure 1. *View of the structure of* 6-*azauracil. Estimated standard deviations for* C–C, C–N, and C-O *bond lengths are* 0·003 Å. *Thermal ellipsoids are drawn at the* 40% *probability level.*

Large, plate-like crystals of 6-azauracil were grown from aqueous solution containing a small quantity of $HgCl_2$. *Crystal data:* $C_3N_3O_2H_3$, $M = 113{\cdot}1$, orthorhombic, $a = 4{\cdot}875(4)$, $b = 17{\cdot}611(5)$, $c = 5{\cdot}022(3)$ Å, $U = 431{\cdot}2$ Å^3, $D_m = 1{\cdot}73(2)$ g cm^{-3}, $Z = 4$, $D_c = 1{\cdot}742$ g cm^{-3}, space group

$P2_12_12_1$. Plate-like crystals of 6-azathymine were grown from absolute ethanol. *Crystal data*: $C_4N_3O_2H_5$, $M = 127{\cdot}1$, orthorhombic $a = 6{\cdot}736(4)$, $b = 13{\cdot}058(5)$, $c = 6{\cdot}342(3)$ Å, $U = 557{\cdot}8$ Å^3, $D_m = 1{\cdot}50(2)$ g cm^{-3}, $Z = 4$, $D_c = 1{\cdot}513$ g cm^{-3}, space group $Pna2_1$. Intensity data for both compounds were obtained using an automatic Picker four-circle diffractometer with Mo-K_α radiation. The structure of 6-azauracil was solved by symbolic addition and tangent refinement procedures[9] and refined to a conventional R-factor of 0·037 using 714 independent data; the structure of 6-azathymine was solved by the Patterson technique and has been refined to an R-factor of 0·059 using 513 non-zero data; the refinement of 6-azathymine will be continued when more data are available.

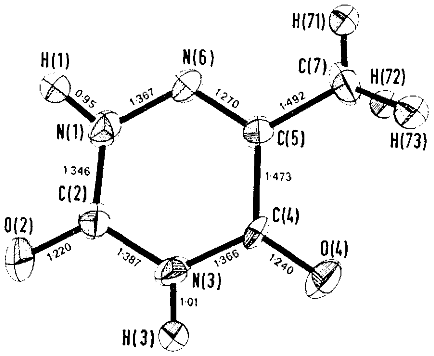

FIGURE 2. *View of the structure of* 6-*azathymine*; *the thermal ellipsoids of the hydrogen atoms have been made artificially small for clarity, while other thermal ellipsoids are at the* 40% *probability level. Estimated standard deviations for* C–C, C–N, *and* C–O *bond lengths are* 0·005 Å.

The structure of 6-azauracil is shown in Figure 1; the bond lengths are similar to those found in uracil,[10] with the exception of the C–O bond lengths. In uracil the C(2)–O(2) bond of 1·215(2) Å is considerably shorter than the C(4)–O(4) bond [1·245(2) Å], while in 6-azauracil these two bonds are of equal lengths. This difference can be explained in terms of the hydrogen bonding schemes in uracil and 6-azauracil. In the former, there are hydrogen bonds to O(4) but not to O(2), and hence the C(2)–O(2) bond has more double-bond character than the C(4)–O(4) bond. In 6-azauracil, as is also found in 6-azauridine,[11] oxygen atoms O(2) and O(4) are each involved in one hydrogen bond to different molecules. Rows of 6-azauracil molecules form infinite helical chains (running along the c-axis) through N(1)–H(1) · · · O(2) hydrogen bonds of length 2·859(3) Å; these rows are connected to each other through N(3)–H(3) · · · O(4) hydrogen bonds of length 2·839(2) Å which form helical chains in the a direction. The lengths of these N–H · · · O hydrogen bonds and the angles of 160(3) and 172(3)° subtended at H(1) and H(3), respectively, are similar to those found in other systems.[10] There is very little base stacking interaction in the crystals of 6-azauracil; the interplanar separation between adjacent molecules is only 3·03 Å, but this is made possible by an almost complete lack of overlap between the two molecules. The C(2) · · · C(5) separation of 3·30 Å between these molecules is less than the normal van der Waals distance of 3·40 Å, but all other separations between stacked pairs are greater than the sum of their van der Waals radii.

The structure of 6-azathymine is depicted in Figure 2, and the bond lengths are similar to those found in 6-azauracil. In thymine, O(4) is involved in hydrogen bonding while O(2) is not,[12] but in 6-azathymine both oxygen atoms are again found to form strong hydrogen bonds to adjacent molecules. The apparent difference between the C(2)–O(2) and C(4)–O(4) distances which we observe in 6-azathymine, while much less than that in thymine, is difficult to explain and may not be significant; further discussion of this apparent anomaly should be postponed until additional data are collected. Rows of 6-azathymine molecules form infinite chains running along the a axis through N(1)–H(1)- · · · O(4) hydrogen bonds of length 2·799(4) Å; adjacent rows which are related by the a glide at $y = 1/4$ are linked by N(3)–H(3) · · · O(2) hydrogen bonds of length 2·791(4) Å; and these pairs of rows are well separated from adjacent pairs. Hence, the hydrogen bonding arrangement leads to a sheet-like structure normal to the c axis, the separation between the sheets being one-half of the c axis length (3·17 Å); there is no overlap between the molecules in neighbouring sheets.

The absence of any hydrogen bonding to N(6) in either of these structures suggests that rotation around the glycosidic bond of the corresponding azanucleosides may be relatively free, allowing interconversion between the *syn* and *anti* conformers. In 6-azauridine the conformation is *anti* in the solid state,[11] but this observation does not preclude free rotation in solution.

(*Received*, 25*th April* 1973; *Com.* 567.)

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