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# Conformation of azidothymidine: an anti-AIDS drug

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**Abstract** The nucleoside antibiotic, 3'-azido-3'-deoxythymidine, or simply, azidothymidine has shown great promise in inhibiting the human immuno deficiency virus and in reducing mortality among AIDS patients. Conformational properties of azidothymidine have been investigated by quantum-mechanical PCILO method and compared with those of the parent nucleoside, thymidine. The results indicate great similarity between them and this similarity is remarkably striking in the situations that prevail in aqueous solution. This result has important biological significance in explaining the drug action of azidothymidine.

**Keywords.** Anti-AIDS drug; azidothymidine; conformation; PCILO; nucleoside antibiotic.

## 1. Introduction

The rapid spread of the previously unknown infectious disease acquired immuno deficiency syndrome (AIDS) has caused a worldwide concern for fighting this disease effectively. AIDS has been conclusively shown to be caused by the human immuno deficiency virus (HIV) by Gallo *et al* (1984) and since then researchers have been engaged in carrying out various studies to understand the life cycle of HIV, its structure and functions (Vogel *et al* 1988; Lapatto *et al* 1989; Malim *et al* 1989; Pang *et al* 1990). At the same time the search is on to find an effective drug to combat AIDS. The antiviral agent, 3'-azido-3'-deoxythymidine or simply, azidothymidine (AZT) has shown great promise in inhibiting HIV replication *in vitro* (Mitsuya *et al* 1985) and in reducing the mortality in AIDS patients *in vivo* (Mitsuya and Broder 1987; Yarchoan and Broder 1987; Yarchoan *et al* 1988). The exact mechanism of AZT's antibiotic action is not yet fully established but there is enough evidence to suggest that AZT inhibits the binding of thymidylate to reverse transcriptase (Ono *et al* 1986) and that AZT may be incorporated in place of thymidine into viral DNA and thereby terminate the DNA chain elongation (St. Clair *et al* 1985). AZT is phosphorylated to its 5'-triphosphate by cellular enzymes which specifically interact with reverse transcriptase (Furman *et al* 1986). However, AZT has caused serious toxicity problems in many AIDS patients (Kolata 1987) and hence there is an urgent need for efficient and less toxic drugs for AIDS.

X-ray crystallographic studies on AZT have been first reported by Camerman *et al* (1987) and their results indicate that there are two independent molecules of AZT in the asymmetric unit cell. The sugar ring puckering in molecule A is C2'-endo, C3'-exo and that in molecule B is C3'-exo, C4'-endo. The glycosyl torsion angle $\chi_{CN}$

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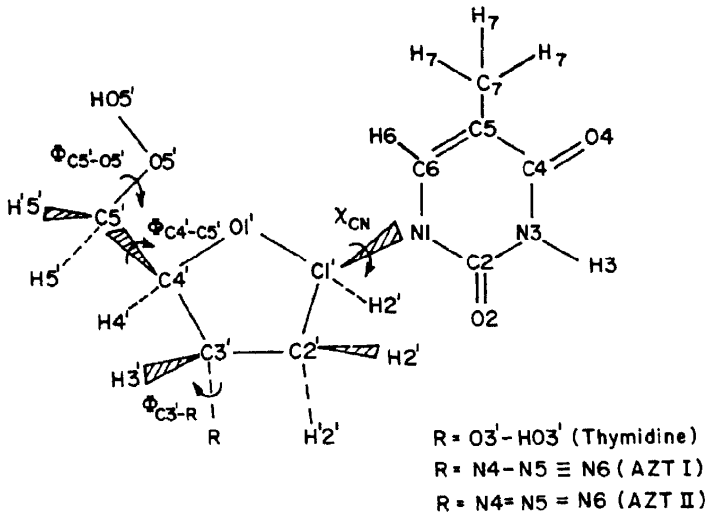



**Figure 1.** Schematic diagram of AZT and thymidine showing the various torsion angles.

(see figure 1) is *anti* for both molecules of AZT: $\chi_{CN}$ = 52·9° for AZT-molecule A and 3·5° for AZT-molecule B. The conformation around the exocyclic C4'-C5' bond is *gg*($\phi_{C4'-C5'}$ = 50·7°) in AZT-molecule A while for molecule B it is *gt*($\phi_{C4'-C5'}$ = 173·6°). An independent X-ray crystallographic study on AZT has also been reported by Parthasarathy and Kim (1988) which indicates almost identical results to those reported by Camerman *et al* (1987). Camerman, *et al* (1987) compared the crystal conformation of AZT molecules A and B with those of thymidine 3'-phosphate moieties A and B of a highly hydrated crystal structure of the dinucleotide, 5'-phosphothymidylyl (3'-5') thymidine reported earlier by Camerman *et al* (1976). Although the two structures are grossly similar in nature to each other, they differ considerably in details. Evidence of this is in the differences between the torsion angles observed in the two structures and this is particularly true for the structure of AZT-molecule B. Camerman *et al* (1987) have also shown diagrams speculating the possible binding of AZT and thymidylate with reverse transcriptase based on the crystal conformations of AZT and thymidylate resulting in DNA chain termination. Their arguments are, however, highly speculative in nature. Firstly, there is no guarantee that the crystal conformations of AZT as observed in the solid state would be preserved exactly in aqueous solution at physiological pH and this is at least true for molecules of the size of AZT or thymidylate. For very large biomolecules such as nucleic acids and proteins where the crystal packing forces and environmental factors cannot dictate the conformation, the agreement between the X-ray structures and the solution conformations is very good. Secondly, the crystal structure of thymidylate utilized for comparison with that of AZT is not on the mononucleotide itself but on a dinucleotide, d(pTpT) and the conformation of mononucleotide in the solid state may not be the same as that of the dinucleotide. Therefore, the comparison between AZT and thymidylate may not be strictly valid.

Swapna *et al* (1989) studied the conformation of AZT by proton and carbon-13 NMR in solution and their results indicate that the sugar pucker exists in C2'-endo and C3'-endo equilibrium. The glycosyl torsion angle is *anti* and the conformation

around C4'-C5' bond is predominantly *gg*. These solution results are obviously at variance with those obtained in the solid state from X-ray crystallography. These authors also reported very briefly the predominance of *gg* conformation around C4'-C5' for both molecules of AZT by the PCILO method. Molecular mechanics studies on the conformation of AZT molecule carried out by Herzyk *et al* (1987) indicate that AZT has C3'-endo sugar pucker and the conformations around the glycosyl and C4'-C5' bonds are, respectively, *anti* and *gg*. These authors have also concluded that AZT has no unusual features but has conformational properties that are very similar to those of standard deoxypyrimidines. These results on AZT are, clearly, at variance with those obtained in the solid state from X-ray crystallography.

The conformation of nucleoside antibiotics has been investigated in our laboratory for several years (Saran 1981, 1987, 1989) and these studies have established an important correlation between the conformation and biological activity of nucleoside antibiotics. AZT is a nucleoside antibiotic which results as a consequence of the replacement of 3'-hydroxyl group of the parent nucleoside, thymidine, by an azido group (figure 1). We have in the present study carried out an extensive and detailed PCILO investigation on AZT to check whether the same correlation holds good for AZT or not.

## 2. Procedure

The method utilized in this study is the quantum-mechanical PCILO method (Pullman and Saran 1976); the details of which can be found in the original papers (Diner *et al* 1969a,b; Jordan *et al* 1969). The various torsion angles which determine the conformation of AZT (figure 1) are defined (Saran *et al* 1972; Pullman and Saran 1976) as:

$$\chi_{CN} = O1' - C1' - N1 - C6,$$

$$\phi_{C4'\text{-}C5'} = C3' - C4' - C5' - O5',$$

$$\phi_{C5'\text{-}O5'} = C4' - C5' - O5' - HO5', \text{ and}$$

$$\phi_{C3'\text{-}O3'} = C2' - C3' - O3' - HO3' \text{ (for thymidine)},$$

with the *cis* planar arrangement of the terminal bonds being taken as angle zero. The *anti* and *syn* regions of glycosyl torsion angle correspond to $\chi_{CN} = 0° \pm 90°$ and $180° \pm 90°$, respectively. The *gg*, *gt* and *tg* conformation around the exocyclic C4'-C5' bond correspond, respectively, to $\phi_{C4'\text{-}C5'} \approx 60°$, 180° and 300° (Saran *et al* 1972; Pullman and Saran 1976).

The computations have been carried out on both molecules A and B of AZT by adopting their input geometry (bond lengths and bond angles) from the crystallographic studies of Camerman *et al* (1987). The azido group can be described by two resonant structures: –N4–N5≡ N6 or –N4=N5=N6 and in our calculations we have considered both the resonant structures of azido group AZT I and AZT II (figure 1). Computations have also been carried out on the parent nucleoside, thymidine by adopting the same geometry as that of AZT and replacing the 3'-azido group by a hydroxyl group. In view of the crystallographic evidence (Camerman *et al* 1976), the torsion angle $\phi_{C3'\text{-}O3'}$ has been fixed in *trans* conformation with $\phi_{C3'\text{-}O3'} = 210°$.

PCILO energies have been computed as a function of $\chi_{CN}$ and $\phi_{C4'\text{-}C5'}$ with preselected values of $\phi_{C5'\text{-}O5'}$ at 30° intervals of the torsion angles. In all, eighteen two-dimensional conformational energy maps have been constructed and the presentation of the results on these maps has been limited to 5 kcal/mol isoenergy curves above the global minimum. For brevity, only a few representative maps have been presented in the text though the results of all the other maps have been discussed.

## 3. Results and discussion

Tables 1 and 2 list the global minima and low energy conformations within 1 kcal/mol for both molecules of AZT as well as the parent nucleoside, thymidine

**Table 1.** Preferred conformation of C2'-endo, C3'-exo AZT-molecule A and thymidine.

| Molecule | Map constructed with $\phi_{C5'\text{-}O5'}$ | Global minimum* $\chi_{CN}$ | Global minimum* $\phi_{C4'\text{-}C5'}$ | Energy† |
|---|---|---|---|---|
| AZT- molecule A | 60 | 240 (*syn*) | 30 (*gg*) | 0·0 |
| (I = −N–N ≡ N) | 180 | 330 (*anti*) | 60 (*gg*) | 1·3 |
| | | 60 (*anti*) | 60 (*gg*) | 1·3 |
| | 300 | 180 (*syn*) | 150 (*gt*) | 2·7 |
| AZT-molecule A | 60 | 240 (*syn*) | 30 (*gg*) | 0·0 |
| (II = −N=N=N) | 180 | 330 (*anti*) | 60 (*gg*) | 2·0 |
| | | 60 (*anti*) | 60 (*gg*) | 2·0 |
| | 300 | 180 (*syn*) | 150 (*gt*) | 2·2 |
| Thymidine | 60 | 240 (*syn*) | 30 (*gg*) | 0·0 |
| | 180 | 330 (*anti*) | 60 (*gg*) | 2·5 |
| | | 60 (*anti*) | 60 (*gg*) | 2·5 |
| | 300 | 180 (*syn*) | 150 (*gt*) | 2·0 |

*Torsion angles in degrees.
†Energy in kcal/mol by taking the energy of the lowest global minimum energy to be zero.

**Table 2.** Preferred conformation of C3'-exo, C4'-endo AZT-molecule B and thymidine.

| Molecule | Map constructed with $\phi_{C5'\text{-}O5'}$ | Global minimum* $\chi_{CN}$ | Global minimum* $\phi_{C4'\text{-}C5'}$ | Energy† | Low energy regions* $\chi_{CN}$ | Low energy regions* $\phi_{C4'\text{-}C5'}$ | Energy† |
|---|---|---|---|---|---|---|---|
| AZT-molecule B | 60 | 0 (*anti*) | 60 (*gg*) | 0·0 | | | |
| (I = −N−N≡N) | 180 | 0 (*anti*) | 60 (*gg*) | 1·7 | 180 (*syn*) | 120 (*gt*) | 2·7 |
| | 300 | 90 (*anti*) | 120 (*gt*) | 5·7 | 330 (*anti*) | 150 (*gt*) | 5·9 |
| AZT-molecule B | 60 | 0 (*anti*) | 60 (*gg*) | 0·0 | | | |
| (II = −N=N=N) | 180 | 0 (*anti*) | 60 (*gg*) | 2·2 | 180 (*syn*) | 120 (*gt*) | 3·2 |
| | 300 | 90 (*anti*) | 120 (*gt*) | 4·5 | 330 (*anti*) | 150 (*gt*) | 4·7 |
| Thymidine | 60 | 0 (*anti*) | 60 (*gg*) | 0·0 | | | |
| | 180 | 0 (*anti*) | 60 (*gg*) | 2·7 | 180 (*syn*) | 120 (*gt*) | 3·2 |
| | 300 | 90 (*anti*) | 120 (*gt*) | 4·5 | 330 (*anti*) | 150 (*gt*) | 4·7 |

*Torsion angles are in degrees.
† Energy in kcal/mol by taking the energy at the lowest global minimum energy to be zero.

along with their energies taking the energy of the lowest global minimum energy to be zero.

### 3.1 *AZT-molecule A* (*C2'-endo*, *C3'-exo*)

The most stable conformation for C2'-endo, C3'-exo AZT-molecule A with both the resonant structures I and II for the azido group is obtained with a preselection of $\phi_{C5'\text{-}O5'} = 60°$. Figure 2 shows the conformational energy map for resonant structure I and it can be seen that a highly localized global minimum occurs at $\chi_{CN} = 240°$ (*syn*) and $\phi_{C4'\text{-}C5'} = 30°$ (*gg*). This global minimum is stabilized by a strong intramolecular hydrogen bonding between O5' of deoxyribose and O2 of thymine base through favourable orientation of HO5' (i.e. $\phi_{C5'\text{-}O5'} = 60°$). Such intramolecular hydrogen bonding has been observed for other nucleoside antibiotics having C2'-endo sugar pucker (see review by Saran 1987, 1989). An identical conformational energy map has been obtained for the resonant structure II. In fact, a glance at the results summarized in tables 1 and 2 indicate that there is no significant effect of the resonant structures I and II for the azido group on the conformational properties of AZT.

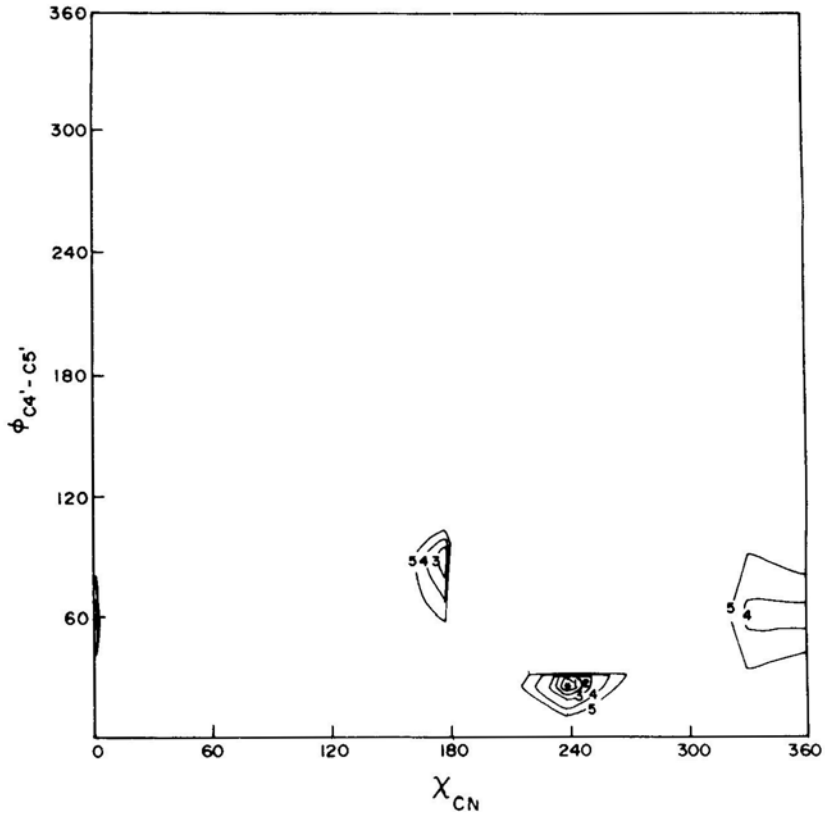



**Figure 2.** ($\chi_{CN} - \phi_{C4'\text{-}C5'}$) conformational energy map for AZT-molecule A (C2'-endo, C3'-exo) with resonant structure I and $\phi_{C5'\text{-}O5'} = 60°$. For this and subsequent figures isoenergy contours (in kcal/mol) have been drawn with respect to the global minimum (denoted by *)

The conformational energy maps for AZT-molecule A with resonant structures I and II constructed with a preselection of $\phi_{C5'\ O5'} = 180^{o}$ are shown respectively, in figures 3 and 4. It can be observed from these two maps that there is a large conformational flexibility as compared to the very restricted flexibility shown in figure 2. Both maps exhibit very similar conformational features. There are two global minima having the same energy at $\chi_{CN}$ = 330° (*anti*) and 60 (*anti*) and both of them are associated with the same $\phi_{C4'\text{-}C5'}$ = 60° (*gg*)· The *syn* region ($\chi_{CN}$ = 150°–240°) are about 2 to 4kcal/mol higher in energy than the global minima. In the preselection of $\phi_{C5'\text{-}05'}$ = 180°, HO5' faces away from the base and, therefore, there is no possibility of intramolecular hydrogen bonding between the atoms of the deoxyribose and the thymine base. The biological significance of the results presented in figures 3 and 4 has been discussed in the next section.

Figure 5 shows the conformational energy map of AZT-molecule A with resonant structure I and $\phi_{C5'\text{-}05'}$ = 300°. The global minimum occurs at $\chi_{CN}$ = 180° (*syn*) and $\phi_{C4'\text{-}C5'}$ =150 (*gt*). This map exhibits larger conformational flexibility as compared to that shown in figure 2. A very similar conformational map has been obtained for the resonant structure II showing the global minimum at the same torsion angles as those observed in the map of figure 5.

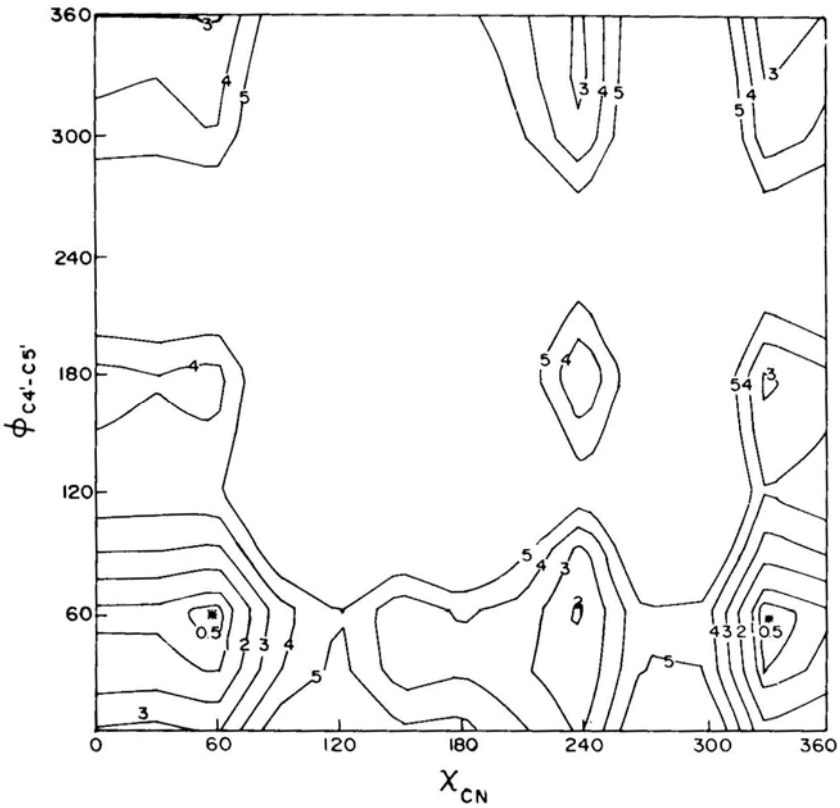
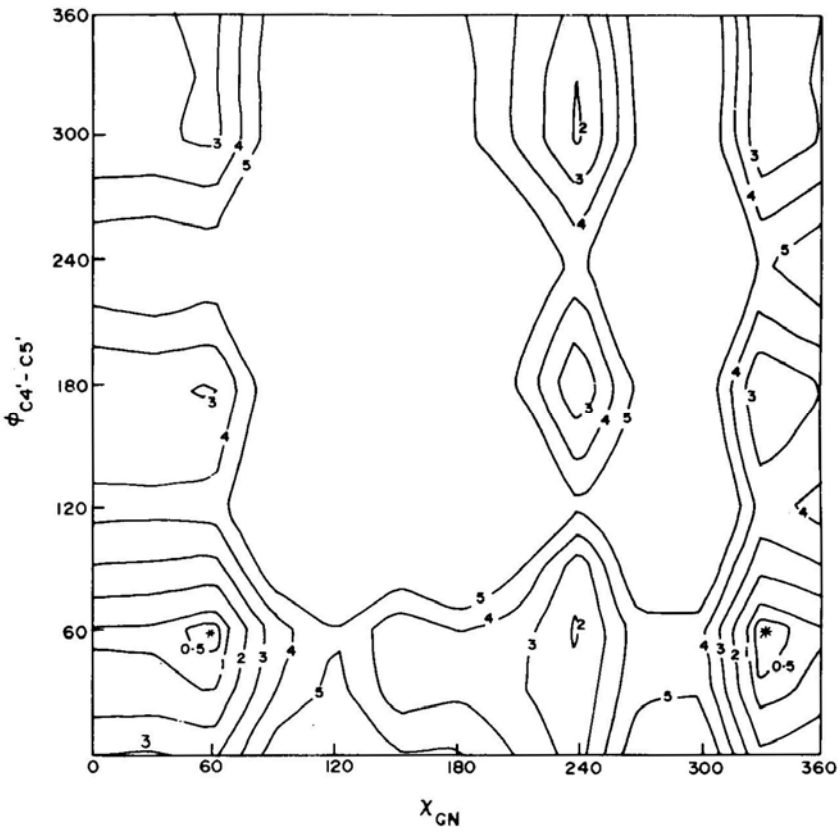



**Figure 3.** ($\chi_{CN}$ –$\phi_{C4'\text{-}C5'}$) conformational energy map for AZT-molecule A(C2′-endo, C3′-exo) with resonant structure I and $\phi_{C5'\text{-}O5'}$ = 180°.




**Figured 4.** ($\chi_{CN}$-$\phi_{C4'-C5'}$) conformational energy map for AZT-molecule A (C2'-endo, C3'-exo) with resonant structure II and $\phi_{C5'-O5'} = 180°$.

### 3.2 *Thymidine* (*C2'-endo*, *C3'-exo*)

PCILO computations carried out for the parent nucleoside, thymidine, with the same C2'-endo, C3'-exo sugar pucker as AZT-molecule A indicate identical conformational preferences (see table 1). A highly localized global minimum is observed in the conformational energy map constructed with $\phi_{C5'-O5'} = 60°$, similar to that shown in figure 2, at $\chi_{CN} = 240°$ (*syn*) and $\phi_{C4'-C5'} = 30°$ (*gg*). This is, again, due to intramolecular hydrogen bonding between 05'-H05' of deoxyribose and O2 of the base.

Figure 6 shows the conformational energy map for thymidine with a preselection of $\phi_{C5'-O5'} = 180°$. There are two global minima at $\chi_{CN} = 330°$ (*anti*) and 60° (*anti*) and both of them are associated with $\phi_{C4'-C5'} = 60°$ (*gg*). It can be seen that the maps shown in figures 3, 4 and 6 have strikingly similar conformational features indicating similar global minima and conformational flexibility.

The conformational energy map for thymidine constructed with a preselection of $\phi_{C5'-O5'} = 300°$ indicates identical conformational features to those shown in figure 5. The global minimum occurs at $\chi_{CN} = 180°$ (*syn*) and $\phi_{C4'-C5'} = 150°$ (*gt*).

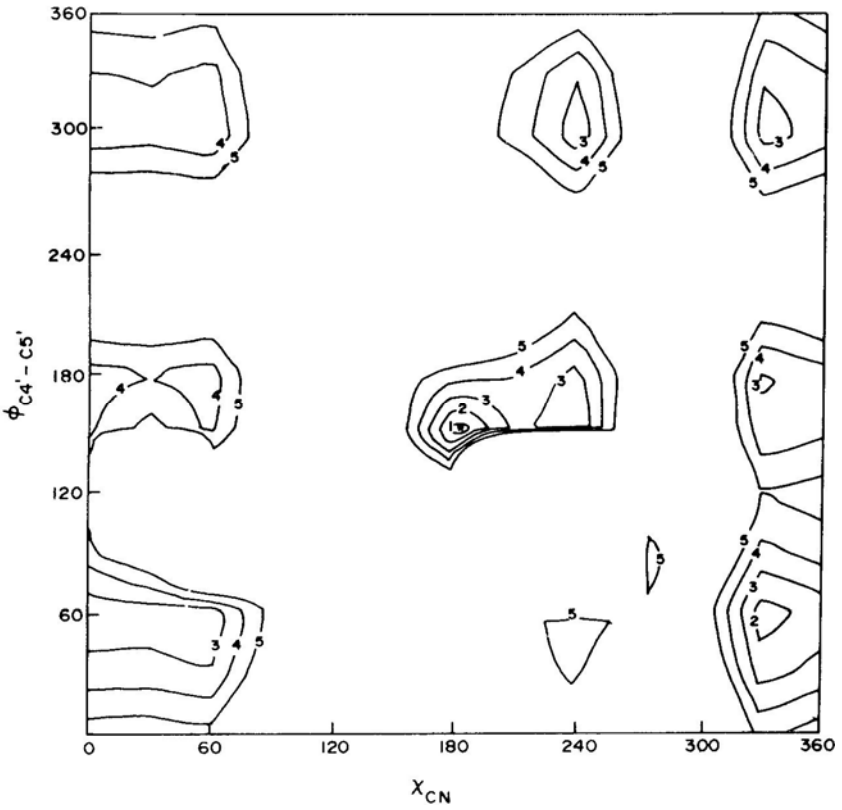



**Figure 5.** ($\chi_{CN}$ -$\phi_{C4'-C5'}$ conformational energy map for AZT-molecule A (C2'-endo,C3'-exo) with resonant structure I and $\phi_{C5'O5'}$=300°.

### 3.3 *AZT-molecule B* (*C3'-exo, C4'-endo*)

The conformational energy maps constructed for C3'-exo, C4'-endo AZT-molecule B with both resonant structures I and II and with $\phi_{C5'-O5'}$ =60° indicate a global minimum at $\chi_{CN}$ = 0° (*anti*) and $\phi_{C4'-C5'}$ = 60 (*gg*) (see table 2). In this sugar puckering there is no intramolecular hydrogen bonding between the atoms of deoxyribose and the base as that observed in the case of C2'-endo, C3'-exo AZT-molecule A (figure 2).

Figures 7 and 8 show the conformational energy maps for resonant structures I and II constructed with $\phi_{C5'-O5'}$ = 180°. The two maps are very similar to each other and the global minimum occurs in both the maps at $\chi_{CN}$ = 0° (*anti*) and $\phi_{C4'-C5'}$ = 60° (*gg*). There is a low energy region within 1 kcal/mol above the global minimum in both the maps at $\chi_{CN}$=180° (*syn*) and $\phi_{C4'-C5'}$ = 120°(*gt*). The preselection of $\phi_{C5'-O5'}$=180° in these maps completely rules out the possibility of intramolecular hydrogen bonding and this has important biological implications (Saran 1981, 1987, 1989). This will be discussed in the next section.

It can be seen from table 2 that for, $\phi_{C5'-O5'}$ = 300° both the resonant structures indicate a global minimum at $\chi_{CN}$ = 90° (*anti*) and $\phi_{C4'-C5'}$ = 120° (*gt*) and a low-

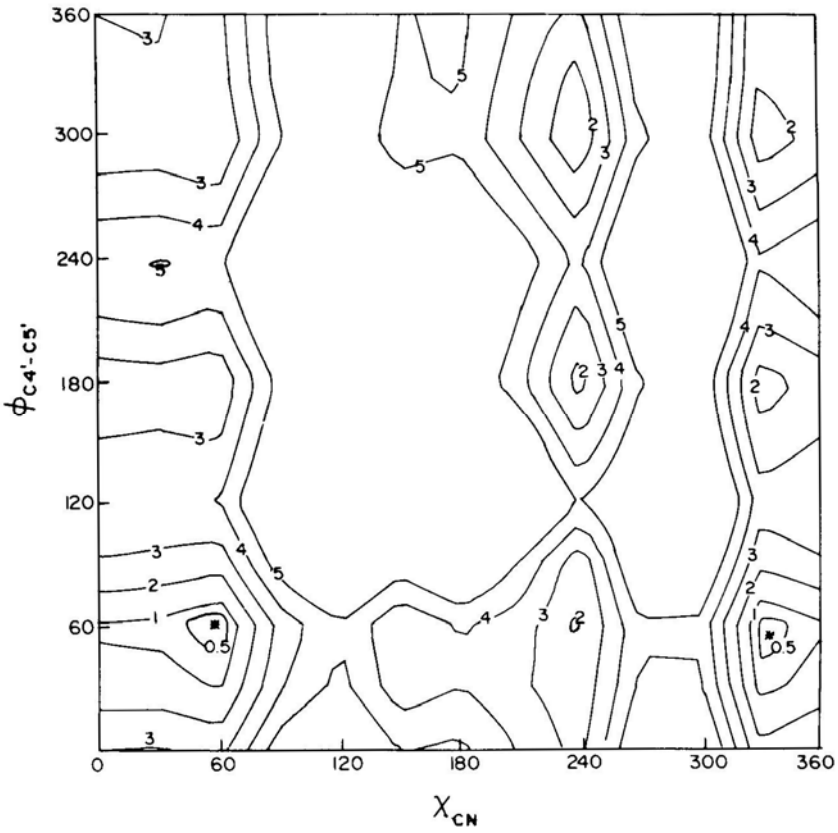



**Figure 6.** ($\chi_{CN}$–$\phi_{C4'-C5'}$) conformational energy map for thymidine (C2'-endo, C3'-exo) with $\phi_{C5'-O5'}$ =180°.

energy region within 1 kcal/mol of the global minimum at $\chi_{CN}$ = 330° (*anti*) and 150° (*gt*). Both maps (not shown) have very similar conformational features indicating that the two resonant structures of the azido group have an almost insignificant effect on the conformation of the molecule.

### 3.4 *Thymidine* (*C3'-exo, C4'-endo*)

The computations carried out for the parent nucleoside, thymidine, having C3'-exo, C4'-endo sugar pucker indicate almost identical results to those for AZT-molecule B (see table 2). The global and local minima observed for thymidine are identical to those for AZT-molecule B. Figure 9 shows the conformational energy map for thymidine constructed with a preselection of $\phi_{C5'-O5'}$ = 180° and it can be seen that the results of this map are remarkably similar to those presented in figures 7 and 8. The minimum occurs at $\phi_{CN}$ =0° (*anti*) and $\phi_{C4'-C5'}$ (*gg*) similar to that in figures 7 and 8 for AZT-molecule B with the two resonant structures. A low energy region also occurs at $\chi_{CN}$ = 180° (*syn*) and $\phi_{C4'-C5'}$ = 120° (*gt*), again similar to that for AZT molecule B.

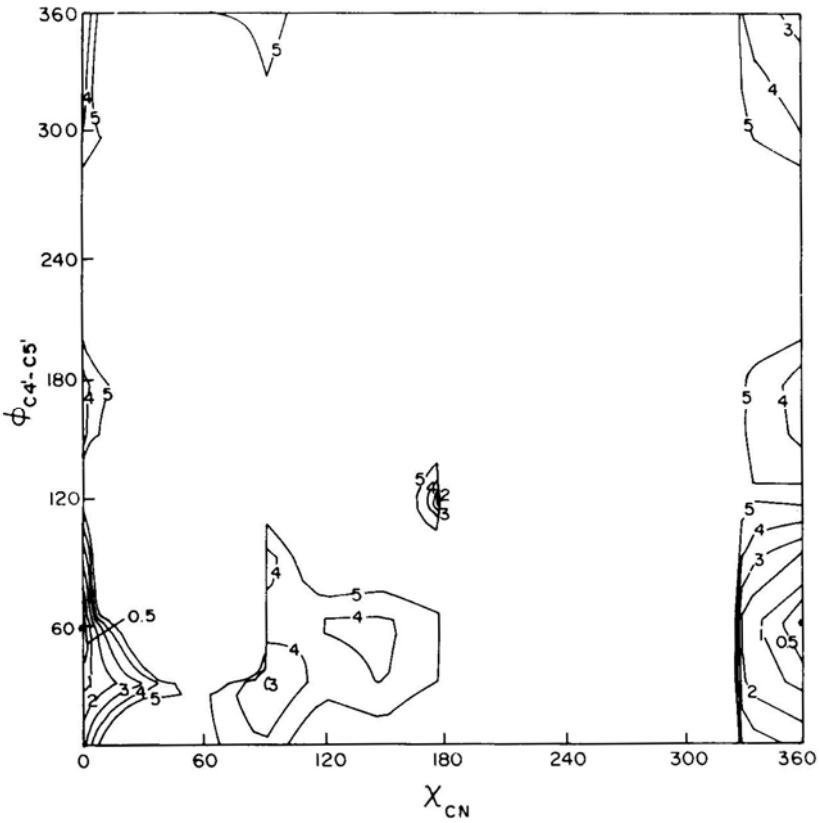



**Figure 7.** ($\chi_{CN} - \phi_{C4'-C5'}$) conformational energy map for AZT-molecule B (C3'-exo, C4'-endo) with resonant structureIand $\phi_{C5'-O5'} = 180°$.

## 4. Biological significance

The results presented in tables 1 and 2 and in figures 3, 4, 6, 7-9 clearly demonstrate that the AZT molecule either in C2'-endo, C3'-exo or in C3'-exo, C4'-endo sugar geometry has similar conformational preferences as those of the parent nucleoside: thymidine. This similarity is quite remarkable in the conformational energy maps constructed with $\phi_{C5'-O5'} = 180°$. Our earlier studies on a number of nucleoside antibiotics (Saran and Chatterjee 1980a, b, 1984; Saran and Patnaik 1981, 1982, 1986; Patnaik and Saran 1984; Saran 1988) have revealed that the aqueous solution situation is very successfully mimicked by carrying out theoretical computations with a preselection of $\phi_{C5'-O5'} = 180°$. In this preselection there is no possibility of intramolecular hydrogen bonding between atoms of the sugar moiety and the base and this is the situation that prevails in aqueous solution because intermolecular hydrogen bonds with water molecules will be preferred to intramolecular hydrogen bonds. This point has been borne out by the excellent agreement between theoretical computations on 8-azadenosine (Saran *et al* 1978), tubercidin (Saran and Mitra 1979), cordycepin (Saran and Patnaik 1981),

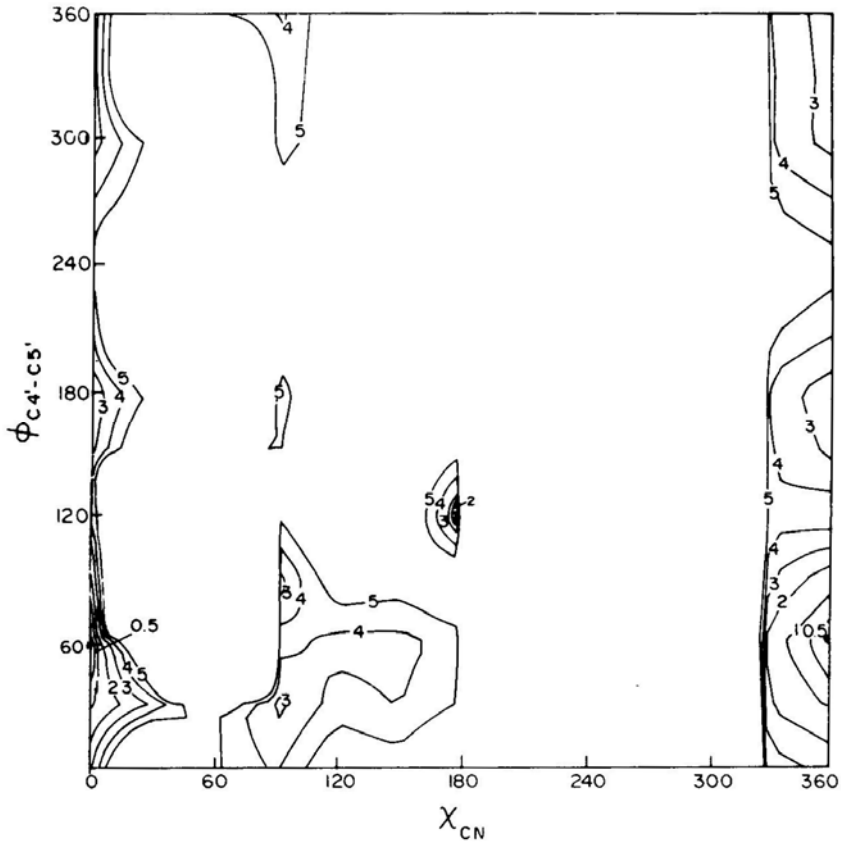



**Figure 8.** ($\chi_{CN}$– $\phi_{C4'-C5'}$) conformational energy map for AZT-molecule B (C3'-exo, C4'-endo) with resonant structure II and $\phi_{C5'-O5'} = 180°$.

propranolol, a *ß*-adrenergic blocking drug (Kulkarni *et al* 1979) and the experimental NMR results in aqueous solution. The results of theoretical computations on 6-azauridine and 6-azacytidine (Mitra and Saran 1978) show exact correspondence with the results from ORD and CD studies in aqueous solution.

Since all biochemical reactions occur in aqueous medium, the results presented in tables 1 and 2 and figures 3, 4, 6 and 7–9 assume great biological significance. Because of the striking similarity in the conformational features, AZT molecules can successfully mimick thymidine and get incorporated in DNA in place of thymidine. Further, AZT molecules can readily get phosphorylated and mimick thymidylate in enzymatic reactions. These theoretical deductions are fully corroborated by the experimental evidence of St. Claire *et al* (1985) and Ono *et al* (1986). In order to explain the biological action of AZT, St. Claire *et al* (1985) proposed that AZT gets incorporated into viral DNA. Once AZT is incorporated into viral DNA, the termination of chain elongation follows because of the absence of 3'-OH functional group in AZT which has been replaced by an azido group. The experiments of Ono *et al* (1986) implicate the competitive binding of AZT with reverse transcriptase as compared to thymidylate binding.

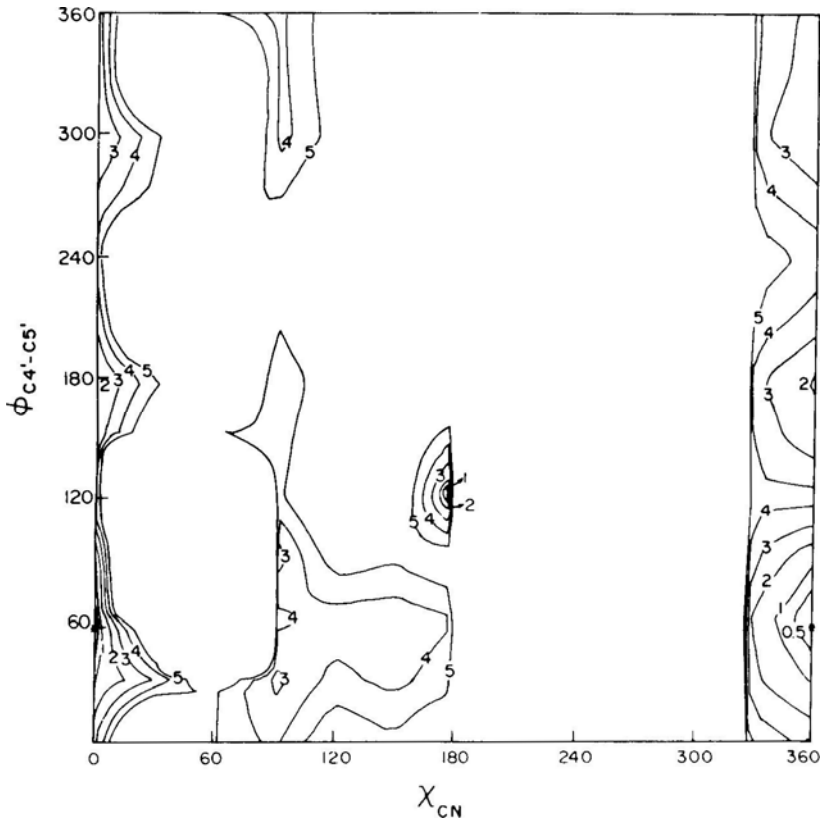



**Figure 9.** ($\chi_{CN} - \phi_{C4'-C5'}$) conformational energy map for thymidine (C3'-exo, C4'-endo) with $\phi_{C5'-O5'} = 180°$ .

## 5. Conclusion

In conclusion, the results of the present investigation indicate that the conformational preferences of AZT are very similar to those of the parent nucleoside: thymidine. This similarity is remarkably striking in situations that prevail in the aqueous solution with the result that AZT molecules can very efficiently mimick thymidine and get incorporated in growing chains of viral DNA and terminate the chain elongation. The correlation obtained earlier for nucleoside antibiotics (Saran 1981, 1987, 1989), thus, holds true for AZT. It then becomes obvious to visualize the drug action of AZT.

Finally, it is relevant here to remark that as discussed earlier, the agreement between X-ray crystallographic results on AZT and the theoretical predictions presented in this paper is not to be expected at all. This is due to the fact that PCILO computations have been carried out on an isolated molecule *in vacuo* whereas the conformation observed in the solid state is dictated by many factors such as conditions for crystallization, crystal-packing forces, and environmental effects. However, when the computations have been carried out with ($\phi_{C5'-O5'} = 180°$ mimicking the situation prevailing in the aqueous solution, the PCILO results on

AZT-molecule A having C2'-endo sugar pucker are in excellent agreement with NMR results obtained by Swapna *et al* (1989) on AZT in aqueous solution; both methods showing a strong preference for *anti* conformation for $\chi_{CN}$ and *gg* conformation around exocyclic C4'-C5' bond. Although PCILO computations have not been carried out for AZT molecule with C3'-endo sugar pucker, similar results showing the predominance of *anti* and *gg* conformation are expected for $\phi_{C5'\text{-}O5'} = 180°$, which will be again in agreement with the molecular mechanics calculation of Herzyk *et al* (1987) and NMR solution studies of Swapna *et al* (1989).

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