Abstracts from the Seventh Annual Meeting of the Molecular Graphics Society

The seventh annual meeting of the Molecular Graphics Society was held at San Francisco, California, USA, from 10 to 12 August 1988. The abstracts that are published below represent nearly all of the papers presented.

Computer Modeling of Potential Anti-AIDS Drugs

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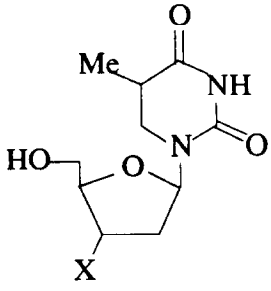
Azidothymidine (AZT) is the first significant drug to halt the running down of the immune system and the spread of the AIDS virus. Like the normal DNA nucleoside, Thymidine, it can become phosphorylated and is then incorporated into the DNA formed by reverse transcriptase. It stops further elongation of the DNA molecule by acting as a chain terminator. It does this because one of the hydroxyl groups on the ribose ring has been replaced by an azido group.

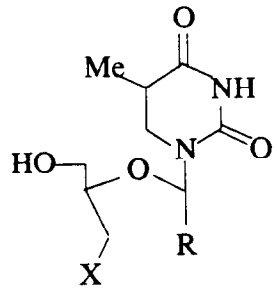


AZT: X= N_3

thymidine: X= OH

It is possible that molecules that have the same basic structure as AZT, but that are acyclic, may also exhibit anti-AIDS activity.

In the figure that follows, compound I is the acyclic parent and is included for comparison. All the compounds I–IV are in the process of being synthesized at Aston, following the results of this modeling study.



I: R = H, X = OH
II: R = H, X = N_3
III: R = CH_3, X = Cl
IV: R = H, X = CN

A crystal structure for thymidine is available and was used as a starting point for the modeling. This conformation was optimized using both the MNDO and the molecular mechanics methods. The thymine base was then incorporated into models of I–IV that were built using standard geometries, and a full conformational analysis was performed on each by twisting all the bonds with free rotation and monitoring the van der Waals energy. Appropriate rotational barriers were included in these calculations. A subsequent molecular mechanics geometry optimization was performed to generate the final structure, which was then analyzed using MNDO.

An important point to emerge from these calculations is that both the molecular mechanics energies and the MNDO heats of formation are lower for thymidine than for any of I–IV. However, the entropy of the acyclic compounds should be greater. The heat of formation of the acyclic parent I is not very different, and all other energy values are reasonable, suggesting that synthesis should be possible and worthwhile in each case.

The predicted three-dimensional structures of I–IV show some considerable differences, suggesting that this series of compounds will provide a range of structural properties resulting in varying binding efficacies. Graphical results will be presented to illustrate these differences for the electrostatic potential and the accessible surface.