The Geometry of a Steroid from Quantum Mechanical Calculation: Progesterone

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A comparison of the molecular geometry of progesterone computed by semi-empirical molecular orbital methods with the *X*-ray crystallographic data suggests that calculation is a satisfactory source of structural parameters for molecules of this type.

The need to know the geometrical disposition of the atoms in a molecule is a prerequisite for a wide variety of fundamental studies. Prior to making a detailed structure–activity study of a series of steroids the geometries of which have not been determined by *X*-ray crystallography, we have attempted to qualify just how well theoretical calculations can predict geometries, considering progesterone as an example.

The concept of receptors for the action of steroids was established by Jensen and Jacobson,[1] and it seems clear that these molecules bind competitively to specific receptors in the target cell. Although there is some controversy about the initial site of binding[2] it seems logical that structural details have a direct action in relation to the receptor interaction in that they may control the biological response. The existence of antagonists that compete for the binding sites with very high affinity demonstrates that the phenomena, although partially independent, maintain certain structural features that control the biological activity.[3] Thus, the study of the steroid–receptor interaction demands a knowledge of the molecular structure.

Experimental steroid structures have been reviewed by Duax.[4] Here we attempt to quantify the quality of predicted molecular geometries derived from semi-empirical quantum mechanical computations in order to have confidence limits for calculations on compounds which have not been synthesised or not studied by experimental structural techniques.

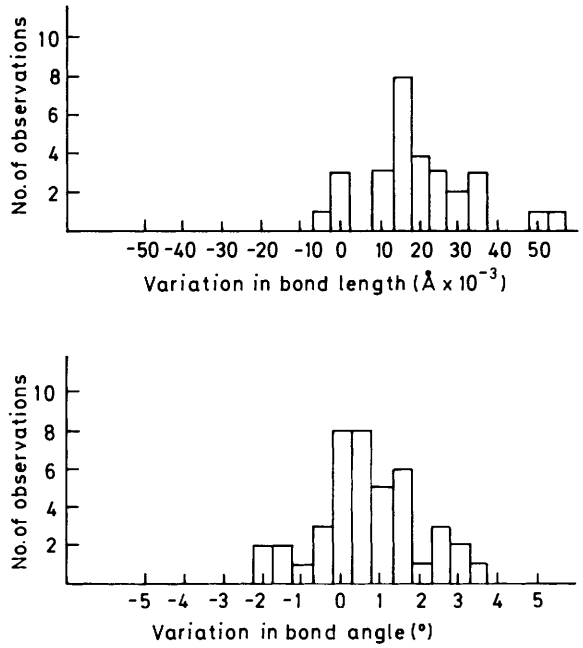

Figure 1. Comparison of calculated and theoretical bond lengths and angles

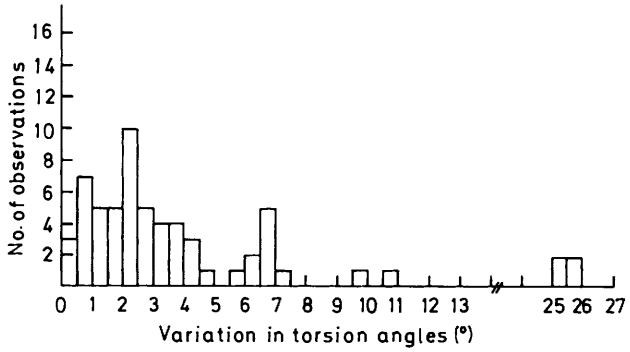

Figure 2. Comparison of calculated and theoretical torsion angles

Computational Aspects

The semi-empirical all-valence-electron molecular orbital (MNDO) method of Dewar and his colleagues[5] is considered the most appropriate to perform semi-empirical calculations on carbon systems. To determine the structure of progesterone we have used the MOPAC program.[6] This is a general purpose molecular orbital package for application in chemistry which includes the MINDO/3 and MNDO hamiltonians. Totally unconstricted geometry optimization was performed in two different ways: first, with standard values for bond lengths and bond angles as starting point, we have built ring *A* and then successively added the rest of the molecule; secondly, by taking a starting geometry from crystallographic data, we have optimized the total structure. The program MOPAC has been adapted for the minicomputer NORSK DATA ND-520. The starting geometries were optimized down to an energy convergence limit of 0.3 kcal mol^{-1} (1.3 kJ mol^{-1}). The initial perturbation increments decreased until three successive perturbation trials were without significant effect on the values of the molecular energy. To check the geometry, the computed cartesian co-ordinates were displayed on a PERQ work station.

Results and Comments

Tables may be obtained from the authors listing cartesian co-ordinates of the fully optimized progesterone molecule found in the calculations. With these results we have established a detailed statistical comparison between the experimental and the theoretical data. This may also be obtained from the authors in the form of lengthy tables.

The analyses of the results are summarized in Figures 1 and 2. These represent the numbers of values observed by our calculation in relation to the difference with respect to experiment. Bond lengths are normally distributed in a way that indicates that the structure obtained from computation has slightly

elongated bonds. This is a constant feature in all the calculations that we have performed with this program on other molecules of this size. Although this discrepancy is within the range of the standard deviation of the experiment, we think it is worth noting. The bond lengths corresponding to C(3)–C(4) and C(20)–C(21) are the only ones which deviate more from the mean; both are situated adjacent to oxygen.

The analyses of steroids by crystallographic methods[7,8] and the co-crystallization of different isomers in the same lattice strongly suggests that the conformations observed in the solid state are at or near the global minimum energy.

The application of semi-empirical quantum mechanical calculations to molecules of the size of progesterone is especially attractive. Geometry optimization has been shown to provide data in good agreement with results from crystallography and other methods.[9] Although discrepancies appear, these do not invalidate the method. We have determined the complete structure of progesterone and have optimized the values obtained by experiment; the results are very much the same. Bond lengths and bond angles are in good agreement with experiment. There appears some discrepancy in the torsion angles for the side-chain, however. Our result (−35°) is in the range of values given for these compounds (0° to −45°). This problem has been discussed recently[10,11] and it must be stressed that we compute a gas-phase structure making no allowance for solid-state effects.

Overall the results justify confidence in the use of the MOPAC computer program to compute steroid geometries.

Acknowledgements

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