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# Quantum-Mechanical Studies on the Conformational and Electronic Properties of Steroids

## I. The Sterane (Perhydrocyclopentanophenanthrene) Ring System and its Constituent Subunits

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The conformation of the sterane (perhydrocyclopentanophenanthrene) ring system, the fundamental ring system of steroids, and the conformation of its constituent subunits have been investigated quantum mechanically by the PCILO method, taking into account all the valence electrons of the system. The results indicate that the conformations which correspond to the B/C and C/D *trans* ring fusion, with the A/B fusion *trans* or *cis*, are by far the more stable ones. The result explains one of the fundamental structural properties of all natural steroids.

Die Konformation des Sterans (Perhydrocyclopentanophenanthren), des grundlegenden Ring-Systems der Steroide, und die Konformation der es aufbauenden Untereinheiten wurde quantenmechanisch mit der PCILO-Methode, bei der alle Bindungselektronen berücksichtigt wurden, untersucht. Die Ergebnisse zeigen, daß die Konformationen bei weitem die stabilsten sind, bei denen die Ringe B/C und C/D *trans* ständig sind, während die Ringe A/B *trans* oder *cis* stehen. Dieses Ergebnis erklärt eine der fundamentalen Struktur-Eigenschaften aller natürlichen Steroide.

La conformation du sterane (perhydrocyclopentanophenanthrene), qui représente le squelette fondamental des steroides, ainsi que la conformation des sous-unités qui le constituent, ont été étudiés par la méthode PCILO, une approximation perfectionnée de la méthode des orbitales moléculaires, tenant compte de tous les électrons de valence. Le résultant principal indique que les deux conformations de beaucoup les plus stables sont celles dans lesquelles la jonction des noyaux B et C ainsi que celle des noyaux C et D est *trans*, alors que la jonction des noyaux A et B peut être *trans* ou *cis*, la première représentant un arrangement légèrement préféré. Ce résultat théorique explique l'une des propriétés structurales fondamentales de tous les composés stéroides naturels.

Quantum-mechanical studies in the field of biochemistry have for a long while been essentially limited (with very few exceptions prominent among which are the amino acid residues of proteins [1–3] to conjugated, $\pi$-electronic systems. Correlatively they have been dealing preferentially with planar or nearly so molecules.

The advent of the all-valence electrons or, still better, the all-electrons molecular orbital techniques lifted these restrictions and offered the possibility of extending the application of quantum-mechanical procedures to saturated (or partially saturated) systems and to the evaluation of molecular conformations. By this we mean, of course, a *theoretical* evaluation by a direct calculation of the total molecular energy as opposed to *empirical* procedures, abundantly developped during the last few years (in particular in the field of polypeptide and polynucleotide structures, see e.g. [4–6]), consisting of partitioning the potential energy

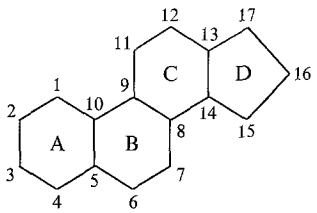



Fig. 1. The sterane ring system

of the system into several discrete contributions (such as non-bonded and electrostatic interactions, barriers to internal rotations, hydrogen bonding etc.) and expressing these different contributions by empirical or semi-empirical potential functions. Because of the importance of molecular conformations for the activity of biological polymers or even smaller sized compounds such an extension offers the possibility of a substantial progress both in the limits and in the scope of the application of quantum theory to biology.

One of the all-valence electrons techniques, the PCILO method [7–10], probably at present one of the most elaborated of such techniques and particularly suitable for treatments of large systems, has been utilized recently in our laboratory for the treatment of the conformation of a number of amino acid residues [11] and work is in progress in view of an extension of these results toward more complex oligo- and polypeptide systems. In the present paper, we inaugurate the application of the same method to the problem of the conformational and electronic structure of steroids, a most fundamental group of biological compounds, generally totally or at least to a large extent saturated. Specifically, this first paper is devoted to the study of some essential aspects of the conformation of the sterane (perhydrocyclopentanophenanthrene) ring system, I, the fundamental skeleton of steroids and of its constituent subunits: cyclohexane, cyclopentane, decalin and perhydrophenanthrene and of perhydroanthracenes. The study of these smaller systems constitutes, among others, a trial of the validity of the procedure as for these compounds, a comparison is possible with different available experimental data (those will nearly always be taken from the excellent review in [12]). It may be mentioned that the simplest of these subunits have already been investigated by some of the all-valence electrons methods (see e.g. [13] for an Extended Hückel treatment) and that, the perhydroanthracene and perhydrophenanthrene systems have also been investigated previously. This was done, however, by a highly parametrized Hückel type procedure [14], the significance of which is difficult to ascertain.

## The Method

The designation PCILO stands for *Perturbative Configuration Interaction using Localized Orbitals.* It belongs, as said, to the all valence electrons procedures studying therefore simultaneously the $\sigma$ and $\pi$ electrons. It takes into account explicitly interelectronic repulsions and proposes to go beyond the self-consistent field approximation in the calculation of the ground state energy by incorporating an appreciable portion of the correlation energy. Its fundamental idea is to choose

a set of reasonable bonding and antibonding orbitals localized on the chemical bonds. Such a set may be constructed on a basis of hybridized atomic orbitals, the bond orbitals being obtained as linear combinations of distinct hybrids taken two by two, each bonding orbital being associated with an orthogonal antibonding one.

The bonding orbitals are then used to construct a fully localized Slater determinant, which represents the zeroth order wave function for the ground state of the system. The antibonding orbitals are utilized to build the excited states and the configuration interaction matrix is constructed on such a set of configurations.

Then, the lowest eigenvalue and eigenstate i.e. the energy and the wave function of the ground state of the system are obtained by a Rayleigh-Schrödinger perturbation expansion truncated after the third term.

As a technical simplification, the principal working hypotheses of the CNDO/2 procedure [15], in particular the hypothesis of complete neglect of differential overlap, have been retained. So was also the general parametrization of this procedure.

For the geometries of the different hexagonal compounds (cyclohexanes, perhydrophenanthrenes, perhydroanthracenes) we use standard bond lengths and angles. The bond lengths are taken equal to

$$C-C=1.54\,\text{Å},$$
$$C-H=1.09\,\text{Å},$$

and the angles between the different bonds to 109°5.

The geometries of cyclopentane in the enveloppe and half-chair forms are taken from Brutcher [16]. The perhydroanthracenes and perhydrophenanthrenes are obtained by the fusion of three cyclohexane rings in the chair form.

To build a sterane, we use the different geometries calculated for perhydrophenanthrenes and we add a cyclopentane in the enveloppe form.

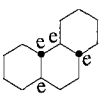
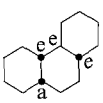
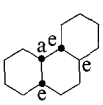
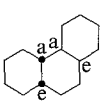
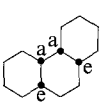
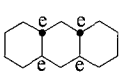
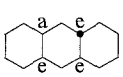
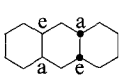
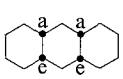
## Results and Discussion

### *A. The Subunits* (Table 1)

*Cyclohexane.* The chair conformation comes out theoretically as being 5.8 Kcal/mole more stable than the boat one. Experimental evidence [12, p. 38] would indicate that this is approximately the enthalpy difference between the chair and the "skew" conformation. The boat conformation being considered to have about 1.6 Kcal/mole more energy than the skew form, it can be inferred that our calculations underestimate, possibly by a factor of 25%, the enthalpy difference between the chair and the boat conformations. This situation is not surprising in view of the utilization in the PCILO method, in its present form, of the CNDO parametrization, which is known to underestimate energy barriers by just this relative amount.

*Cyclopentane.* The two fundamental conformations considered, the "half-chair" and the "enveloppe" are theoretically of very close energy with the former slightly favoured, the difference between the two forms being anyway much smaller than that between the two main forms of cyclohexane. This result is in agreement

Table 1. *Theoretical results on conformational energies: trial compounds*

| Compound | Conformation | $\Delta E$(Kcal/mole) |
|---|---|---|
| *Cyclohexane* | chair | 0 |
| | boat | 5.8 |
| *Cyclopentane* | half-chair | 0 |
| | enveloppe | 0.7 |
| *Decalin* | *trans* | 0 |
| | *cis* | 2.0 |
| *Perhydrophenanthrene* | | |
|  | trans-anti-trans | 0 |
|  | cis-anti-trans | 2.3 |
|  | cis-syn-trans | 2.4 |
|  | cis-anti-cis | 3.9 |
|  | cis-syn-cis | 222 |
| *Perhydroanthracene* | | |
|  | trans-syn-trans | 0 |
|  | cis-anti-trans | 2.3 |
|  | cis-anti-cis | 4.6 |
|  | cis-syn-cis | 113 |

with the experimental impossibility of distinguishing the two forms [12, p. 200]. The situation may be different in substituted cyclopentanes in which one conformation may be stabilized (e.g. methylsubstitution seems to stabilize the "enveloppe" form), a problem, which we shall discuss in the next publication of this series.

*Decalin.* With this molecule we enter the important problem of the conformation of *fused* cycloalkane rings, which will be in the center of our preoccupations in connection with the problem of the structure of steroids. The much greater conformational stability of the "chair" over the "skew" or "boat" conformations of cyclohexane suggests *a priori* the persistance of the chair conformation in the majority of compounds resulting from such fusion. This assumption is verified in the case of decaline for which therefore only the corresponding conformers have been considered theoretically. In such conditions the *trans* form is predicted in this case to be about 2 Kcal/mole more stable than the *cis*-one. This value compares satisfactorily with the experimental one of 2.7 Kcal/mole for the enthalpy difference between the two forms as deduced from a number of thermochemical studies [12, p. 231]. As in the case of the conformers of the cyclohexane ring itself, the theoretical value is here again, however, about 25% below the experimental one, a result which may again be considered as a consequence of the CNDO parametrization.

*Perhydrophenanthrenes.* The relative stabilities of five possible stereoisomers are predicted by our calculations to be in the order:

$$\text{Trans-anti-trans} > \text{cis-syn-trans} \approx \text{cis-anti-trans} > \text{cis-anti-cis} > \text{cis-syn-cis}\,.$$

It is remarkable to observe that these results parallel completely the semi-empirical evaluation of the relative stabilities of these compounds by the general rules of conformational analysis [12, p. 233]. In the limits of the existing scarce indirect evidence they also agree with experimental data.

*Perhydroanthracenes.* Four fundamental conformers have been considered in this case and they are all known. The calculations indicate the following order of decreasing stability:

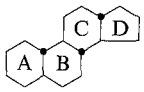
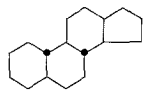
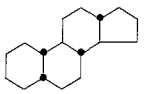
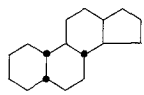
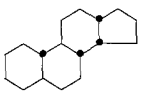
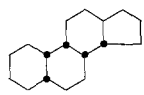
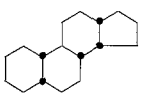
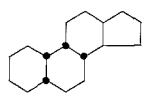
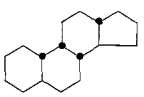
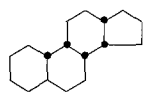
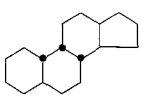
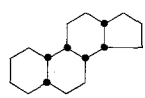
$$\text{trans-syn-trans} > \text{cis-anti-trans} > \text{cis-anti-cis} > \text{cis-syn-cis}\,.$$

In this case again the results of the calculations coincide with the semi-empirical evaluation of the relative stabilities of these compounds by the rules of conformational analysis [12, p. 235]. Moreover, among those the relative stability of the first two conformers has been confirmed by equilibrium studies.

### *B. Steranes*

Table 2 contains the results of the evaluation of the total molecular energies corresponding to the principal conformational structures acceptable for the sterane ring system. The most striking result of these calculations is *the prediction that the two conformers trans-anti-trans-anti-trans and cis-anti-trans-anti-trans (the first two in the table) should be particularly stable with respect to all the other conformers of the system.* A closer examination of the structures involved indicates

Table 2. *Theoretical results on conformational energies in the sterane ring system (Kcal/mole with respect to the most stable conformation taken as energy zero)*

| | | | |
|---|---|---|---|
|  | trans-anti-trans-anti-trans |  | trans-anti-trans-anti-cis 124 |
|  | cis-anti-trans-anti-trans 2 |  | cis-anti-trans-anti-cis 126 |
|  | trans-anti-trans-syn-cis 4 |  | cis-syn-cis-syn-trans 251 |
|  | cis-anti-trans-syn-cis 7 |  | cis-syn-cis-anti-cis 317 |
|  | trans-syn-cis-anti-trans 29 |  | trans-syn-cis-syn-cis 937 |
|  | trans-syn-cis-anti-cis 77 |  | cis-syn-cis-syn-cis 1161 |

that this particular stability of these two conformers must be due to the fact that these are the only two conformers in which both the B/C and the C/D rings are fused together in the *trans* conformations. On the other hand, the two preferred conformers, which differ from each other only in the *trans* or *cis* arrangement of the A/B rings are of comparable stability with the former *(trans-trans-trans)* slightly more stable.

This striking result means therefore that *we may expect the fundamental sterane system to exist essentially in conformations in which the* B/C *and the* C/D *rings are trans but in which the* A/B *rings may be either trans or cis with perhaps a somewhat greater probability for this last arrangement of being also trans.*

Now, although no quantitative energy data are available on the sterane molecule, *the preceeding results correspond to a general situation in steroid chemistry and in fact represent one of the common characteristics of steroids.* Thus, in all naturally occurring steroids rings B and C as well as rings C and D are attached *trans*[1]. It is only in the attachement of rings A and B that both arrangements are

[1] Very recently, however, two steroids have been shown by *X*-rays to have the A/B and the C/D ring junctions both *cis*. These are digitoxigenin, the aglycone of digitoxin and one of the active ingredients of digitalis [17] and batrachotoxinin A, a frog venom and a steroidal alkaloid [18]. Both molecules are complex structures, containing in particular substituents at $C_{13}$, $C_{14}$ and at other carbons of ring D; batrachotoxinin even has a seven membered ring E formed by bridging the groups attached to $C_{13}$ and $C_{14}$. Their theoretical investigation which is thus particularly interesting is intended.

found. The most common are the A/B *trans* conformers. Such is for instance the situation in all natural saturated sterols, with the only exception of coprostanol. On the other hand, the bile acids are A/B *cis* compounds. (The A/B *trans* and *cis* compounds are frequently referred to as $5\alpha$ and $5\beta$ conformers.) These preliminary calculations account therefore already for one of the general characteristics of the conformation of steroids. An inspection of the models corresponding to the "unstable" conformers indicates that their instability is due to too close contacts between some of their constituent atoms. In this respect, we recall, however, that as already stated, the calculations have been carried out with standard distances and angles. The true conformers, if existing, would certainly "optimize" the situation and relieve a part of the strain and hindrance by appropriate deformations of the standard configurations. For this reason, the excess energies calculated for the "unstable conformers" with respect to the stable ones cannot be considered as having a quantitative significance. Their relative order is expected, however, to give an overall indication of the relative stabilities.

Naturally, more complete calculations are thus now needed to account for the finer aspects of the situation, and, in particular, because of the predominant role of the first two conformers of Table 2, for the above mentioned flexibility of the A/B arrangement between saturated sterols and bile acids. Such refinements are in progress in our laboratory.

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