POSITIONAL AND CONFORMATIONAL DEPENDENCE OF LONG-RANGE INTERACTIONS IN 3,16- AND 3,17-ANDROSTANEDIONES

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Abstract

The 5α- and 5β-conformations of androstane, androstan-3-one, androstan-16-one, androstan-17-one, androstane-3,16-dione and androstane-3,17-dione have been calculated by the SCF MNDO method, using full geometry optimization, in order to assess the dependence of long-range electronic interactions of the carbonyl groups on their location and on the conformation of the steroid ring system.

1. Introduction

Relatively simple derivatives – alkyl, carbonyl, hydroxy and/or unsaturated – of the perhydrocyclopentanophenanthrene (sterane or gonane, 1) ring system are important, biologically-active molecules known as steroids. A great variety, and dramatic change, of biological activity is achieved by negligible alterations of the

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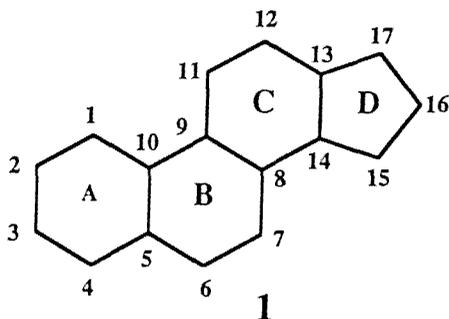
compositions and/or conformation of this basic molecular structure. Thus, for androstane, a dimethyl sterane for which 5α and 5β conformations are feasible, only the former constitutes the basic hydrocarbon ring system for the important human sexual hormones. Even more surprisingly, those substituted in the 3- and 17-positions are usually those naturally-occurring entities that are especially active.

We have recently become interested in the PE spectra of steroids [1–6]. Specifically, the long-range electronic interactions between substituents located at both ends of the basic skeleton, as expressed by the splitting of the substituent lone pair orbitals of the disubstituted derivatives, provides a rationale for such interest. Since only the 3-, 17- and 3,17-derivatives are readily accessible, our measurements have been narrowly restricted. The results, somewhat expected, indicated that the 3,17-interaction in 3,17-androstanedione is not detectable (relative, that is, to the PE spectra of 3- and 17-androstanone) and, therefore, the splitting must be assumed to be quite small [3]. This is in agreement with SCF MNDO calculations, and suggests that the 3,17-derivative should exhibit additivity relative to the 3- and 17-compounds [5,6].

On the other hand, experiments concerned with fast intramolecular electron transfer from donor to acceptor groups of a disubstituted androstane system indicate that 3,16 electronic interaction should be operational, and measureable [7]. Such conclusions derive also from a variety of PE studies involving compounds with groups distantly located in alicyclic molecular frameworks [8]. For androstane-3,16-dione, for example, the MNDO results predict a substantial interaction of the two carbonyl groups and non-additivity [6]. Since we cannot record the PE spectra of the non-existent 16-androstanone and androstane-3,16-dione, we intend to synthesize these compounds and to initiate a quantum chemical study of the conformational (i.e. 5α- versus 5β-derivatives) and positional (i.e. 3,16- versus 3,17-derivatives) dependence of long-range electronic interactions of carbonyl groups, as expressed by a comparison of MNDO results for the basic hydrocarbons, 3-, 16- and 17-androstanones, and the corresponding androstanediones. From this study, we expect to gain confidence in MNDO predictive capabilities and some insights into the mechanism that controls structure–activity relationships in steroids.

2.   Calculations

MNDO SCF MO calculations were performed using QCPE 464 (IBM MOPAC) [9] adapted for the Siemens 7.580 S (turbo version) at the Computing Center of the University of Düsseldorf.

Full geometry optimization was obtained for all compounds. The starting geometry was always assumed to consist of standard bond lengths and angles ($r_{CC} = 154$ pm, $r_{CH} = 108$ pm, $r_{CO} = 122.5$ pm, $\angle CCC = 109.5°$ and $120.0°$, $\angle CCH = 109.5°$, $\angle COC = 120.0°$) and crystallographic dihedral angles.

3.   Results and discussion

The total SCF energy and the calculated heats of formation are given in table 1. The energies of the highest occupied molecular orbitals are given in fig. 1. The contribution of the oxygen 2p orbitals to the HOMO and SHOMO eigenvectors

Table 1

Heats of formation (ΔH_f [kJmol^{-1}]) and total SCF energies (E_{tot} [aJ]) of investigated compounds

Compound	ΔH_f [kJmol^{-1}]	E_{tot} [aJ]
5α-androstane	− 105.13	− 462.18
5β-androstane	− 101.34	− 462.17
5α-androstan-3-one	− 212.13	− 509.16
5β-androstan-3-one	− 207.83	− 509.15
5α-androstan-16-one	− 216.16	− 509.17
5β-androstan-16-one	− 212.44	− 509.16
5α-androstan-17-one	− 221.97	− 509.18
5β-androstan-17-one	− 217.68	− 509.17
5α-androstane-3,16-dione	− 322.45	− 556.15
5β-androstane-3,16-dione	− 318.15	− 556.14
5α-androstane-3,17-dione	− 328.41	− 556.16
5β-androstane-3,17-dione	− 323.18	− 556.15

Table 2

The oxygen 2p-orbital constituents of the highest and second highest occupied MOs for some diketones

Compound	Orbital (type)	2p-orbital component of the oxygen atom in position					
		3			16 (17)		
		x	y	z	x	y	z
5α-androstane-3,16-dione							
	HOMO (n_O)	− 0.008	0.343	− 0.125	− 0.310	− 0.506	0.144
	SHOMO (n_O)	0.013	− 0.582	0.195	− 0.195	− 0.321	0.090
5β-androstane-3,16-dione							
	HOMO (n_O)	0.024	0.603	0.242	− 0.017	0.356	0.053
	SHOMO (n_O)	− 0.012	0.341	0.139	0.032	0.643	− 0.094
5α-androstane-3,17-dione							
	HOMO (n_O)	0.001	− 0.034	0.020	0.440	− 0.517	− 0.041
	SHOMO (n_O)	0.016	0.676	0.230	− 0.025	0.029	0.001
5β-androstane-3,17-dione							
	HOMO (n_O)	0.002	− 0.003		− 0.096	− 0.280	− 0.615
	SHOMO (n_O)	− 0.026	0.663	0.272	0.001	0.001	

of the disubstituted compounds is given in table 2. Some conclusions follow from these data:

(i)   the 5α- are more stable than the corresponding 5β-derivatives;

(ii)   considerable long-range interactions should exist in both the 5α- and 5β-androstane-3,16-diones; and
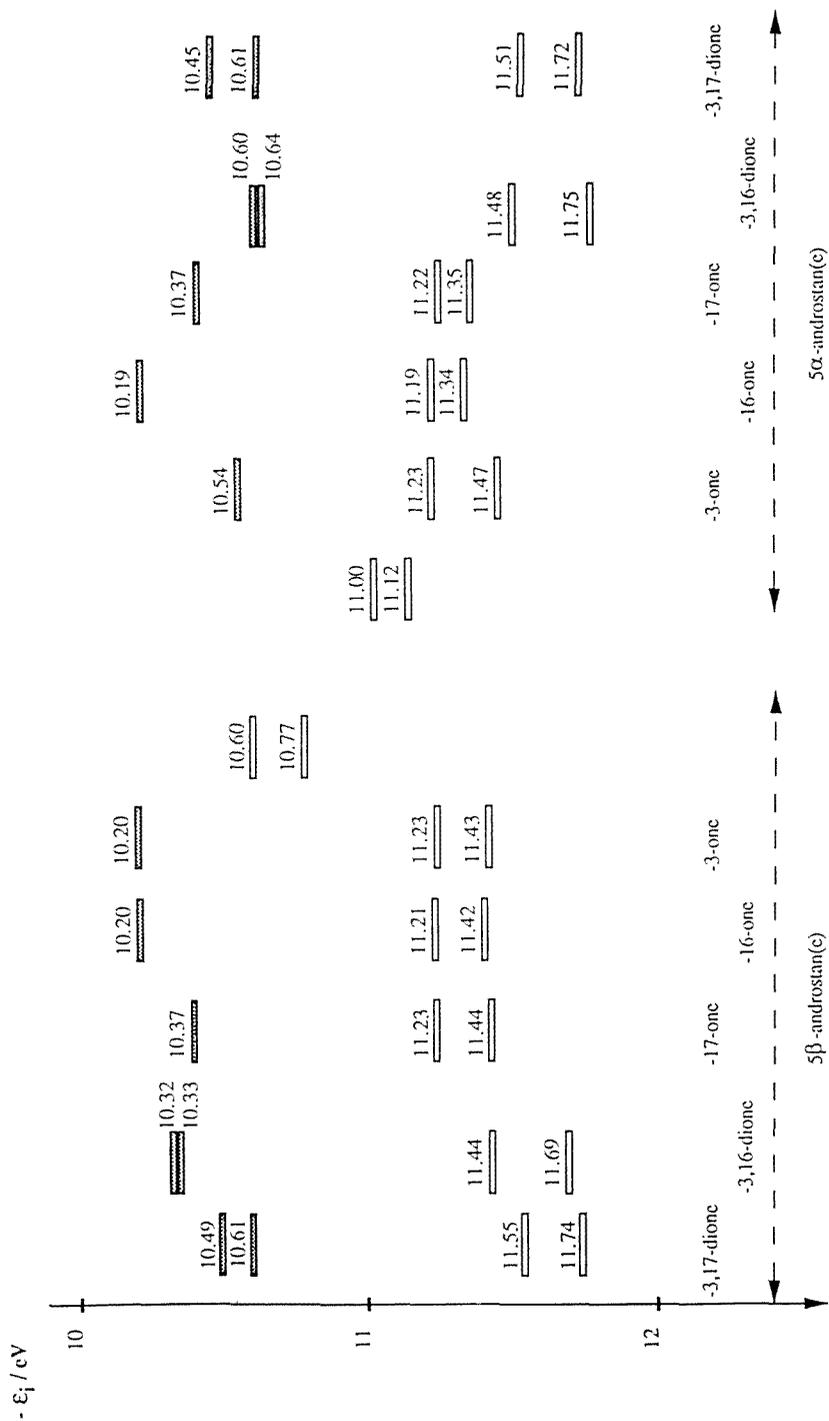
Fig. 1. Correlation diagram for the highest MOs of the investigated compounds.

(iii)   negligible long-range interactions should occur in both the 5α- and 5β-androstane-3,17-diones.

Any search for the origin of the long-range interactions must consider the symmetry properties of the two highest occupied (HOMO and SHOMO) σ-orbitals of androstane. These are so-called ribbon orbitals, the HOMO consisting of carbon 2p orbitals aligned along the short axis (i.e. transversal or T-type) and the SHOMO consisting of carbon 2p orbitals aligned along the long axis (i.e. longitudinal or L-type) of the steroid ring system. This alignment is much less obvious in the 5β-derivatives, in which ring A does not lie in the mean plane of the other rings. The primary reason for the lack of 3,17- and the existence of 3,16-interaction, particularly evident in the 5α-derivatives, resides in the symmetry properties of the oxygen lone pair molecular orbitals n_O of the corresponding monosubstituted compounds. The lone pair orbital of the 3-one can interact only with T-type σ-orbitals, while that of 17-one can interact only with the L-type. Consequently, a mutual σ-interaction cannot occur in the 3,17-derivative. In the 16-one, on the other hand, the lone pair orbital interacts with both T- and L-type σ-orbitals. Thus, in the 3,16-derivative one observes a strong mixing, even though the lone pair orbital energies for the monosubstituted compounds are quite different. However, since the σ-orbitals are essentially degenerate in 5β-3-one and 5β-16-one, a particularly strong mixing should occur in the 5β-3,16-dione. This strong interaction rationalizes the larger splitting of the two higher energy σ-levels (0.25 eV) in the 5β-3,16-dione relative to all other 5β-derivatives (~ 0.2 eV).

The long-range interaction, expressed as participation of distant oxygen atomic orbitals in the same lone pair MO, is shown in table 2. The importance of symmetry and energy considerations for the magnitude of this interaction is obvious. Since nature has decreed that the noninteracting (or negligibly interacting) 3,17-disubstituted compounds are biologically important and highly active steroids, we can surmise that the property is crucial to their mode of action.

The magnitude of the 3,16-interaction must be investigated by other, additional experiments (e.g. by PE spectroscopy), and, finally, it is necessary to investigate the dependence of long-range interactions on other positions of substitution, other types of substituents, and different basic ring systems. Such work is in progress.

Acknowledgements

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