Revue Roumaine de Chimie, **2007**, *52*(8–9), 759–764

Dedicated to Professor Victor-Emanuel Sahini on the occasion of his 80th anniversary

THEORETICAL STUDY OF DHEAS: THE ELECTRONIC PROPERTIES OF A COMPLEX BETWEEN DHEAS AND SEROTONIN BY COMPARATIVE CALCULATIONS HF AND DFT[1]

Josette WEINBERG,[a*] Dan A. LERNER[b] and Constantin BĂLĂCEANU-STOLNICI[c]

[a]"Ilie Murgulescu Institute of Physical Chemistry", Bucharest 060021, Splaiul Independenței 202, Roumania
[b]Ecole Nationale Supérieure de Chimie de Montpellier (UMR 5618-ENSCM-CNRS-UM I),Montpellier, rue de l'Ecole 8, France
[c] Ecological University of Bucharest, Bucharest, str. Franceza 22, Roumania

Received May 9, 2006

Molecular parameters of the steroid DHEAS (dehydroepiandrosterone sulphate), the major form of DHEA (the active form of steroidal hormone) in the body, the serotonin and their possible complex have been computed in an ab initio comparative study . The 6-31G* basis set and the B3LYP functional were employed. . The aim of this study is to emphasize by DFT calculation the possible existence of a complex between DHEAS and serotonin, that may have the properties of a new drug. A Natural Bond Orbital (NBO) analysis offers supplementary details for the structure of the complex.

INTRODUCTION

The steroid DHEAS (dehydroepiandrosterone sulphate), the major form of DHEA (the active form of steroidal hormone)in human plasma, is like a reservoir from which DHEA is generated. Because DHEAS hardly crosses the blood-brain barrier and because DHEA sulfotransferase activity has been measured, it appears that whatever the origin of DHEA, the formation of DHEAS is likely to occur directly in the brain, thus corresponding to the definition of "neurosteroids" .[2]

Recently, several attempts were made to find a new class of antidepressant drugs with a dual activity displayed at the level of the 5-HT_1A serotonin receptors and serotonin transporters.[3]

Together, these data led to a new basis for the rational design of receptor-selective compounds (serotonin) with a predetermined efficiency .[4]

Many recent studies on biological systems were carried out to identify the active molecules involved in vivo and to understand their interactions and functions.

The advances made in various areas of chemistry with the help of the supramolecular paradigm emphasize the importance of a theoretical analysis of intermolecular interactions in relevant couples of weakly bound biologically active molecules. The supramolecular approach advocated by Lehn provides a universal model to study such interactions .[5]

The present paper targets such a goal by characterizing DHEAS, generated in the brain, and the neurotransmitter serotonin, as well as their association in a complex. The electronic structure of DHEA has been described [1,6]and a possible complex between DHEA and serotonin has been also described .[7]

METHODS

The initial input for serotonin and for DHEAS were obtained from a molecular mechanics calculation (MM^+ force field).[8,9]The molecular geometries were optimized without any constraints. The ab initio calculations were carried out using the Gaussian 98 program.[10] Calculations were carried out with the 3-21G* and 6-31G* basis

* Corresponding author:josettecarline@yahoo.ro

sets. The geometries of DHEAS, serotonin and of their complex were optimized at the 3-21G* level, starting from an INDO guess. A stationary point was found. At this point, a refinement was carried out by a single point at the 6-31G* level (Raffenetti integral calculation was used) and at the B3LYP/6-31G* level.[11]

In the last part of this paper, an analysis of the molecular wave function performed in terms of localized electron-pair bonding units using the NBO program is given.[12,13] This analysis is deemed very important to understand the various interactions involving each component of the complex under the study.

Computed HOMO and LUMO orbitals were drawn with the MOLEKEL program.[14] The structure and the numbering of selected atoms in the DHEA–serotonin complex are shown in Fig. 1.

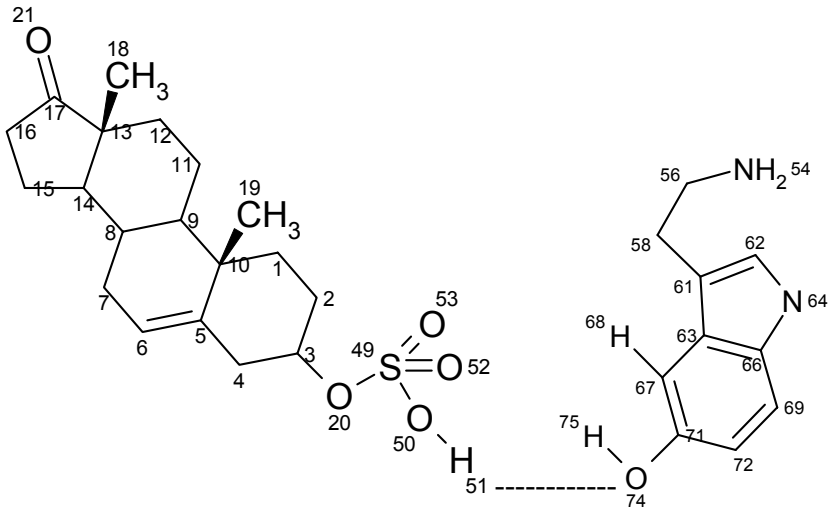

Fig. 1 – The Numbering of the Atoms in the complex SEROTONIN-DHEAS.

RESULTS AND DISCUSSION

Structure and bonding in the molecular units and their intermolecular complex

The formation of the DHEAS–serotonin complex is analyzed in terms of geometry, charge and energy parameters.

The different nature of the overall molecular constitution of the two biomolecules, do not offer enough support for a significant association of the π-π stacking type.

The strongest association involves hydrogen bonds.

There are several possible patterns for hydrogen bonding (O–H...O, O–H...N, involving the various heteroatom combinations).

The bonding association O(74)….H(51) has a length of 1.56 Å, for the given type. The geometry of association is further characterized by the O(50)-H(51)…O(74) angle value (159.3^o) and the value (–162.7^o) for the dihedral angle, O(74)-H(75)…H(51)-O(50).

It should be noted that the atoms participating to the hydrogen bond are almost collinear, suggesting that this interaction is the dominant one in the association.

Generally, the DFT results can be credited with a higher confidence in the quantitative respects because of their treatment of correlation effects. On the other hand, it is acknowledged that the regular DFT functionals face intrinsic problems in the long-range regime.[11] Therefore, the comparative use of HF and DFT methods in computing weakly bonded systems is a technical necessity. In our system, the heat of formation being in the range -10 and -18 kcal mol^{-1} is in favor of a strong hydrogen bonding.Selected reactivity parameters for DHEAS, serotonin and for the complex obtained at the two specified levels are shown in Table 1.

The following details from Table 1 can be noted:

A slightly higher stability for the complex is predicted from the DFT data.

The dipole moment in the complex is smaller than the sum of the individual components, suggesting a not action with the hydrogen bonding; that is due to some polarization of the electron density and to conformational changes in the side-chain of serotonin and of DHEAS.

At the HF/6-31G* level, the frontier orbitals in the complex are localized on serotonin.

Conversely in the B3LYP/6-31G* model, one notes that the frontier orbitals in the complex derive from the HOMO of serotonin and the LUMO of DHEAS.

Table 1

Reactivity Parameters calculated at the HF/6-31G* and B3LYP/6-31G* levels

Method	Reactivity Parameter	DHEAS	SEROTONIN	DHEAS-SEROTONIN	$E_{complex}$-($\Sigma E_{comp.}$) (a.u.)
HF/6-31G* at the HF optimized geometry	Total Energy (a.u.)	-1507.55	-569.404	-2076.97044	
	HOMO (a.u.)	-0.35312	-0.26497	-0.28215	
	LUMO (a.u.)	0.15323	0.14169	0.12586	-0.01644
	μ(D)	4.34	2.33	1.04	
B3LYP/6-31G* at the HF optimized geometry	Total Energy (a.u.)	-1514.82	-572.982	-2087.82679	
	HOMO(a.u.)	-0.2450	-0.18745	-0.20537	
	LUMO (a.u.)	-0.02816	-0.00132	-0.02581	-0.02946
	μ(D)	4.26	2.29	1.39	

The HOMO orbital (at the HF/6-31G* level) in DHEAS is mainly localized on the π_{CC} double bond orbital (C5–C6) (Fig. 2). However, the B3LYP results (Fig. 3) show that this orbital is localized on the D ring, being mostly a π C=O system involved in a hyperconjugation like out-of-phase combination with the C–H bonds of the saturated skeleton.

The HOMO–LUMO gap in the DFT calculations is smaller than in the HF case. This is a consequence of systematic positive energy shifts in the occupied MOs and negative energy shifts in the virtual ones, due to the nature of the HF and KS functions.

In serotonin, the HOMO and LUMO orbitals are seen as pure π orbitals. Because the orbital shape in a π - type system is merely determined by topological reasons, the frontier orbital shapes are similar in the HF and DFT calculations. The frontier orbitals from serotonin lose their almost pure p-nature, and acquire a hybrid character in the complex .This reveals a subtle influence of the electronegativity factors involved in the donor–acceptor interactions that is accounted for in the frame of the DFT approach. It is seen (Figs.4-7) that in complex, unlike 6-31G*, from B3LYP calculations the HOMO is on serotonin and LUMO is placed on DHEAS.

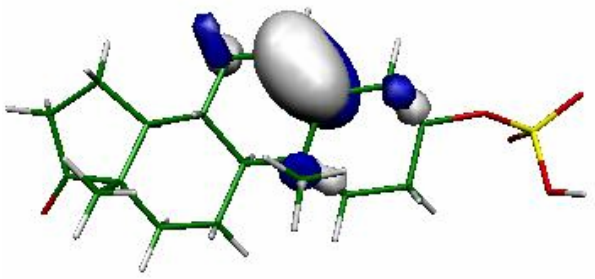

Fig. 2 – The HOMO of the DHEAS independent molecule in the HF/6-31G* calculations.

Fig. 3 – The HOMO of the DHEAS molecule alone in the B3LYP/6-31G* calculations.

A detailed description of these interactions is obtained from a comparative analysis of the atomic charges in the isolated molecules and in their association complex (Table 2).

Table 2 shows that atom O(74) from serotonin acquires the largest negative charge. A similar trend, but of smaller magnitude, is observed for the other electro-negative atoms of the hydrogen bridge, namely atom O(50) from DHEAS. A larger positive increase of the charge is noted for the bridge hydrogen, H(51). It is also interesting to note that the inductive effect produces a positive charge increase on atom H(75) from the outer O–H bond of the intermolecular association region.

Fig. 4 – The LUMO of DHEAS molecule in B3LYP/6-31G* calculations.

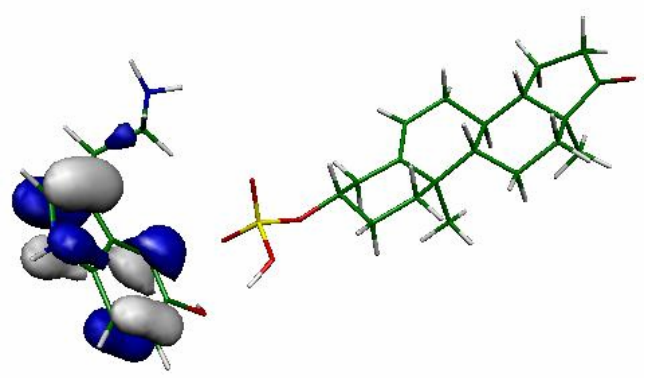

Fig. 5 – The HOMO of the complex molecules in HF/6-31G* calculations.

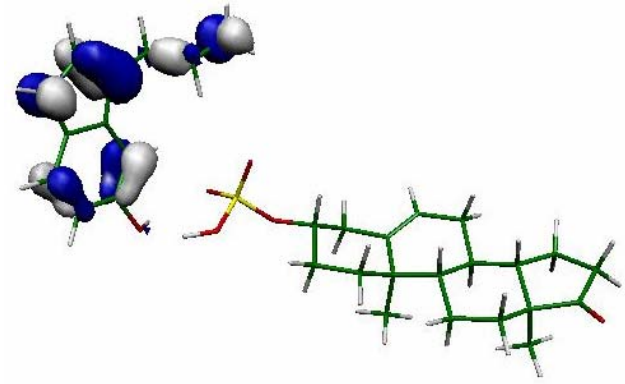

Fig. 6 – The HOMO of the complex molecules in B3LYP/6-31G* calculations.

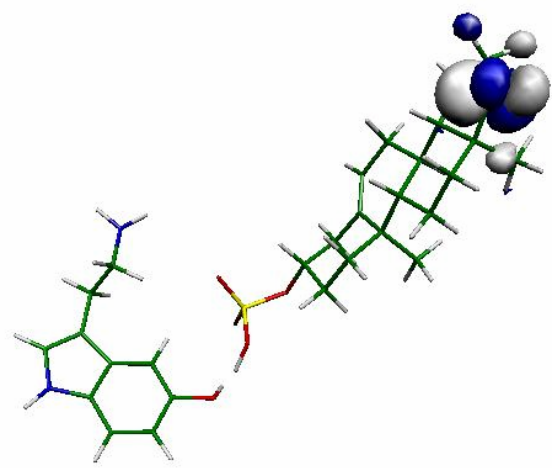

Fig. 7 – The LUMO of the complex molecules in B3LYP/6-31G* calculations.

The effect of the association with DHEAS is then an activation of serotonin induced by this electronic distribution change. The resulting activation mechanism of serotonin would then be due to a possibly significant structural rearrangement.

Table 2

Total atomic charges on selected atoms in the molecular components and in the association complex, from HF and DFT Mulliken population analysis

	HF			DFT		
	Fragment	Complex	Variation	Fragment	Complex	Variation
ATOM	DHEAS	DHEAS–Serotonin	ΔQ	DHEAS	DHEAS–Serotonin	ΔQ
O52	-0.6254	-0.6968	-0.0714	-0.5498	-0.6158	-0.0660
S49	1.7502	1.7738	0.0236	1.4962	1.5093	0.0131
O50	-0.7707	-0.8302	-0.0595	-0.6417	-0.6929	-0.0312
H51	0.5081	0.5930	0.0849	0.4500	0.4817	0.0317
		Serotonin			Serotonin	
O74	-0.7877	-0.8676	-0.0799	-0.6303	-0.7332	-0.1029
H75	0.4473	0.5040	0.0567	0.3617	0.4239	0.0622
N54	-0.8764	-0.8833	-0.0069	-0.7102	-0.7110	-0.0008
C56	-0.3194	-0.1310	-0.1884	-0.3786	-0.2162	-0.0624
C58	-0.1168	-0.3136	-0.1968	-0.1795	-0.3957	-0.2162
N64	-0.8567	-0.8599	-0.0032	-0.8090	-0.8160	-0.0070

Comparing the methods, one may see that the DFT- based population analysis gives smaller absolute charge values on each atom. This can be regarded as a better account of the density using DFT, as the HF approach seemingly overestimates the absolute values of the charge separation in covalent polar bonds.

NBO analysis of the complex

The natural bond orbital (NBO) method [12, 13]offers supplementary structural information.

For example, for the double bond between C(5) and C(6), one observes that the corresponding hybrid orbitals, with C(5) s (38.72%) and p 1.58 (61.28%), C(6) s(37.83%) and p 1.64 (62.17%) correspond to a rather higher s percentage than the usual 33%. The larger s content can be associated with the strengthening of the bond. The NBO shows that the π bond is established, as expected with pure p-AOs (C5 s(0.03%) and p 99.99 (99.97%) in BD (2) C5–C6).

Very interesting are the hybrid orbitals associated with the intermolecular hydrogen bond formed by the sequence of atoms O(50)–H(51)...O(74). The hybrid orbitals of the O(50) are close to the regular sp^3 (s: p =27:73 % composition).

The NBO analysis shows that the hybrid composition is not so standard and is in fact better characterized by an sp^3 differential hybridization. The lone pair devoted to the H(51)… O(74) hydrogen bond has the nonstandard composition s(40.86%)p 1.45(59.14%). The hybrids along the S(49)-O(50) and O(50)-H(51) bonds have the following compositions: s(15.71%)p5.53(84.29%) and s(22.31%)p3.48(77.69%) respectively. The first one is almost a pure p-AO and the last one has a hybrid character sp^3. The heterogeneous nature of the bond is measured by the 84.29% participation of the oxygen pure orbitals in S-O bond. Similarly in the described O-H bond, the oxygen hybrid orbital percentage is 77.69%.

The perturbation donor-acceptor analysis of the NBO method offers information about intermolecular interactions. The most important intermolecular donor-acceptor contacts occurs between : an antibonding NBO function (NBO nr.204 BD^*(1)O(50)-H(51) and NBO nr.232 BD^*(1)C(71)-O(74), corresponding to an energy of 9.75 Kcal/mol and respectively NBO function 146. LP (2) O (74) and NBO nr.204. BD*(1) O 50 - H 51 corresponding to an energy of 73.83 Kcal/mol. This one that is too great, from the NLMO analysis gives the 93.565% composition LP (2) O74 : s(22.91%)p 3.37(77.09%). That suggests that the lone pair devoted to the H(51)…O(74) hydrogen bond has an sp^3 character.

CONCLUSIONS

DHEAS should form, like also DHEA, an association complex with serotonin through hydrogen bonding.

The heat of formation for this complex by 6-31G* calculation is about -10 Kcal/mol unlike the complex between DHEA with serotonin where the heat of formation is –7.6 Kcal/mol; so the complex of DHEAS is more possible to form.

From the comparatives calculations the possibility of the complex to be formed between DHEAS and serotonin is emphasized by B3LYP model.

By B3LYP model the frontier orbitals in the complex are due to serotonin (HOMO) and to DHEAS (LUMO).

The changes in electronic distribution brought about by complexation, lead to the hypothesis that a change in the reactivity of DHEAS and serotonin could result from their interaction.

REFERENCES

1. D. A. Lerner , J. Weinberg and C. Bălăceanu-Stolnici, *Rev.Roum. Chim*., **2002**, *47*, 893-901.
2. P. Robel and E. E Baulieu., *Ann.New York Acad.Sci.,* **1995**, *774*, 82-110.
3. D. A. Shapiro, K. Kristiansen, W. R. Kroeze, B. L. Roth , *Molecular Pharmac*, **2000**, *58*, 877-886
4. H. Weinstein., R.Osman, *Neuropsychopharm,* **1990**, *3*, 397-409
5. J. M. Lehn," Supramolecular Chemistry: Concepts and Perspectives", VCH, Weinheim, 1995.
6. N. S. Bhacca, F. R. Fronczek and A. Sygula, *J.Chem.Crystall*., **1996**, *26*, 483-87.
7. D. A. Lerner, J. Weinberg, F. Cimpoesu and C. Bălăceanu-Stolnici, *J. Mol. Mod.,* **2006**, *12,*2, 146-151
8. N. L. Allinger *„J. Am. Chem. Soc.,***1977***, 99*, 8127; N. L. Allinger, Yuh YH Quantum Chemistry Program Exchange, Bloomington, Indiana, Program #395
9. U. Burkert,. N. L. Allinger, *Molecular Mechanic*s, **1982**, ACS Monograph 177 modified to incorporate nonbonded cutoffs
10. Gaussian **98** (Revision A.1), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala,

Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1998.

11. C. J.Cramer, "Essentials of Computational Chemistry", John Wiley&Sons Ltd, 2002.
12. A. E. Reed, L. A. Curtiss, F .Weinhold , *Chem. Rev.,* **1988,** *88,* 899.
13. The NBO3.0 program,. E.D. Glendening, A.E.Reed, J.E.Carpenter, F.Weinhold, Copyright **1996-2001**, University of Wisconsin.
14. MOLEKEL (Version 4.2) by Stefan Portmann, Copyright (C) **2000-2002 CSCS/ETHZ.**