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A comparison of Conceptual DFT and Molecular Electron Density Theory (MEDT) descriptors of local chemical reactivity properties: Oxytocin and Vasopressin peptide hormones as test cases

Abstract

Herein we present the results of a study of the global and local chemical re-activity of the peptide hormones Oxytocin and Vasopressin based on the calculation of descriptors coming from Conceptual DFT as well as from Molecular Electron Density Theory for their consideration as a tool to explain the molecular interactions, and as a useful complement to those approximations based on Molecular Docking. The knowledge of the values of the global and local descriptors of the molecular reactivity of the Oxytocin and Vasopressin peptide hormones that have been studied through our proposed methodology could be useful in the development of new drugs based on these compound or some analogs relying in the chemical interaction between these peptides and their biological receptors of protein kind. It can be concluded that both approximations to the local chemical reactivity based on the descriptors are equally valid and complement each other, while the choosing of the Population Analysis used in their calculation is not a crucial point to be considered.

Keywords: oxytocin, vasopressin, conceptual DFT, chemical reactivity, molecular electron density theory, local chemical reactivity properties

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Norma Flores-Holguín,[1] Juan Frau,[2] Daniel Glossman-Mitnik[1,2]

[1]Department of Environment and Energy, Advanced Materials Research Center, Mexico

[2]Department of Chemistry, University of the Balearic Islands, Spain

Correspondence: Daniel Glossman-Mitnik, Laboratorio Virtual NANOCOSMOS, Departamento de Medio Ambiente y Energia, Centro de Investigacion en Materiales Avanzados, Miguel de Cervantes 120, Complejo Industrial Chihuahua, Chihuahua, Chih 31136, Mexico, Tel +526144391151, Email daniel.glosman@cimav.edu.mx

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Introduction

There has been an increasing interest during the last years on the study of cyclic peptides (CP), especially those that can be obtained from marine sources, because of their potential pharmacological applications to fight several diseases. Oxytocin and vasopressin are non-apeptides belong in to the CP class with a similar sequence of amino acids while both presenting a single disul de bridge and they represent nice examples of drugs that have been incorporated in the practice of Medicinal Chemistry.

From the medicinal chemistry point of view, both peptide hormones exert their action by interacting with the active sites of their respective receptors which are generally proteins. These processes are theoretically studied through the recently presented eld of Computational Peptidology whose techniques have been already described and discussed.[1,2] One of these techniques is called Molecular Docking which has been proven as a useful and indispensable tool in Medicinal Chemistry.[3,4] How-ever, it has already found that this process can only be performed accurately for peptides not exceeding three amino acids long,[1,2] making it necessary to resort to some other techniques acting not as a replacement of Molecular Docking but as complementary ones.

Within Computational Chemistry and Molecular Modeling practice, it is common to resort to Conceptual DFT,[5,6] also called Chemical Reactivity Theory, which uses a series of global and local descriptors to predict the interactions between molecules and understand the way in that chemical reactions proceed. For this reason, we have been studying with great success the chemical reactivity properties of a series of carbohydrates involved in the Maillard reaction, some small peptides, several melanoidinic colorants[7–13] and lately, a family of anticancer peptides of marine origin.[14] In all these studies, a search was performed to and the most well-behaved density functional by resorting to a procedure proposed by the authors.[7–14]

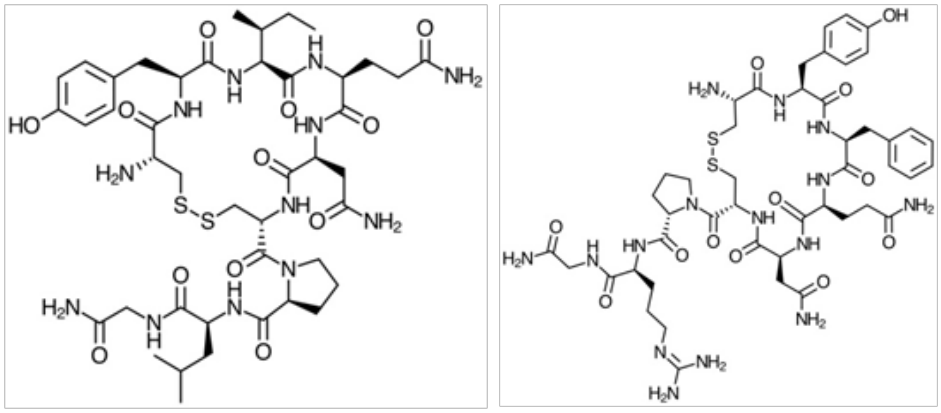
Indeed, there are other complementary models to study the chemical re-activity of molecular systems like that proposed by Domingo,[15] which he named Molecular Electron Density Theory (MEDT). With this new model, some new chemical reactivity descriptors has been defined and have incorporated to the phletora of useful tools for the understanding of the chemical interactions between molecules.[16,17] Thus, the objective of this work is to perform a comparative study the chemical reactivity of the Oxytocin and Vasopressin peptide hormones by resorting to Conceptual DFT, and to compare these predictions with the results that can be obtained by the calculation of the Parr functions as descriptors coming from MEDT at the same level of theory.

Settings and computational methods

In the same way as we have proceeded in our recent studies,[7–14] the computational tasks in this work have been done by considering the popular Gaussian 09 software.[18] Following the conclusions obtained from those studies, the MN12SX density functional[19] is chosen again because it can be considered well-behaved according to our proposed mentioned criteria. Accordingly, the calculation of the electronic properties used a model chemistry based on the mentioned density functional in connection with the Def2TZVP basis set while a smaller Def2SVP was considered for the prediction of the most stable structures.[20,21] In order to obtain accurate results, all calculations were performed using water as the solvent simulated with the SMD model.[22]

Results and discussion

The molecular structures of the Oxytocin and Vasopressin peptide hormones, which are depicted in Figure 1, were pre-optimized in the gas phase by resorting to the Density Functional Theory-Tight Binding (DFTBA) model available in Gaussian 09. The resulting conformers were processed as it is customary within Computational Chemistry to obtain the desired calculated properties according to the techniques mentioned in the previous section. As previously stated, the first step was to verify that the model chemistry considered in this study corresponded to a well-behaved density functional and for this objective we resorted to several descriptors proposed by us[7–14] that can help in the verification of our designed procedure. The results of this analysis are presented in Table 1.



(a) (b)

Figure 1 Graphical sketches of the molecular structures of the peptide hormones:

a) Oxytocin

b) Vasopressin

Table 1 Electronic energies of the neutral, positive, and negative molecular systems (in au) of Oxytocin and Vasopressin; the HOMO, LUMO, and SOMO orbital energies (in eV); and the J_I , J_A, J_{HL} and ΔSL descriptors calculated with the MN12SX density functional and the Def2TZVP basis set using water as the solvent simulated with the SMD parameterization of the IEF-PCM model

	Eo	E+	E-	HOMO	LUMO
Oxytocin	-4029.049	-4028.824	-4029.078	-6.082	-0.763
Vasopressin	-4306.618	-4306.392	-4306.649	-6.13	-0.815
	SOMO	**J_I**	**J_A**	**J_{HL}**	**ΔSL**
Oxytocin	-0.804	0.029	0.02	0.035	0.04
Vasopressin	-0.86	0.023	0.024	0.033	0.045

From Table 1, the results for the descriptors show values that are consistent with our previous findings for the case of the melanoidins[7–13] and peptides of marine origin,[14] that is, the MN12SX density functional is capable of giving HOMO and LUMO energies that allow to verify the agreement with the approximate Koopmans' theorem.

After that verification, the values of the chemical reactivity descriptors coming from Conceptual DFT and whose definitions are provided as the Electronegativity $\chi = -\frac{1}{2}(I + A) \approx \frac{1}{2}(\varepsilon_L + \varepsilon_H)$ [5,6] the global hardness $= \eta = (I-A) \approx (\in_L - \in_H)$,[5,6] the electrophilicity $\omega = \frac{\mu^2/2\eta = (I+A)^2}{4(I-A)} \approx \frac{(\in_L - \in_H)^2}{4(\in_L - \in_H)}$,[23] the electrodonating power $\omega^- = \frac{(3I+A)^2}{16(I-A)} \approx \frac{(3\in_H + \in_L)^2}{16\eta}$,[24] the electroaccepting power $\omega^+ = \frac{(I+3A)^2}{16(I-A)} \approx \frac{(\in_H + 3\in_L)^2}{16\eta}$,[24] and the net electrophilicity $\Delta\omega^{\pm} = \omega^+ - (-\omega^-) = \omega^+ + \omega^-$,[25] where $\in_H$ and $\in_L$ are the energies of the HOMO and LUMO, respectively, which results for the Oxytocin and Vasopressin peptides are presented in Table 2.

If we now focus on the local reactivity descriptors coming from either Conceptual DFT or MEDT, then the definitions will be: Nucleophilic Fukui Function $f^+(r) = \rho_{N+1}(r) - \rho_N(r)$ [5,6] Electrophilic Fukui Function Dual Descriptor $\Delta f(r) = \left(\frac{\partial f(r)}{\partial N}\right)_{v(r)}$,[26–31] Nucleophilic Parr Function $P^+(r) = \rho^{ra}{}_s(r)$,[16,17] and Electrophilic Parr Function $P^+(r) = \rho^{ra}{}_s(r)$,[16,17] where N+1(r), N (r), and N 1(r) are the electronic densities at point r for a system with N + 1, N, and N 1 electrons, respectively, and $\rho^{rc}{}_s(r)$ and $\rho^{ra}{}_s(r)$ are related to the atomic spin density (ASD) at the r atom of the radical cation or anion of a given molecule, respectively.[32]

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Table 2 Global reactivity descriptors for the Oxytocin and Vasopressin molecules calculated with the MN12SX density functional with the Def2TZVP basis set and the SMD solvation model using water as the solvent

	Electronegativity (χ)	**Chemical hardness (η)**	**Electrophilicity (ω)**
Oxytocin	3.4225	5.319	1.1011
Vasopressin	3.4725	5.315	1.1344
	Electrodonating Power (ω^-)	**Electroaccepting power (ω^+)**	**Net electrophilicity ($\Delta\omega^{\pm}$)**
Oxytocin	4.2459	0.8234	5.0693
Vasopressin	4.3372	0.8647	5.2019

Tables 3 & 4 present the results of the calculation of these local reactivity descriptors for the Oxytocin and Vasopressin peptide hormones, respectively, in relation with the graphical sketches showing their molecular structures and the numbering of the atoms in Figures 2 & 3. From the results on Tables 3 & 4, the nucleophilic and electrophilic sites for chemical reactivity are predicted with great accuracy. Moreover, there is a nice accordance between the results coming from the Condensed Dual Descriptor fk and the Nucleophilic and Electrophilic Parr Functions P^+_k and P_k which represents a good starting point with warranty of success for the use of these peptide hormones as precursors of pharmaceutical drugs.

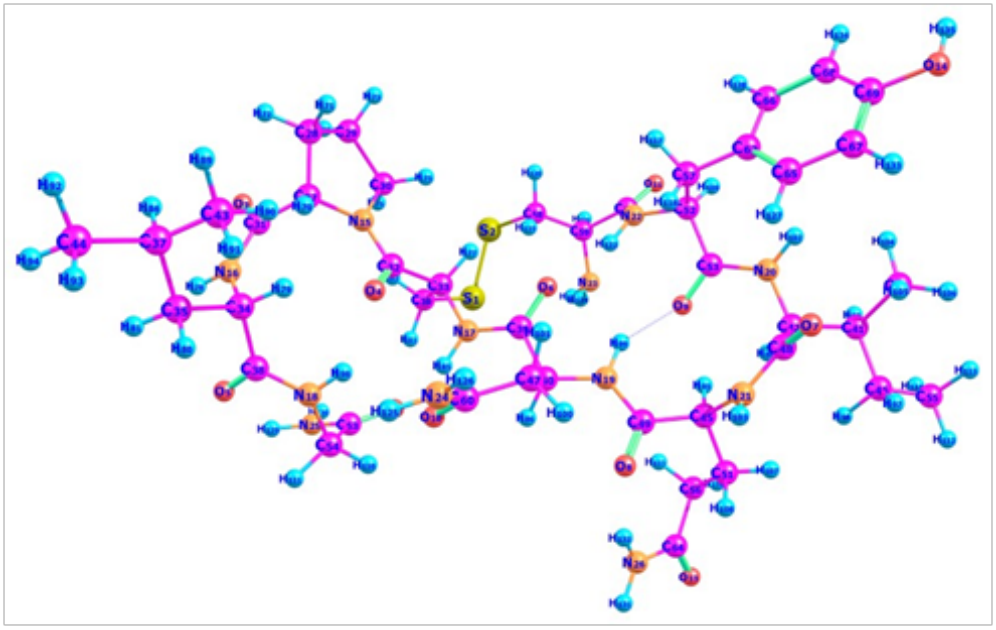

Figure 2 Graphical sketch of the molecular structures of the Oxytocin peptide hormone showing the numbering of the atoms.

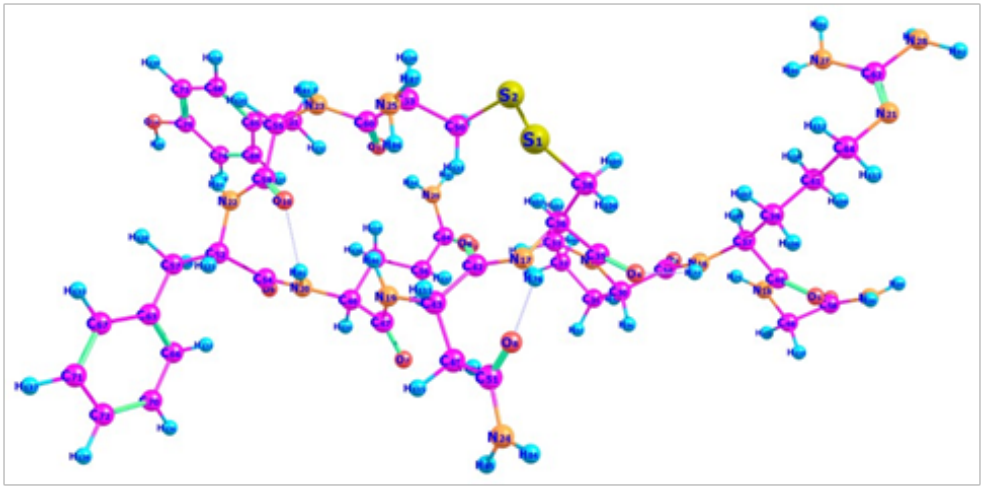

Figure 3 Graphical sketch of the molecular structures of the Vasopressin peptide hormone showing the numbering of the atoms.

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Table 3 Local reactivity descriptors for the Oxytocin molecule calculated with the MN12SX density functional with the Def2TZVP basis set and the SMD solvation model using water as the solvent: Condensed Dual Descriptor Δf_k, Nucleophilic Parr Function P+ k and Electrophilic Parr Function P^-_k ; M stands for Mulliken Population Analysis, N corresponds to Natural Population Analysis and H means Hirshfeld Population Analysis

Atom	Δf_k (M)	Δf_k (N)	P_k^+ (M)	P_k^- (M)	P_k^+ (H)	P^-_k (H)
1S	-6.34	-2.64	0	0.0348	0	0.0322
2S	-5.7	-2.74	0.0001	0.0311	0.0001	0.0282
9O	1.1	0.85	0.0185	0.0065	0.0201	0.0056
11O	-2.3	-1.85	0.0008	0.0185	0.0006	0.0159
14O	-12	-10.9	0.0018	0.1781	0.0006	0.1659
22N	-1.69	-1.26	-0.0002	0.021	0.001	0.0161
23N	-5.11	-2.21	0.0001	0.0336	0	0.0265
53C	3.15	2.1	0.048	0.0069	0.0373	0.0038
58C	-1.31	0	0.0001	0.0059	0.0001	0.0071
59C	-1.3	-0.08	0.0002	0.0056	0.0001	0.0095
62C	-17.27	-17.38	-0.0693	0.3714	0.0288	0.2054
65C	11.43	9.86	0.185	-0.0551	0.1343	0.0211
66C	23.79	19.15	0.396	-0.0255	0.2446	0.0365
67C	15.82	11.57	0.3298	0.112	0.2034	0.0933
68C	9.37	6.6	0.2075	0.0822	0.1629	0.0798
69C	-11.77	-10.73	-0.059	0.1853	0.0334	0.1583

Table 4 Local reactivity descriptors for the Vasopressin molecule calculated with the MN12SX density functional with the Def2TZVP basis set and the SMD solvation model using water as the solvent: Condensed Dual Descriptor Δf_k, Nucleophilic Parr Function P^+_k and Electrophilic Parr Function P^-_k ; M stands for Mulliken Population Analysis, N corresponds to Natural Population Analysis and H means Hirshfeld Population Analysis

Atom	Δf_k (M)	Δf_k (N)	P_k^+ (M)	P_k^- (M)	P_k^+ (H)	P^-_k (H)
10O	1.16	0.75	0.0209	0.0080	0.0222	0.0068
14O	-16.31	-13.27	0.0016	0.2102	0.0007	0.1952
59C	3.24	2.07	0.0453	0.0074	0.0352	0.0036
65C	-24.15	-19.52	-0.0718	0.4345	0.0232	0.2359
68C	20.67	18.56	0.3669	-0.0547	0.2318	0.0264
69C	9.01	9.76	0.1953	-0.0461	0.1366	0.0346
73C	7.54	6.54	0.2425	0.1099	0.1799	0.0976
74C	9.78	8.54	0.3016	0.1194	0.1917	0.1071
75C	-16.61	-12.45	-0.0643	0.2113	0.0293	0.1827

Conclusion

The results of the calculations of the global and local chemical reactivity of the Oxytocin and Vasopressin peptide hormones based on the calculation of descriptors coming from Conceptual DFT as well as from Molecular Electron Density Theory for their consideration as a tool to help in the design on new pharmaceutical drugs relying in the chemical interaction between these peptides and their biological receptors of protein kind, and also as a useful complement to those approximations based on Molecular Docking. It can be concluded that both approximations to the local chemical reactivity based on the descriptors are equally valid and complement each other, while the choosing of the Population Analysis used in their calculation is not a crucial point to be considered.

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Conflicts of interest

Authors declare that there is no conflicts of interest.

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