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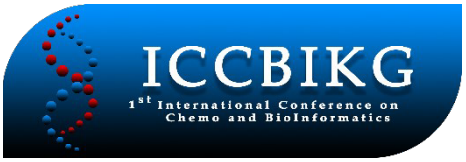

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DFT approach of the redox properties of brimonidine and varenicline

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Abstract: The redox properties of two quinoxaline derivatives, brimonidine and varenicline, previously studied electrochemically, were evaluated by performing a computational study. On the basis of some useful quantum chemical parameters the differences and similarities between their redox features were explained. The obtained results support the experimental findings that the redox processes of both compounds are under strong influence of the solution pH, whereas the reduction of brimonidine occurs easier than the reduction of varenicline, at corresponding pH values.

Keywords: brimonidine, varenicline, redox process, molecular orbital energy, quantum chemical parameters

1. Introduction

The redox properties of brimonidine and varenicline, quinoxaline derivatives with different pharmacological effects (antiglaucoma and smoking cessation agent, respectively), were previously examined electrochemically [1-3]. Electrochemical studies showed similarities and differences due to the different molecular structures. The redox processes were shown to be under the strong influence of the solution pH and the substituents/condensed ring on the quinoxaline core, contented in both drugs (**Figure 1**). The reduction process, presented as a two-electron process involving two H^+, occurred at the quinoxaline moiety (reduction of the C=N bond of the pyrazine ring within the quinoxaline core), in a wide pH range (2.0 – 12.0), since the additional two-electron reduction step involving two 2 protons was strongly influenced by the pH of solution and was observed only in acidic media [1-3]. With the aim of confirming and explaining the comparison of the electrochemically studied redox mechanisms of two quinoxaline derivatives, a computational study was performed.

2. Computation calculation

The geometric structures (**Figure 1**) of brimonidine and varenicline, their corresponding forms which are formed by reduction or oxidation, both in molecular and ionized forms, were optimized at the B3LYP/6-31G (d,p) level of DFT in the gas phase using the Gaussian 03 program [4]. The *Polarizable Continuum Model* (PCM) [5], was applied with B3LYP/6-31G (d,p)^{water} basis set to compute the energies of the *Highest Occupied Molecular Orbital Energy* (E_{HOMO}) and the *Lowest Unoccupied Molecular Orbital Energy* (E_{LUMO}), which were used to calculate quantum chemical based reactivity molecular descriptors: chemical potential (μ), electronegativity (χ), hardness (η), global softness (S), and electrophilicity index (ω) [6]. This methodology has already been successfully implemented in investigations of the electrochemical behavior of compounds [3, 7].

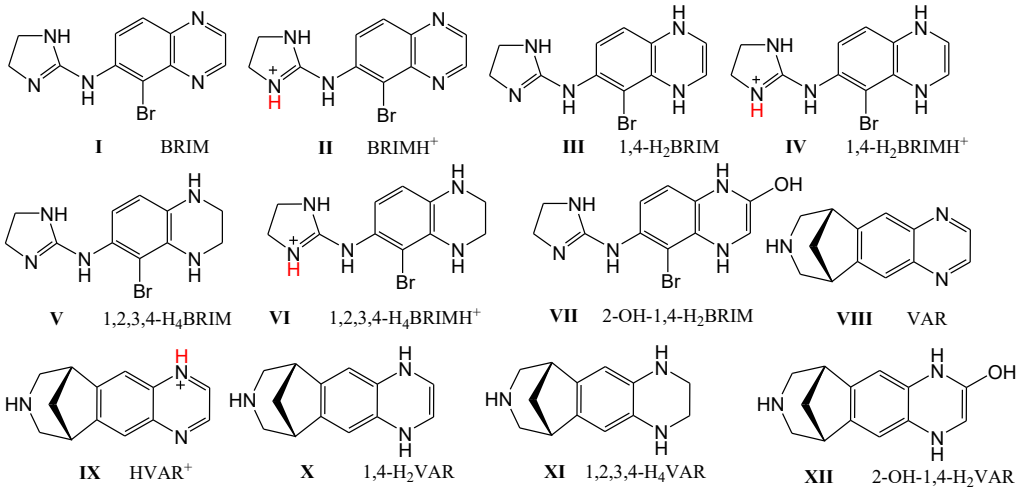

Figure 1. Chemical structures of investigated compounds.

3. Results and discussion

To consider the similarities and differences in redox behavior in pH dependent manner, in addition to the molecular forms present in the neutral/basic conditions (I, III, V, VII, VIII, X, XI, XII), the protonated forms of brimonidine(II, IV, VI) present in the acidic experimental conditions (pH≤3), as well as the protonated form of varenicline (IX), were examined. The results of the DFT study are shown in **Table 1**. The E_{HOMO} and E_{LUMO} molecular orbitals, calculated using the PCM approach, are shown in **Figure 2**. Both frontier orbitals are dominantly distributed at the quinoxaline moiety in brimonidine and varenicline, indicating that the electron transfer reactions will occur at the quinoxaline core. A higher E_{HOMO} value indicates the ability of a molecule to donate electrons to the acceptor and thus to be more easily oxidized. A lower E_{LUMO} value reflects the ability of a molecule to accept the electrons and a greater tendency to be reduced [3, 7]. The E_{LUMO} value (**Table 1)** of the protonated brimonidine form IV (-0.720), formed in the first reduction step, is more than twice lower than the value of the corresponding nonprotonated form III (-0.310), as well as the E_{LUMO} value of II (-5.26), in a relation to corresponding nonprotonated form I (-2.09)

Table 1. Quantum mechanical parameters of investigated compounds calculated at B3LYP/6-31G (d,p)PCM level.

	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
E_{LUMO}	-2.09	-5.26	-0.31	-0.72	3.01	-0.26	-0.32	-1.94	-3.33	0.03	0.12	0.29
E_{HOMO}	-5.72	-9.76	-4.27	-4.31	-2.33	-5.15	-4.34	-5.86	-5.84	-4.11	-4.93	-3.32
ΔE gap	3.63	4.50	3.96	3.59	5.33	4.90	4.02	3.93	2.51	4.14	5.05	3.61
μ	-3.91	-7.51	-2.29	-2.52	0.34	-2.71	-2.33	-3.90	-4.59	-2.04	-2.40	-1.52
χ	3.91	7.51	2.29	2.52	-0.34	2.71	2.33	3.90	4.59	2.04	2.40	1.52
η	1.82	2.25	1.98	1.80	2.67	2.45	2.01	1.96	1.26	2.07	2.52	1.81
S	0.28	0.22	0.25	0.28	0.19	0.20	0.25	0.25	0.40	0.24	0.20	0.28
ω	4.20	12.53	1.32	1.76	0.02	1.50	1.35	3.87	8.37	1.01	1.14	0.64

In the case of varenicline, the E_{LUMO} value of IX (-3.330), is lower compared with nonprotonated VIII (-1.936). In both cases, the lower E_{LUMO} values of the protonated forms indicate that the reduction process of brimonidine and varenicline is easier under acidic conditions. The E_{HOMO} values of completely reduced forms of brimonidine which could be formed in the second, V (-2.325) and VI (-5.154), indicate a higher tendency of the nonprotonated form V to the reverse oxidation process, suggesting that the redox equilibria would be more shifted toward the reduction process in the case of the protonated form VI, which is present in solution at the pH of the experiments (pH ≤ 3) [1-3]. These results support the experimental findings that the reduction process is affected by pH of the solution since the second reduction step is experimentally detected only in acidic conditions [1-3].

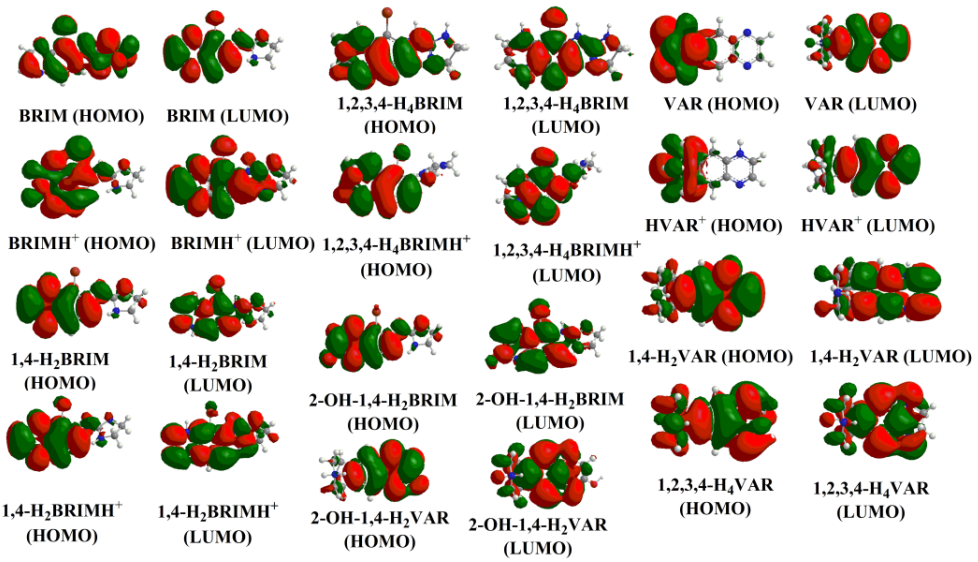

Figure 2. B3LYP/6-31G (d,p) calculated HOMO and LUMO orbitals for investigated compounds.

The highest values (Table 1) for the electrophilicity index (ω) [6] were observed for the protonated forms II (12.533) and IX (8.337), indicating that the reduction process

occurs more easily in acidic conditions. The differences in ω values between brimonidine and varenicline confirm the experimental findings that the reduction of brimonidine occurs easier than the reduction of varenicline, at corresponding pH values [2]. For IX the highest value for softness (S) (0.389) and the lowest value for chemical hardness (η) (1.255) are observed suggesting that IX has the most pronounced tendency for polarization of electron density and change of electronic configuration [6], which could explain the difference in the redox behavior between varenicline and brimonidine.

3. Conclusions

The obtained computational results supported and strengthened experimental findings that the redox processes of brimonidine and varenicline are strongly pH dependent, with the reduction of brimonidine being easier than that of varenicline, at corresponding pH values.

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References

[1] M.M. Aleksic, V. Radulovic, N. Lijeskic, V. Kapetanovic., *Electrochemical response and determination of varenicline at boron doped diamond, glassy carbon and hanging mercury electrodes*, Curr. Anal. Chem, 8 (2012) 133-142.

[2] M.M. Aleksic, V. Radulovic, D. Agbaba, V. Kapetanovic., *An extensive study of electrochemical behavior of brimonidine and its determination at glassy carbon electrode*, Electrochim. Acta, 106 (2013) 75– 81.

[3] J. Rupar, M.M. Aleksic, K. Nikolic, M.R. Popovic-Nikolic., *Comparative electrochemical studies of kinetic and thermodynamic parameters of Quinoxaline and Brimonidine redox process*, Electrochim. Acta, 271 (2018) 220-231.

[4] Gaussian 03 (Revision C.02.), Gaussian, Inc, Wallingford, 2004.

[5] M. Cossi, G. Scalmani, N. Rega, V. Barone., *New developments in the polarizable continuum model for quantum mechanical and classical calculations on molecules in solution*, J. Chem. Phys, 117 (2002) 43.

[6] R.G. Parr, W. Yang., *Density-functional Theory of Atoms and Molecules*, Oxford University Press, New York, 1989.

[7] A.H. Shah, W. Zaid, A. Shah, U.A. Rana, H. Hussain, M.N. Ashiq, R. ah, M.A. Zia, H.-B. Kraatz., *pH Dependent electrochemical characterization, computational studies and evaluation of thermodynamic, kinetic and analytical parameters of two phenazines*, J. Electrochem. Soc, 162 (2015) H115