PHYSICAL CHEMISTRY 2016

13th International Conference on
Fundamental and Applied Aspects of
Physical Chemistry

Proceedings
Volume II

B E L G R A D E
September 26-30, 2016

PHYSICAL CHEMISTRY 2016

13th International Conference on
Fundamental and Applied Aspects of
Physical Chemistry

Proceedings
Volume II

B E L G R A D E
September 26-30, 2016

ISBN 978-86-82475-33-0
Title: Physical Chemistry 2016 (Proceedings)
Editors: Željko Čupić and Slobodan Anić
Published by: Society of Physical Chemists of Serbia, Studentski trg 12-16, 11158, Belgrade, Serbia.
Publisher: Society of Physical Chemists of Serbia
For Publisher: Slobodan Anić, President of Society of Physical Chemists of Serbia
Printed by: "Jovan", Printing and Publishing Company; 200 Copies
Number of pages: 3+434; Format B5; printing finished in September 2016

Text and Layout: "Jovan"

200 - *Copy printing*

THEORETICAL STUDY OF IONIZATION OF SARTANSIN AQUEOUS MEDIA

M. Popović[1], G. Popović[2], K. Nikolić [1], M. Grujić[1] and D. Agbaba[1]

[1]Department of Pharmaceutical Chemistry, (majap@pharmacy.bg.ac.rs)
[2]Department of General and Inorganic Chemistry, University of Belgrade-Faculty of Pharmacy, Vojvode Stepe 450, 11000 Belgrade, Serbia

ABSTRACT

In this study the order of ionization in the molecules ofirbesartan, losartan, and valsartan has been investigated. Irbesartan and losartan are ampholytes, valsartan isdiacid with close values of ionization constants. In order to get better insight in the overlapped protolytic equilibria of sartanstheoretical study was performed. Energy calculation of the optimized structures of equilibrium forms was performed at the B3LYP/6-31G (d,p) level of the Density Functional Theory (DFT). Results of theoretical study confirmedprediction that in allexamined compoundshigher pK_a valuescan be attributed to the ionization of tetrazole.

INTRODUCTION

Angiotensin II Receptor Blockers (ARB), also known as sartans, are used in the treatment of hypertension, cardiac insufficiency, myocardial infarction, and diabetic nephropathy.Not only the conformation of the sartans active form is important for pharmacological activity but also their ionization state in physiological conditions that can affect partitioning between plasma and biomembranes [1]. Irbesartan and losartan are ampholytes with one acidic (tetrazole ring) and one basic center (imidazole ring), while the valsartan is diprotic acid (carboxylic group and tetrazole ring) (Figure 1). The pK_a values of examined sartans were determined potentiometrically: pK_{a1} 3.88and pK_{a2} 4.55 for irbesartan; pK_{a1} 3.27 and pK_{a2} 4.60 for losartan; pK_{a1} 3.79 and pK_{a2} 4.55 for valsartan [2]. Ionization processes include equilibrium forms that can differ in physico-chemical properties. In order to estimate the extent of ionization at any given pH value it is necessary to assign thepK_a values to corresponding ionizable centers. The main aim of theoretical study was to obtain a better insight in the overlappedprotolyitic equilibriaand properties ofsartans equilibrium forms.

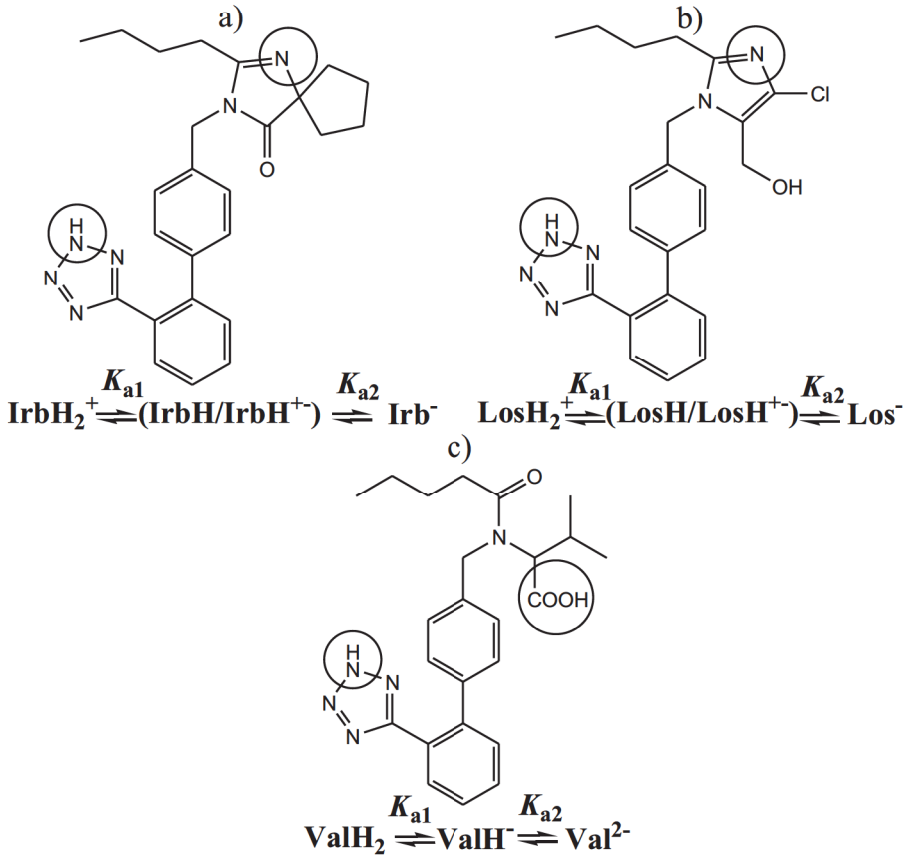

Figure 1. Ionization profiles of a) irbesartan, b) losartan, c) valsartan. Equilibrium forms: cationic ($IrbH^+$, $LosH^+$), molecular (IrbH, LosH, $ValH_2$), zwitterionic ($IrbH^{+-}$, $LosH^{+-}$), monoanionic (Irb^-, Los^-, $ValII^-$), dianionic (Val^{2-}).

EXPERIMENTAL

Chemical structures of each equilibrium form of examined sartans that can exist in solution were built in ChemBioDraw Ultra 13.0 program and copied to ChemBio3D Ultra 13.0 program in order to create their 3D-models. Irbesartan and losartan are ampholytes which may exist in four equilibrium forms in a solution (cationic, anionic, zwitterionic, and molecule), while the valsartan is diacid with three equilibrium forms (molecular, monoanionic, and dianionic). Geometry optimizations of each of the elevenequilibrium forms were performed at the B3LYP/6-31G (d,p) level of the DFT[3, 4] in the gas phase using the Gaussian 09 program [5]. Optimized molecular

models were used for all further calculations. The PCM [6] in the B3LYP/6-31G (d,p)^{water} basis set[3, 4] was applied to compute the electronic descriptors, energies of the highest occupied and the lowest unoccupied molecular orbital (E_{HOMO} and E_{LUMO}),chemical potential (μ), electronegativity (χ), hardness (η), global softness (S), electrophilicity index (ω), dipole moment, and charges [7].

RESULTS AND DISCUSSION

Potentiometrically determined p$K_a$values of examined sartans are very close which point out to overlapped protolytic equilibria. Order of ionization can be predicted based on the analysis of chemical structure only in case of valsartan (lower pK_a value of carboxylic group than tetrazole). Irbesartan and losartan contain imidazole ring as a basic center with pK_a value lower than the pK_a of tetrazole as an acidic center.

Table 1. SCF energies of sartans calculated at B3LYP/6-31G(d,p) level of DFT. Energies are given in hartrees. (Equilibrium forms are explained on Figure 1).

Sartan	Form	SCF_{Gas}	SCF_{PCM}	ΔSCF
Irbesartan	IrbH	−1373.29323	−1373.31279	−0.01956
	$IrbH^{+-}$	−1373.29353	−1373.29109	0.00244
	Irb^-	−1372.74810	−1372.83809	−0.08755
	$IrbH_2^+$	−1373.69218	−1373.77253	−0.08035
Losartan	LosH	−1716.12055	−1716.14021	−0.01966
	$LosH^{+-}$	−1716.11971	−1716.12615	−0.00644
	Los^-	−1715.58099	−1715.66139	−0.08040
	$LosH_2^+$	−1716.52008	−1716.59122	−0.07114
Valsartan	$ValH_2$	−1431.48628	−1431.509456	−0.023176
	$ValH^-$	−1430.93597	−1431.027103	−0.091133
	Val^{2-}	−1430.32750	−1430.552276	−0.224776

Energy calculation of the optimised molecular models was performed at theB3LYP/6-31G (d,p) [3] level of the DFT [4] in a gas phase and in water solution. The energies of optimised molecular models were computed by applying self-consistent field method (SCF) for transfer the molecules from gas (SCF_{Gas}) to aqueous phase (SCF_{PCM}) [8] and differences between the energies were calculated (ΔSCF= SCF_{Gas}- SCF_{PCM}) and listed in Table 1.

Value ΔSCF is higher for anionic forms of losartanand irbesartan in relation to their corresponding cationic forms, as well as for dianionic

valsartan form compared to its monoanionic form. Larger ΔSCF values were observed for anions formed by deprotonation oftetrazole(Irb^-, Los^-, Val^{2-}) which indicate that more energy is required for ionization of tetrazole in comparison to the ionization of the imidazole and carboxyl group. Based on these results, pK_{a2} values (4.55, 4.60, 4.55) can be attributed to the tetrazole ring of irbesartan, losartan and valsartan, respectively. Accordingly, pK_{a1} values (3.88, 3.27, 3.79) correspond to imidazole ring of irbesartan, imidazole of losartan, and carboxylic group of valsartan, respectively.In case ofampholytes in which pK_a of acidic group is greater than the pK_a of the basic group is expected that in a solution molecular form is dominant in a relation to zwitterionic.

CONCLUSION

Experimentaly determined pK_a values of irbesartan, losartan, and valsartan have beenattributed to the corresponding ionizable groups based on results obtained in theoretical study. Defining the ionization of sartans can help with determination of the equilibrium form which is required for achieving a better bioavailability as well as with more accurately explanation of the mechanism of interaction between sartans and their target site of action.

Acknowledgement

This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, Contract No. 172033.

REFERENCES

[1] Lemke T. L., Williams D. A., Roche V. F., Zito S. W., Foye's Principles of Medicinal Chemistry, Lippincott Williams & Wilkins, 2013.
[2] Grujic M., Popovic M., Popovic G., Nikolic K., Agbaba D., Protolytic equilibria of sartans in micellar solutions of differently charged surfactants. Accepted for publication in J. Pharm. Sci.
[3] Becke A. D., J. Chem. Phys., 1993, **98**, 5648-52.
[4] Lee C., Yang W., Parr R. G., Phys. Rev. B., 1988, **37**, 785.
[5] Gaussian 09, Revision D.01, Frisch M. J. et al.
[6] Cossi M., Scalmani G., Rega N., Barone V., J. Chem. Phys., 2002, **117**, 43-54.
[7] Fleming I., Molecular orbitals and organic chemical reactions.Wiley-VCH: Weinheim, Germany, 2009.
[8] Floris F. M., Filippi C., Amovilli C., J. Chem. Phys. 2012, **137**, 075102.