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THEORETICAL STUDY OF THE ELECTRONIC STRUCTURE OF THE ORGANIC SALT OF KETOROLAC WITH MONOETHANOLAMINE

Abstract: The DFT method was used to analyze some quantum-chemical parameters of known compounds - ketorolac and monoethanolamine and their organic salt. And also an analysis of the surface of the electrostatic potential of the salt and its main components was carried out. Furthermore, non-covalent interactions of salt are visualized using MultiWFN and VMD program packages.
Key words: Ketorolac, monoethanolamine, organic salt, electronic structure, DFT, Non-covalent interactions, ORCA program
Language: English

Introduction

Ketorolac (5-benzoyl-1,2-dihydro-3H-pyrolo[1,2-a]pyrrole-1-carboxylic acid) is one of the compounds with high therapeutic value due to its strong anti-inflammatory and analgesic effect [1,2]. Organic salt of ketorolac with tromethamine is a well-known medical product marketed under the name "Ketorolac tromethamine". The bulk of the literature data is devoted to the study of biological activity and the analysis of ketorolac tromethamine by instrumental methods [2]. Ketorolac acts by inhibiting the bodily synthesis of prostaglandins. Ketorolac in its oral and intramuscular preparations is a racemic mixture of (S)-(–)- ketorolac, the active isomer, and (R)-(+)-ketorolac. One of the important features of the non-steroidal anti-inflammatory drug is the presence of a carboxylic acid moiety [3].

It is also known that monoethanolamine (MEA) is a good organic base and has hydrogen-bond donor sites. On the other hand, MEA is an essential component of cell membranes, closely resembling that of choline chemical behavior. Some complexes of ethanolamine with organic and inorganic compounds appear to be promising for optical second harmonic generation and electrooptical properties [4]. Therefore, the preparation of multicomponent organic

crystals from such multifunctional molecules as carboxylic acids and MEA is expected to display interesting networks and useful properties. With this background, a class of salts formed by MEA with carboxylic acids was prepared to investigate their supramolecular synthons.

However, there are few works on the chemical modification of ketorolac [5]. Recently published work by Zeinab Fathalla and co-workers [6] devoted to the crosslinking of ketorolac tromethamine with chitosan nanoparticles. A work of this type may allow the creation of ketorolac-containing fibers or other materials that will be useful in patient care in medical practice in the future. This requires a study of the salt-forming ability of ketorolac with various amines. In this paper, the ability of ketorolac to co-crystallize with various types of amines was tested using the example of ketorolac and monoethanolamine (MEA). Furthermore, an electronic structure of the organic salt was studied by DFT method [7]. Since the electronic structure plays an important role in the manifestation of the chemical and biological activity of compounds [8]. Therefore, theoretical parameters are fruitfully applied in the field of QSAR [9].

Materials and methods

Ketorolac, ethanolamine and the solvent used in this work are commercially available and were used without further purification. Crystals of ketorolac and ethanolamine suitable for diffraction work were grown from an aqueous solution of ethanolamine by slow evaporation.

Data for the crystal structure determinations were collected on an Oxford Diffraction Xcalibur-R CCD diffractometer (CuKa-radiation, λ=1.54184 Å, ω-scan mode, graphite monochromator) at 293 K [10]. The structure was solved and refined using program packages SHELXT [11] and SHELXL [12], respectively. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were inserted at calculated positions and constrained with isotropic thermal parameters.

DFT studies have been performed using hybrid method of Becke [13] with three parameters and correlation functions of Lee, Yang and Parr [14] (B3LYP) and by using Pople's large basis set including diffuse and polarization functions RHF/6-311++G(d,p)[19]. All calculations were carried out using ORCA 5.0 program package [15]. The geometry of organic salt has been taken from crystallographic information (cif) file and used for single point calculations. The results of calculations have been visualized by Avogadro [16], Multiwfn [17] and VMD [18] program packages.

Results and discussions.

Organic salt of Ketorolac with MEA is a neutral system consisting of two ionic molecules. But organic salt has a higher dipole moment (Table 1.). Optimizations of the salt structure by several methods bring to movement of a H atom of –NH_3^+ group to the oxygen atom of COO^- group. Therefore, a DFT study of electronic structure of organic salt was carried out on the basis of XRD data. Popl's basis set with diffuse function for H and heavy atoms are mostly used for H-bonded and ionic systems [7]. Therefore, it has been tested for single point calculation of the organic salt. Electrostatic potential (ESP) surface analysis was carried out to determine electron-rich and electron poor centers of the salt.
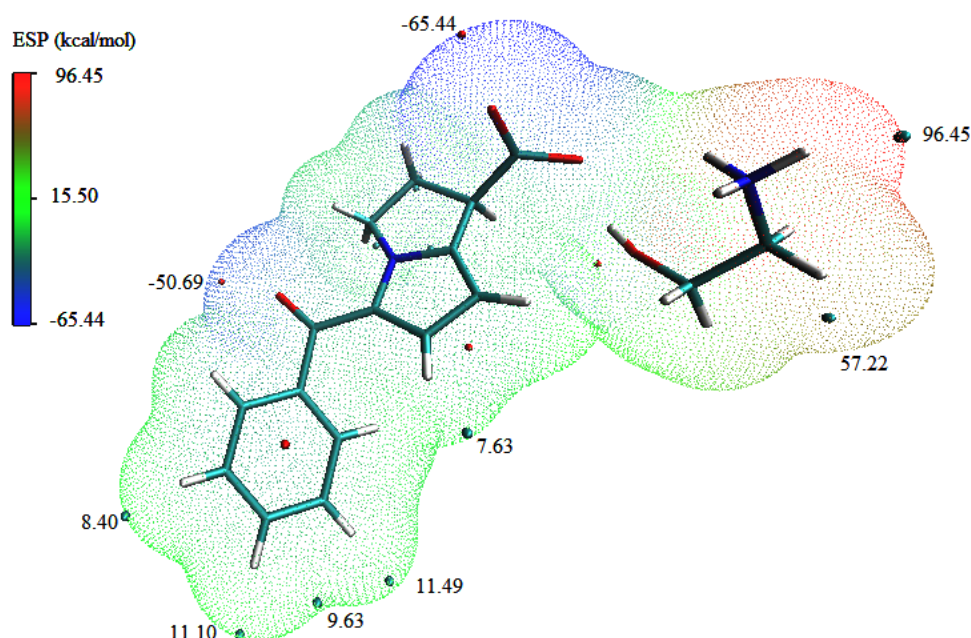

Fig.1. The ESP surface maxima and minima for organic salt.

ESP surface analysis has been carried out by Multwfn program package [17] on the basis of ORCA wave function file and the results visualized by VMD program package [15]. The ten ESP surface maxima (0.66, 1.54, 2.57, 7.63, 8.40, 9.63, 11.10, 11.49, 57.22 and 96.45 kcal/mol) and five minima (-17.83, -20.30, -29.00, -50.69 and -65.44 kcal/mol) have been determined around the structure of organic salt (Fig. 1). The largest maximum (96.45 kcal/mol) is located in vicinity of hydrogen atom of $-NH_3^+$ group. The next largest maximum (57.22 kcal/mol) is also located in MEA part (Fig. 1). On the contrary, the lowest (-65.44 kcal/mol) and the next lower (-50.69 kcal/mol) minima are in the ketorolac part of the organic salt. One of the minima is located in the vicinity of the oxygen atom (-29.00 kcal/mol) of MEA. The other two minima are localized on the surface of the aromatic rings. The most used quantum-chemical parameter in theoretical chemistry is the energy of the highest occupied (HOMO) and the lowest unoccupied MOs (LUMO), and also electron densities on them

[18]. These frontier orbitals play a driving role in orbital-controlled chemical reactions [19]. Besides, some indices can be determined on the basis of the energy of frontier MOs. The calculated quantum-chemical parameters (QCP) of ketorolac MEA complex are given in the table 1. To compare the obtained results of the complex, the data of the initial molecules were also included in the tabulated data. According to the tabular data, the level of HOMO of the organic salt is increased compared to the level of HOMO of the parent compounds. At the same time, the level of LUMO of organic salt is decreased relative to the level of LUMO of parent compounds. These changes led to a decrease in the energy gap between the HOMO and LUMO of the organic salt relative to those of the initial compounds, which indicates a relatively high reactivity of the product. The energy gap is an important parameter in chemistry that indicates the stability and reactivity of molecules [20]. The higher reactivity of the complex also confirms its dipole moment (Table 1).

Table 1. Quantum-chemical parameters of the organic salt.

| QCP	Complex	keterolac	MEA
E_{HOMO} (eV)	-5.13	-6.24	-6.53
E_{LUMO} (eV)	-1.86	-1.75	-0.37
$|\Delta E| = E_{HOMO} - E_{LUMO}$ (eV)	3.27	4.49	6.16
Ionization Potential, $I = -E_{HOMO}$ (eV)	5.13	6.24	6.53
Electron Affinity, $A = -E_{LUMO}$ (eV)	1.86	1.75	0.37
Electronegativity, $\chi = (I + A)/2$ (eV)	3.49	3.99	3.45
Chemical hardness, $\eta = (I - A)/2$ (eV)	1.63	2.25	3.08
Chemical potential, $\mu_p = -(I + A)/2$ (eV)	-3.49	3.99	3.45
Chemical softness, $\sigma = 1/(2\eta)$ (eV^{-1})	0.31	0.22	0.16
Electrophilicity index, $\omega = \mu_p^2/2\eta$ (eV)	3.73	3.55	1.93
Dipole moment, μ (Debye)	16.92	2.99	1.44
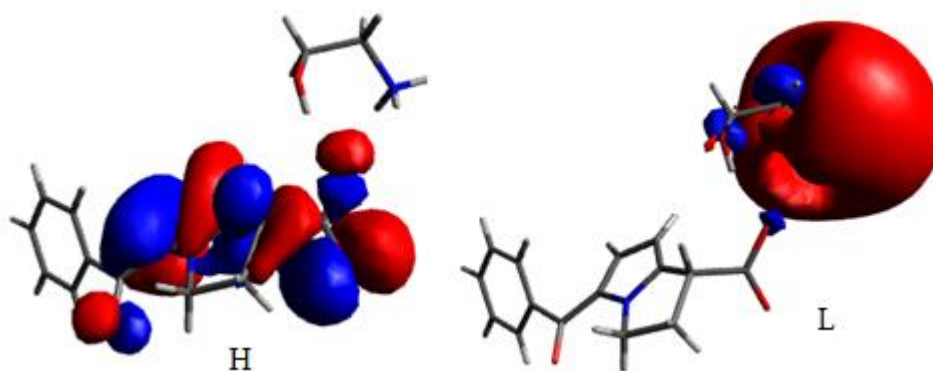
Fig.2. The electron densities on HOMO (H) and LUMO (L) of organic salt.

Orbital composition analysis with Mulliken partition shows the higher composition (47.76 %) of oxygen atom of carboxyl group in HOMO. And also, the compositions of C atoms of five-membering unsaturated rings in HOMO are equal to

approximately 35 %. The LUMO is located in MEA tart of the salt (Fig. 2).

In recent years, with the development of computing technologies, computer programs used in chemistry have been greatly developed. Among other things, programs have been developed that are used to

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calculate and visualize weak interactions in a molecular system based on the results of quantum chemical calculations. Non-covalent interactions (NCI) have been determined for many organic and coordination compounds [21]. Non-covalent interactions are represented as reduced density gradients (RDG) versus electron density multiplied by the sign of the second Hessian eigenvalue. The nature of specific interactions is highlighted in red-blue-green on the RDG color map. The strong attractive force (H-bond) is shown in blue and the strong repulsive force (steric effect) is shown in red. Weak interactions (van der Waals interactions) are highlighted with a green isosurface (Fig. 3). NCI analysis showed the presence of attractive (H-bond) and repulsion (VdW) forces between two molecules of organic salt [22].
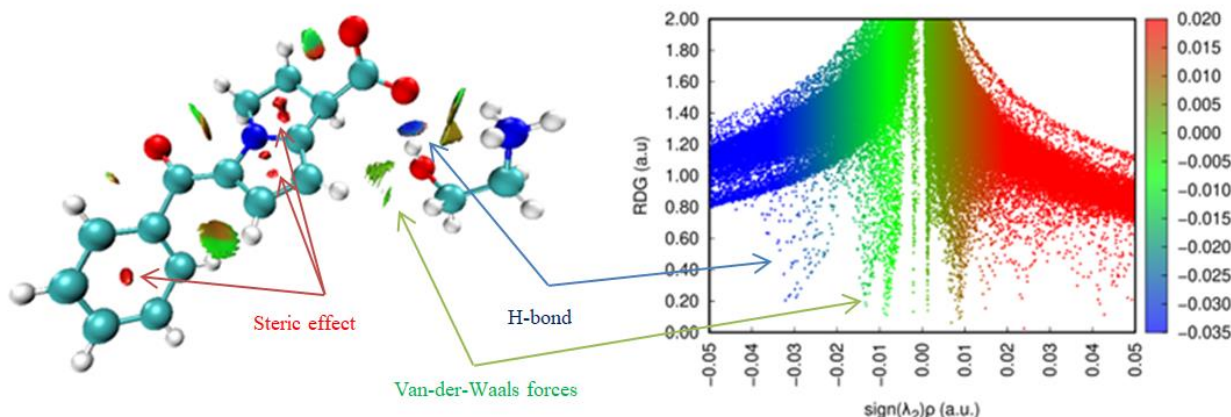

Fig.3. The NCI plot of organic salt and its color-filled RDG map.

Conclusions

So, a theoretical analysis of the electronic structure of the Ketorolac–MEA complex was carried out using a modern calculation method based on the density functional theory. The value of the dipole moment, energy gap and level of frontier MO's show a very high reactivity of the obtaining complex. The obtained theoretical data may encourage chemists to obtain new organic salts of ketorolac with various amines and to discover cross-linking with amine-containing fibers.

References:

1. Andreeva, N. S., & Skorodenok, E. V. (2015). *Problems of turnover of analgesics Disaster medicine: training, science and practice.* (p.121). Moscow. (in Russian).
2. Mallinson, T. (2017). A review of ketorolac as a prehospital analgesic (angl.) *Journal of Paramedic Practice.* London: MA Healthcare, pp. 522-526.
3. Loll, P. J., Picot, D., Ekabo, O., & Garavito, R. M. (1996). Synthesis and Use of Iodinated Nonsteroidal Antiinflammatory Drug Analogs as Crystallographic Probes of the Prostaglandin H2 Synthase Cyclooxygenase Active Site *Biochemistry*, 35,23, 7330-7340.
4. Nagalakshmi, R., Krishnakumar, V., Hagemann, H., & Muthunatesan, S. (2011). Polarized Raman and hyperpolarizability studies of Hydroxyethylammonium (L) tartrate monohydrate for quadratic nonlinear optics, *J. Mol. Struct,* 17-23.
5. Saenz-de-Viteri, M., Gonzalez-Salinas, R., Guarnieri, A., & Guiaro-Navarro, M. (2016). *Concepción. Patient considerations in cataract surgery - the role of combined therapy using phenylephrine and ketorolac (angl.) Patient Preference and Adherence*, 1795—1801.
6. Fathalla, Z.M.A., Khaled, K. A., Hussein, A.K., Alany, R.G., & Vangala, A. (2015). Formulation and corneal permeation of ketorolac tromethamine-loaded chitosan nanoparticles: *Drug Dev Ind Pharm*, 1520-5762.
7. Valadbeigi, Y. (2016). Effect of Mono- and Di-hydration on the Intramolecular Proton Transfers

and Stability of Cyanuric Acid Isomers: A DFT Study, *J. Chem. Sci,* 1237-1244.

8. Petelski, A.N., Peruchena, N.M., Pamies, S.C., & Sosa, G.L. (2017). Insights into the self-assembly steps of cyanuric acid toward rosette motifs: a DFT study, *J. Mol. Model.*, 263.

9. Hanwell, M.D., Curtis, D.E., Lonie, D.C., Vandermeersch, T., Zurek, E., & Hutchison, G.R. (2012). Avogadro: an advanced semantic chemical editor, visualization, and analysis platform, *J. Cheminform.*, 17.

10. (2009). *Xcalibur. Oxford diffraction Ltd. CrysAlisPro.* Version.1.171.33.44, 2009.

11. Sheldrick, G.M. (2015). SHELXT - integrated space-group and crystal-structure determination, *Acta Cryst.*, 3-8.

12. Sheldrick, G.M. (2015). Crystal structure refinement with SHELXL, *Acta Cryst.* 71, 3-8.

13. Becke, A.D. (1988). Density-functional exchange-energy approximation with correct asymptotic behavior. *Phys. Rev. A*, 3098-3100.

14. Lee, C., Yang, W., & Parr, G. (1988). Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density, *Phys. Rev. B.,* 785-789.

15. Neese, F. (2017). Software update: the ORCA program system, version 4.0, Wiley Interdisciplinary Reviews: *Computational Molecular Science*, 327.

16. (n.d.). Retrieved from http://avogadro.cc/

17. Lu, T., & Chen, F. (2012). Multiwfn: A multifunctional wavefunction analyzer. *J. Comput. Chem.*, 580-592.

18. Bendjeddou, A., Abbaz, T., Gouasmia, A., & Villemin, D. (2016). Molecular structure, HOMO-LUMO, MEP and Fukui function analysis of some TTF-donor substituted molecules using DFT (B3LYP) calculations, *Int. Res. J. Pure Appl. Chem.*, 1−9.

19. Miar, M., Shiroudi, A., Pourshamsian, K., Oliaey, A.R., & Hatamjafari, F. (2021). Theoretical investigations on the HOMO-LUMO gap and global reactivity descriptor studies, natural bond orbital, and nucleus-independent chemical shifts analyses of 3-phenylbenzo[d]thiazole-2(3H)-imine and its para-substituted derivatives: Solvent and substituent effects, *J. Chem. Res.*, 147-158.

20. Rauk, A. (2001). Orbitalinteraction. Theoryof Organicchemistry. *Wiley-Interscience,* 2001, 356.

21. Tan, S.L., Jotani, M.M., & Tiekink, E.R.T. (2019). Utilizing Hirshfeld surface calculations, non-covalent interaction (NCI) plots and the calculation of interaction energies in the analysis of molecular packing, *Acta Cryst.*, 308-318.

22. Laplaza, R., Peccati, F., Boto, R.A., Quan, C., Carbone, A., et al. (2021). NCIPLOT and the analysis of noncovalent interactions using the reduced density gradient. Wiley Interdiscip. Rev.: *Comput. Mol. Sci.,* 1497.

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