chemistry proceedings

MDPI

Proceeding Paper

Molecular Mobility of Different Forms of Ketoprofen Based on DFT Calculation Data †

K. A. Logacheva [1], A. V. Belushkin [1,2,3], P. A. Gergelezhiu [1], A. B. Eresko [2], S. N. Malakhov [3], E. V. Raksha [2,*], L. I. Savostina [1] and D. M. Chudoba [2]

[1] Institute of Physics, Kazan Federal University, Kazan, Russia; kalogacheva@stud.kpfu.ru (K.A.L.); avbelushkin@gmail.com (A.V.B.); polinagergelez@mail.ru (P.A.G.); savostina.kpfu@gmail.com (L.I.S.)
[2] Joint Institute for Nuclear Research, Frank Laboratory of Neutron Physics, Dubna, Russia; a_eresko77@mail.ru (A.B.E.); dmn@nf.jinr.ru (D.M.C.)
[3] National Research Center "Kurchatov Institute", Moscow, Russia; s.malakhov@mail.ru (S.N.M.)
* Correspondence: elenaraksha@jinr.ru
† Presented at The 28th International Electronic Conference on Synthetic Organic Chemistry (ECSOC 2024), 15–30 November 2024; Available online: https://sciforum.net/event/ecsoc-28.

Abstract: Ketoprofen is a representative of the group of non-steroidal anti-inflammatory drugs widely used in modern medical therapy. The intramolecular dynamics of ketoprofen is of particular importance, since the mobility of its main structural fragments will be one of the key factors determining the efficiency of drug binding to the enzyme. Investigations of such processes taking into account the acid-base properties of ketoprofen have not been carried out. DFT calculations for molecular, anionic and ion-pair forms of ketoprofen were performed at BP86/def2-TZVP level of theory using ORCA software. The intramolecular dynamics of the main structural fragments was investigated for the molecular, anionic and ion-pair forms of ketoprofen. The most stable conformers were revealed for all considered forms and barriers of intramolecular rotation were estimated. It was shown that the structures of the ketoprofen forms studied are labile but characterized by different mobility.

Keywords: ketoprofen; DFT calculations; intramolecular dynamics; vibrational frequencies; rotational barriers

Citation: Logacheva, K.A.; Belushkin, A.V.; Gergelezhiu, P.A.; Eresko, A.B.; Malakhov, S.N.; Raksha, E.V.; Savostina, L.I.; Chudoba, D.M. Molecular Mobility of Different Forms of Ketoprofen Based on DFT Calculation Data. *Chem. Proc.* **2024**, *6*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s): Name

Published: 15 November 2024

Copyright: © 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Ketoprofen (2-(3-benzoylphenyl)propionic acid) is a representative of the group of non-steroidal anti-inflammatory drugs (NSAIDs) widely used in modern medical therapy due to their anti-inflammatory, antipyretic, and analgesic activity [1,2]. In modern research practice ketoprofen is often used as a model compound to study the influence of various factors on their biological properties as well as to develop new methodologies for the identification of compounds of this class by various methods [1–5]. Determination of the detailed mechanism of action of ketoprofen requires studying the structure and dynamics of the molecule, including the configuration, charges and mobility of fragments. In this case, the intramolecular dynamics of ketoprofen will be of particular importance, since the mobility of its main structural fragments will be one of the key factors determining the efficiency of drug binding to the enzyme [6]. Investigations of such processes taking into account the acid-base properties of ketoprofen have not been carried out. Therefore, analysis of the intramolecular dynamics of ketoprofen, considering its possible forms—molecular, anionic and ion-pair (Figure 1) is of current interest. And the question how does a change in the electronic environment affect the structure, dynamics and properties of ketoprofen is still the matter of discussion.

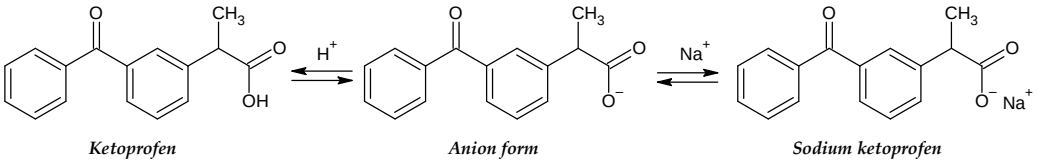


Figure 1. Chemical structure of the considered forms of ketoprofen.

In this paper we present results of the DFT-investigation of intramolecular dynamics of the main structural fragments of ketoprofene (Keto) in molecular and anion form. Contact ion pair of ketoprofen anion with sodium cation is also considered as a small cluster model of sodium ketoprofen (KetoNa).

2. Methods

All DFT calculations were performed using the ORCA 5.0.3 software package [7]. Molecular geometry optimization of the molecular, anionic and ion-pair forms of Keto followed by vibrational frequencies calculations as well as conformational analysis were carried out at BP86/def2-TZVP level of theory using the approximation of isolated molecule. Equilibrium configurations of stable conformers were applied for joint analysis of experimental and calculated data. Only S-enantiomers were considered in calculations for all Keto forms as they are responsible for Keto bioactivity in vivo [8]. Visualization of the stable conformers geometries as well as calculated IR-spectra of the Keto forms considered were performed with the Chemcraft 1.8 software [9]. Spectral convolution was performed with Gaussian functions having a full width at half-maximum of 10 cm^{-1}, and by setting the intensity at the band maximum equal to the calculated absolute infrared intensity.

Ketoprofen and sodium ketoprofen samples used in experimental investigations were from NERA group (FLNP, JINR) collection. All compounds were spectroscopy grade and used without additional purification.

Experimental infrared spectra of the Keto and its sodium salt were recorded at room temperature using a Nicolet iS50 IR Fourier spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) with a built-in ATR accessory. The spectral range was 4000–400 cm^{-1}.

3. Results and Discussion

The study of intramolecular dynamics of the main structural fragments was investigated for the molecular, anionic and ion-pair forms of Keto as an onset. In the structure of the ketoprofen molecule, three key fragments can be distinguished—an internal aromatic ring with two substituents—benzoyl fragment and a propionic acid residue. Their relative position determines the spatial configuration of Keto in all of its forms. Thus, torsion angles α (O^3-C^2-C^4-C^6), β (C^2-C^4-C^6-C^7), and γ (C^7-C^8-C^9-C^{10}) (Figure 2) were chosen as coordinates of internal rotation.

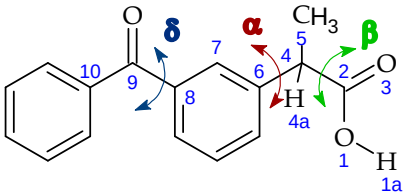


Figure 2. Atom numbering in Keto and its considered forms.

As a result of intramolecular rotation of main structural fragments in molecular, anion and ion pair forms of Keto the most stable conformers were revealed for all considered forms. Also, barriers for intramolecular rotation were estimated. It was shown that the structures of the Keto forms studied are labile but characterized by different mobility (Figure 3). For all forms of Keto, the benzoyl fragment is characterized by the lowest mobility

(estimated barriers are within 9–32 kJ/mol). The least labile is the anionic form of Keto (estimated barriers are within 11–32 kJ/mol). Dissociation of Keto leads to a decrease in the mobility of its structural fragments, and the formation of contact ion pairs reduces this effect. Structures of the most stable conformers for considered forms of Keto are presented in Figure 4. Some key parameters of molecular geometry and electron structure of them are listed in Table 1.

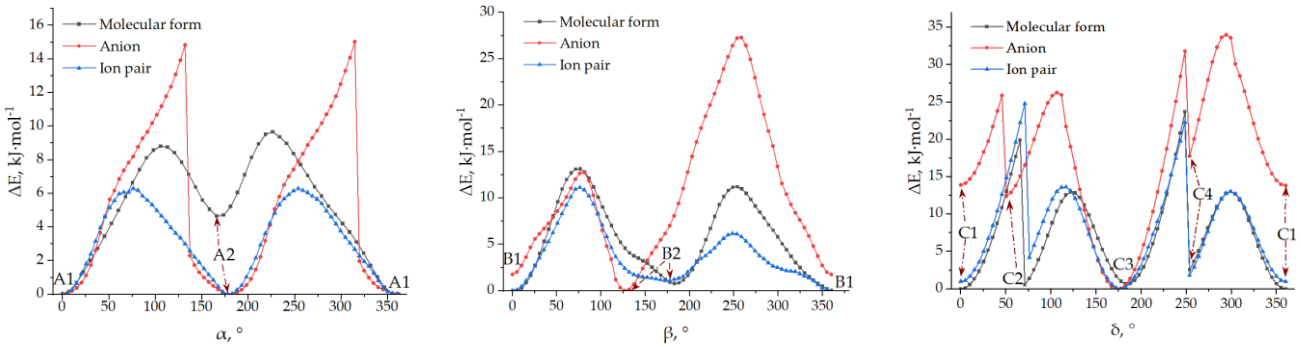
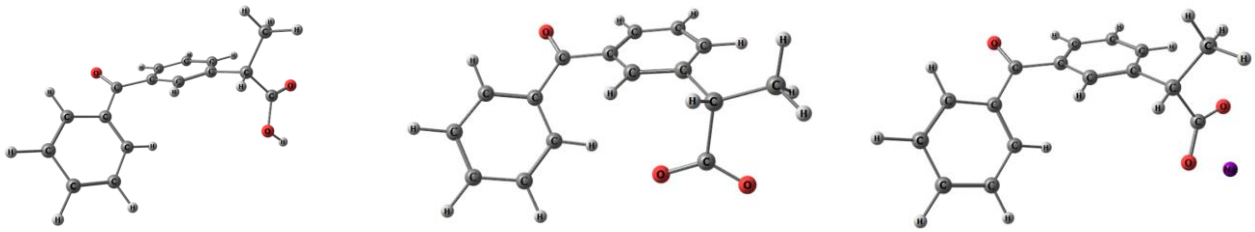


Figure 3. Curves of intramolecular rotation along with α, β and δ coordinate in molecular, anion and ion pair forms of Keto.



Molecular ***Anion*** ***Ion pair***

Figure 4. Structure of the most stable conformers for the Keto forms considered.

Table 1. Some key parameters of molecular geometry and electron structure of the most stable conformers Keto forms considered. Atom numbering corresponds to that on Figure 2.

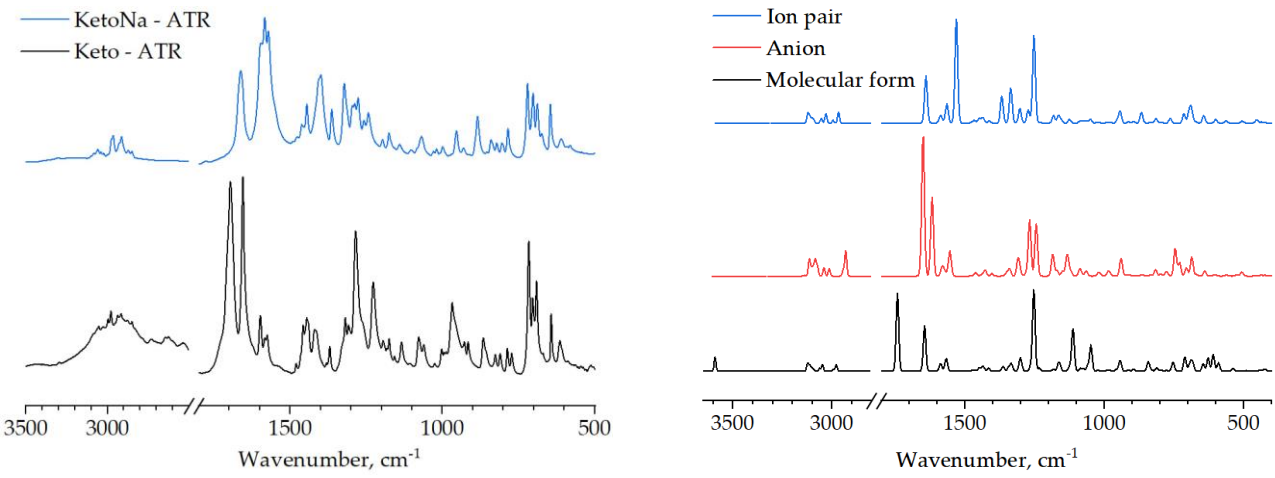
Parameters	Molecular	Anion	Ion Pair
C^2-O^3, Å	1.215	1.260	1.274
C^2-O^1, Å	1.365	1.250	1.276
C^2-C^4, Å	1.526	1.632	1.547
C^4-H^{4a}, Å	1.100	1.104	1.099
C^4-C^6, Å	1.536	1.526	1.537
C^4-C^5, Å	1.528	1.498	1.522
O^3-C^2-O^1, °	122.59	130.34	124.31
O^3-C^2-C^4, °	125.88	114.28	117.52
α (O^3-C^2-C^4-C^6), °	92.2	−54.3	−96.3
β (C^2-C^4-C^6-C^7), °	122.8	70.2	116.8
γ (C^7-C^8-C^9-C^{10}), °	−32.3	−27.3	−29.8
μ, D	3.07	7.22	9.19
E_{HOMO}, eV	−5.84	−1.02	−5.43
E_{LUMO}, eV	−2.93	0.06	−2.53
ΔE (LUMO-HOMO), eV	2.91	1.08	2.90
Q (O^1), e	−0.343	−0.421	−0.543
Q (O^3), e	−0.286	−0.454	−0.524
Δq (O^1-O^3), e	0.057	0.033	0.019

For the purpose of comparative analysis, experimental FTIR-ATR-spectra of Keto and KetoNa samples were measured (Figure 5a). They are in good agreement with the previously obtained data for these compounds [10,11]. For the most stable conformers of Keto in all forms considered, IR-spectra were calculated and visualized (Figure 5b). Joint analysis of the molecular modeling results and experimental data on vibrational frequencies for Keto and sodium ketoprofen was performed. A good agreement was obtained between the experimental and DFT-calculated vibrational frequencies of the objects under study (Equations (1)–(3)). It should be noted that in correlation (Equation (1)) for Keto signals of O-H groups were not considered. Since all calculations were performed in the isolated molecule approximation, the value for the O–H stretching obtained corresponded to that for the free hydroxide groups (3592 cm^{-1}), while the experimentally observed values corresponded to the O–H stretching of H-bonded hydroxide groups (3306 cm^{-1}). Moreover, bands at 2641 cm^{-1} and 2723 cm^{-1} in experimental spectra correspond most likely to the O–H stretching in dimers, that can be distinguished in crystalline structure of Keto [12]. Noticeable difference between the calculated (1743 cm^{-1}) and experimental (1697 cm^{-1}) frequencies of C=O stretching is also due to the intermolecular H-bonds. Therefore, for more complete description of the experimental vibrational spectra of Keto, further studies taking into account intermolecular interactions are necessary.

$$\text{Molecular form: } \nu_{exp} = (0.986 \pm 0.004)^{*}\nu_{DFT},\ R = 0.99953 \quad (1)$$

$$\text{Anion form: } \nu_{exp} = (0.963 \pm 0.011)^{*}\nu_{DFT},\ R = 0.99845 \quad (2)$$

$$\text{Ion-pair form: } \nu_{exp} = (0.954 \pm 0.007)^{*}\nu_{DFT},\ R = 0.99932 \quad (3)$$



(**a**) (**b**)

Figure 5. Experimental FTIR-ATR spectra of Keto and KetoNa (**a**) and DFT-calculated spectra for Keto in molecular, anion and ion-pair forms (BP86/def2-TZVP level of theory) (**b**).

When moving from the molecular form (Keto) to the salt form (KetoNa), the vibrations for the carbonyl group C=O disappear in the spectrum and those corresponding to the carboxylate anion appear. They correspond to 1583 cm^{-1} and 1400 cm^{-1} bands (antisymmetric and symmetric stretching vibrations, respectively) in the experimental spectrum of KetoNa. The vibrational frequencies obtained for the ion-pair form are in better agreement with the experimental IR-spectroscopy data for sodium ketoprofen as compared to the anion data (Equations (2) and (3)). Thus, ion-pair form of the Keto can be considered as a small cluster model of sodium ketoprofen.

4. Conclusions

Quantum chemical modeling of the intramolecular dynamics of the molecular, anionic and ion-pair forms of ketoprofen showed that by varying the electronic environment of its reaction center, it is possible to regulate the mobility of the main structural fragments of ketoprofen, that may contribute to its bioactivity. Correct results for describing the dynamics of its most labile salt form can be obtained using a combination of complementary methods of vibrational spectroscopy in combination with a cluster model for quantum chemical calculations. For more complete description of the experimental vibrational spectra of ketoprofen, further studies taking into account intermolecular interactions are necessary and they will be the next step of our investigations.

Author Contributions: Conceptualization, D.M.C. and E.V.R.; methodology, E.V.R., D.M.C. and L.I.S.; software, L.I.S.; validation, K.A.L., E.V.R. and L.I.S.; formal analysis, K.A.L. and P.A.G.; investigation, K.A.L., P.A.G., A.B.E., S.N.M. and E.V.R.; resources, D.M.C., A.V.B., S.N.M., A.B.E. and L.I.S.; data curation, K.A.L. and P.A.G.; writing—original draft preparation K.A.L. and E.V.R.; writing—review and editing, A.V.B., A.B.E., S.N.M., E.V.R., L.I.S. and D.M.C.; visualization, K.A.L. and S.N.M.; supervision, A.V.B. and D.M.C.; project administration, D.M.C.; funding acquisition, D.M.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data supporting the findings of this study are available within the paper and from the corresponding author upon request.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Tsoupras, A.; Gkika, D.A.; Siadimas, I.; Christodoulopoulos, I.; Efthymiopoulos, P.; Kyzas, G.Z. The Multifaceted Effects of Non-Steroidal and Non-Opioid Anti-Inflammatory and Analgesic Drugs on Platelets: Current Knowledge, Limitations, and Future Perspectives. *Pharmaceuticals* **2024**, *17*, 627. https://doi.org/10.3390/ph17050627.
2. Cunha, R.S.; Cruz, P.F.; Costa, T.; Almeida, Z.L.; Lima, M.E.F.d.; Serpa, C.; Chaves, O.A. Revisiting and Updating the Interaction between Human Serum Albumin and the Non-Steroidal Anti-Inflammatory Drugs Ketoprofen and Ketorolac. *Molecules* **2024**, *29*, 3001. https://doi.org/10.3390/molecules29133001.
3. Amin, M.O.; Al-Hetlani, E.; Lednev, I.K.; Detection and identification of drug traces in latent fingermarks using Raman spectroscopy. *Sci. Rep.* **2022**, *12*, 3136. https://doi.org/10.1038/s41598-022-07168-6.
4. Isik, I.B.; Tekin, N.; Sagdinc, S.G. The analyses of solvent effects on infrared spectra and thermodynamic parameters, Hirshfeld surface, reduced density gradient and molecular docking of ketoprofen as a member of nonsteroidal anti-inflammatory drugs. *J. Molec. Struct.* **2022**, *1250*, 131861. https://doi.org/10.1016/j.molstruc.2021.131861.
5. Rodríguez-Ortega, P.G.; Sánchez-Valera, M.; López-González, J.J.; Montejo, M. Fourier Transform Infrared Spectroscopy and Vibrational Circular Dichroism Assisted Elucidation of the Solution-State Supramolecular Speciation in Racemic and Enantiopure Ketoprofen. *Appl. Spectr.* **2022**, *76*, 216–227. https://doi.org/10.1177/00037028211060073.
6. Mastova, A.V.; Selyutina, O.Y.; Polyakov, N.E. Stereoselectivity of Interaction of Nonsteroidal Anti-Inflammatory Drug S-Ketoprofen with L/D-Tryptophan in Phospholipid Membranes. *Membranes*, **2022**, *12*, 460. https://doi.org/10.3390/membranes12050460.
7. Neese, F.; Wennmohs, F.; Becker, U.; Riplinger, C. The ORCA quantum chemistry program package. *J. Chem. Phys.* **2020**, *152*, 224108.
8. Aberg, G.; Ciofalo, V.B.; Pendleton, R.G.; Ray, G.; Weddle, D. Inversion of (R)- to (S)-ketoprofen in eight animal species. *Chirality* **1995**, *7*, 383–387. https://doi.org/10.1002/chir.530070513.
9. Zhurko, G.A. Chemcraft—Graphical Program for Visualization of Quantum Chemistry Computations. Ivanovo, Russia, 2005. Available online: https://chemcraftprog.com (accessed on 1 September 2024).
10. Liu, L.; Gao, H. First principles study on the molecular structure and vibrational spectra of ketoprofen. *Spectrochim. Acta A Mol Biomol. Spectrosc.* **2012**, *97*, 329–339. https://doi.org/10.1016/j.saa.2012.06.021.
11. de Oliveira Junior, H.; Borges, B.A.; Barbosa, T.W.L.; Batista, A.; Braga, M.T.L.; de Araújo, M.B.; Bonfilio, R. A New Crystalline Ketoprofen Sodium Salt: Solid-State Characterization, Solubility, and Stability. *J. Pharm. Sci.* **2022**, *111*, 1674–1681. https://doi.org/10.1016/j.xphs.2021.11.011.
12. Briard, P.; Rossi, J.C. Ketoprofene. *Acta Cryst. C* **1990**, *46*, 1036. https://doi.org/10.1107/S0108270189004968.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.