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# *Conformational behaviour, intra-molecular hydrogen bonding, gas phase acidities and hydrolysisstudy of fibrate-type antihyperlipidemic drugs*

Badania konformacji, wewnątrzcząsteczkowego wiązania wodorowego, kwasowości w fazie gazowej oraz termodynamiki hydrolizy leków z grupy fibratów

## INTRODUCTION

The fibrates are - besides the statins - the most important drugs used nowadays in the treatment of hyperlipidemic diseases. A comprehensive recent review on their use for more than 40 years is available for an interested reader [2]. Although they were introduced in 1970s and are still successfully used worldwide, the mechanism of their action was completely unknown to 1990s.

The current knowledge about them [3] connects the fibrate action with activation of PPAR-gamma receptors, which modulates expression of some particular genes. However, many questions remain still unanswered and other mechanisms of their action are possible.

There are very few papers related to pharmacophore hypotheses of fibrates. There was suggested [1], that beta-sitosterol contains similar three-dimensional similarity to the fibrates. Also, some structural analogy with 7-hydroxy-benzopyran-4-one derivatives [7] and benzocoumarin derivatives [9] is taken into the account. No clear and exact pharmacophore model was suggested and no one did a full docking study to any active site with molecular explanation.

Concerning the topicality of the subject and the hope of introducing new better agents with the same mechanism of action we have decided to perform a theoretical study of these drugs, with the main concentration of the active fragment. This subject is almost absent in the literature. The only one DFT study with a fibrate was done by Le et al. [6]. They modelled fenofibrate using time dependent density functional theory (TDDFT) method at the B3LYP/6-31G(d), B3LYP/6-311G(d,p) and B3LYP/6-311++G(d,p) levels in order to predict the HOMO-LUMO band in the UV spectrum in various solvents.

From chemical point of view, fibrates are derivatives of fibric (2-methyl-2-phenoxypropionic) acid and this compound can be treated as a model system for the theoretic investigation, as the Ph-O-C(-CH)(-CH)-COOH moiety is believed to be responsible for the action. Historically, first drug from this group was clofibric (4-chlorofibric) acid. It was used in the free form and as the ethyl ester — clofibrate. Other esters, such as: etofibrate, simfibrate, pirifibrate, ronifibrate

or theofibrate undergo hydrolysis in vivo, releasing free clofibric acid. The further research on fibrates focused on different para-substituents, improving pharmacokinetic parameters and lowering side effects. Bezafibrate contains an N-ethylbenzamide substituent, whereas ciprofibrate posesses dichlorcyclopropyl group. 4-Chlorobenzoyl substituent with isopropyl estrification resulted in fenofibrate, which undergoes hydrolysis in vivo to active fenofibric acid (also directly manufactured and used as drug in several countries).

The purpose of this study is to model conformational preferences of the active fragment of fibrates, estimate the energy of ionisation of this fragment, look closely to intramolecular hydrogen bond and estimate hydrolysis thermodynamics of estrified fibrates. The results can be helpful in further investigation of action of these drugs.

## EXPERIMENTAL

All calculations were performed using Gaussian 09 under GNU/Linux at computational cluster, mainly at B3LYP/6-31+G(d) level of theory. Additional conformational calculations were performed under Molecular Operating Environment (MOE) 2007.09 on single PC under Windows XP.

## RESULTS AND DISCUSSION

*Conformational study on fibric acid and its anion*

As the fibric acid is the active moiety of fibrates, the first stage of the investigation was a careful conformational study of free (unsubstituted at 4th position) fibric acid. This compound has 3 rotatable bonds; additionally the carboxyllic hydrogen can be also rotated. A rigid screening PES scan at HF/STO-3G level was performed, identifying all local minima of obtained multidimensional matrix. Additionally, the most possible careful systematic search of conformational space was done inside MOE. This resulted in about 54 geometries supposed to be local minima during rigid PES scan and 16 conformations inside MOE. All of them were then subjected to geometry optimization at B3LYP/6-31+G(d) level. Fourteen unique stable geometries were identified, two symmetrical ones and six existing in stereo pairs. Their geometries are depicted in Figure 1, ordered by increasing energy. The other initial geometries minimized to one of these 14.

One supposed minimum identified with AM1 scan was found to be saddle point with one imaginary frequency (conformer A with carboxyllic hydrogen pointing to opposite side).

The most important distances and angles are summarized in Table 1. Since there is no crystallographic reference to any fibrate in non-estrified form, the crystallographic data of fenofibrate [5] is presented as the only one available reference. Our results are in good agreement with study of Le et al. [4], who used the same method for fenofibrate to predict its UV spectra. Some isomers were reoptimized at 6-311++G(d,p) level, but, similar to the cited study, the changes of bond lengths and angles were negligible, so 6-31+g(d) basis set was assumed to be satisfactory level of theory to perform geometry optimization.

Analyzing these geometrical parameters one can conclude that conformers A and C contain a hydrogen bond between carboxyllic hydrogen and phenoxy oxygen. The COO…H bond length is

substantially longer in these conformers. The frequencies of O-H stretching (Table 3) are also visibly lowered and their intensity is also several times increased. The distance between hydrogen and phenoxy oxygen is equal to 1.8586 Å and 2.0177 Å, respectively.

The most stable conformer possesses also the shortest length of CO…OH bond (as increasing of COO…H bond length causes approaching the oxygen to the carbon). In general, conformers with lower energy have the phenoxy oxygen located closer to the phenyl ring plane (B and D), however hydrogen bond in A and C is stronger and distorts this relation. The dipole moment of the hydrogen-bonded conformers is visibly higher than the others.

Only 3 stable geometries of fibric acid anion were identified - one symmetric and almost exactly the same as conformer A (and denoted as A) and one asymmetric, very similar to conformer B (denoted as B), existing also in two mirrored orientations (Figure 2). The energy differences between them at B3LYP/6-31+G(d) level are $\Delta\Delta E$=27.20 kJ/mol, $\Delta\Delta H$=27.49 kJ/mol and $\Delta\Delta G$=23.53 kJ/mol.

*Conformational study of bezafibrate and its anion*

Bezafibrate has 7 rotatable bonds and its conformational space is quite large for reasonable rigid PES scan. We have performed thorough systematic conformational search inside MOE, identifying 13 conformers existing in mirrored stereoconfigurations (26 total geometries). Four conformers with lowest energy possess a hydrogen bond between the carboxyllic hydrogen and amide oxygen, resulting in whole molecule being twisted. The most stable conformer without hydrogen bond contains fibric fragment analogous to conformer A of fibric acid. The geometry of para-substituent corresponds to the most stable geometry of 4-Chloro-N-(phenylethyl)-benzamide found in systematic search in MOE.

The most stable conformer with hydrogen bond and most stable one without it are presented in Figure 3. The distance between the carboxyllic hydrogen and amide oxygen is equal to 1.8318 Å. The vibrational frequency is lowered to 3411.58 $cm^{-1}$ with strongly increased intensity 736.23, whereas the conformer without hydrogen bond vibrates at 3673.87 $cm^{-1}$ with intensity equal to 55.83.

Conformational search of bezafibrate anion inside MOE identified 117 geometries, majority of them existing in stereo pairs. The most stable geometry (Figure 3, Table 2), optimized at B3LYP/6-31+g(d) level, possesses two intramolecular hydrogen bonds between carboxyllic oxygen and two hydrogens: amide hydrogen and one benzene hydrogen. The NH stretching vibrational frequency is lowered to 3448 $cm^{-1}$ and has increased intensity equal to 262.97. The C-H stretching frequency is lowered to 3159 $cm^{-1}$ with strong intensity 145.08. In comparison, the same frequencies in bezafibrate (conformer A) are respectively: 3619 $cm^{-1}$ with intensity 18.55 and 3189 $cm^{-1}$ with intensity 10.4. The lengths of these bonds are: 2.2247 Å and 2.1839 Å, respectively.

The other geometries of bezafibrate anion form one or two intramolecular bonds between carboxyllic oxygens and some hydrogens in second benzene ring. Several geometries without hydrogen bond were found, but as they have the highest (and much higher from others) energy, we have not made further optimization. The second stable geometry, optimized at B3LYP/6-31+G(d) (Figure 3D) have visible two weak hydrogen bonds between carboxyllic group and two hydrogens of the second ring. The distances are: 2.2579 Å of bond closer to amide group and 2.4730 Å of bond closer to chlorine. The C-H stretching frequencies are respectively: 3157 $cm^{-1}$ with intensity 53.73

and 3199 $cm^{-1}$ with intensity 18.43. The opposite hydrogens stretch both at 3220 $cm^{-1}$ with intensities 10.4. The energetic differences between two most stable bezafibrate anion geometries at B3LYP/6-31+G(d) level are $\Delta E$=0.81 kJ/mol, $\Delta H$=0.01 kJ/mol and $\Delta G$=-2.89 kJ/mol (the difference of G has an opposite sign due to change of entropy).

Concluding, the geometry of bezafibrate, both in free and anionic form, is strongly affected by intramolecular hydrogen bonds.

*Geometries of clofibric acid, ciprofibrate and fenofibric acid*

The substitution of fibric acid with chlorine in 4 (para-) position creates a molecule of clofibric acid, an active form of majority of fibrate-type drugs. The chlorine atom has no visible influence on distances and angles of fibric moiety. Scanning conformational space under MOE identified analogous geometries to fibric acid. We have optimized geometry of two most stable conformers (analogous to A and B). The geometry is almost exact, but substitution of chlorine lowers significantly the dipole moment.

The ciprofibrate molecule has 2,2-dichlorcyclopropyl substituent at para- position. There is the only one optimal geometry of this substituent relative to unsubstituted benzene ring (2,2-dichlorcyclopropylbenzene has only one stable geometry). Incorporating this substituent to fibric acid results in two minima with a difference in energy around 0.6 kJ/mol. We have used deeper minimum for further modelling. Again the geometry and conformational preferences of fibric acid moiety was unaffected.

The fenofibric acid molecule has 4-chlorbenzoyl substituent attached at 4 (para-) position. Analogously, diphenylmethanone molecule possesses only one stable geometry but there are two minima in fenofibric acid, being mirrored along ring plane with similar energy difference. Also deeper minimum of this substituent was used in the modelling. The distances of fibric moiety are almost unaffected by these substituents.Energies of two most stable conformers of each substance are given in Table 1.

*Proton affinities and hydrolysis enthalpy of fibrates*

The proton affinities of fibrates were calculated as enthalpy ($\Delta H$) of reaction: HA -> H+ + A- at 298.15 K. The enthalpy of the proton was assumed to be standard value 5/2 RT (6.20 kJ/mol). The values of proton affinities are similar and they are collected in Table 3.

Thermodynamic parameters of hydrolysis of clofibrate (as ethyl ester of clofibric acid) and fenofibrate (as isopropyl ester of fibric acid) were calculated and collected in Table 4. The low values confirm easy hydrolysis of these drugs in vivo to active free acids.

## CONCLUSIONS

All above calculations were done in the gas phase and one can ask about influence of water to fibrate molecule behaviour. Fibrates have very weak predicted solubility in water (Table 4), no strict experimental data are available. There can be suspected, that water has almost negligible influence to their geometry and conformational preferences. It was confirmed by Le et al. [6] at B3LYP level with

various basis sets and also by our trials with several PCM solvation models. Although symmetric conformer A with intramolecular hydrogen bond is real global minimum of PES (potential energy surface in conformational space), there can be suspected that fibrates act biologically at asymmetric conformation due to low energy difference of conformers and inpresence of symmetrical conformation in case of bezafibrate. The another issue is, that systems with intramolecular hydrogen bonding are modelled with lower accuracy on their energetic properties, and the chosen method and basis set can make strong difference [8]. Our trials at various higher levels does not revert the energetic preference of conformers, but no sure conclusion can be drawn here. Considering anion as active form, there is no clear and evident answer either. Symmetric anion geometry has visibly lower energy, but it is also non-present in the case of bezafibrate. The intramolecular hydrogen bonding is present in most conformations of bezafibrate, whereas other drugs have also low energy conformers without it.

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Table 1. Distances and angles of fibric acid conformers and its anion (B3LYP/6-31+g(d))

| | A | A- | B | B- | C | D | E | F | G | H | Ref. [] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Distances | | | | | | | | | | | |
| C… COOH | 1.5483 | 1.5914 | 1.5420 | 1.5943 | 1.5476 | 1.5435 | 1.5439 | 1.5387 | 1.5386 | 1.5632 | 1.5517 |
| C…OOH | 1.2092 | 1.2624 | 1.2137 | 1.2599 | 1.2082 | 1.2086 | 1.2097 | 1.2134 | 1.2066 | 1.2059 | 1.2071 |
| CO…OH | 1.3436 | 1.2478 | 1.3502 | 1.2520 | 1.3508 | 1.3596 | 1.3602 | 1.3497 | 1.3629 | 1.3580 | 1.3378 |
| COO…H | 0.9805 | — | 0.9761 | — | 0.9791 | 0.9768 | 0.9762 | 0.9760 | 0.9756 | 0.9712 | |
| PhO…C | 1.4636 | 1.4758 | 1.4367 | 1.4695 | 1.4586 | 1.4320 | 1.4353 | 1.4500 | 1.4408 | 1.4469 | 1.4362 |
| Ph…OC | 1.3898 | 1.3584 | 1.3757 | 1.3529 | 1.3905 | 1.3760 | 1.3885 | 1.3845 | 1.3831 | 1.3899 | 1.3603 |
| Angles | | | | | | | | | | | |
| HC-C-CH | 111.77 | 111.13 | 110.58 | 110.64 | 110.89 | 110.33 | 111.14 | 111.26 | 111.15 | 110.71 | |
| C-C=O | 121.59 | 111.94 | 124.63 | 115.28 | 123.45 | 125.06 | 126.71 | 124.31 | 126.96 | 122.28 | 122.90 |
| C-C-OH | 116.27 | 118.01 | 112.44 | 114.92 | 114.77 | 112.28 | 111.20 | 112.97 | 110.65 | 118.16 | 111.25 |
| C-O-H | 107.56 | — | 107.85 | — | 106.83 | 106.92 | 106.69 | 106.71 | 111.28 | | |
| Ph-O-C | 111.37 | 120.84 | 112.02 | 123.19 | 113.29 | 111.76 | 112.56 | 112.02 | 111.69 | 110.66 | 121.03 |
| Dihedrals | | | | | | | | | | | |
| Ring plane to PhO-C | 87.64 | 86.94 | 13.25 | 8.05 | 48.11 | 13.81 | 77.14 | 88.72 | 86.99 | 84.71 | |
| Ring plane to Ph-O | 3.67 | 5.03 | 1.58 | 0.25 | 3.32 | 1.28 | 3.57 | 4.37 | 4.37 | 3.70 | |
| O-C-C=O | 179.98 | 179.99 | 145.50 | 160.77 | 132.20 | 31.17 | 6.27 | 139.64 | 0.02 | 65.05 | |

Table 2. Distances and angles of bezafibrate conformers and its anion (B3LYP/6-31+g(d))

| | B1 | B2 | B1- | B2- |
|---|---|---|---|---|
| Distances | | | | |
| C…COOH | 1.5530 | 1.5431 | 1.5902 | 1.5864 |
| C…OOH | 1.2154 | 1.2092 | 1.2535 | 1.2584 |
| CO…OH | 1.3389 | 1.3581 | 1.2678 | 1.2570 |
| COO…H | 0.9911 | 0.9767 | — | — |
| PhO…C | 1.4746 | 1.4317 | 1.4924 | 1.4704 |
| Ph…OC | 1.3839 | 1.3750 | 1.3742 | 1.3589 |
| Angles | | | | |
| HC-C-CH | 111.54 | 114.36 | 111.38 | 110.32 |
| C-C=O | 123.51 | 125.21 | 115.75 | 115.26 |
| C-C-OH | 112.38 | 112.07 | 116.74 | 116.02 |
| C-O-H | 110.96 | 107.03 | — | — |
| Ph-O-C | 118.48 | 123.44 | 116.53 | 121.28 |
| Dihedrals | | | | |
| Ring plane to PhO-C | 84.21 | 12.21 | 89.50 | 35.13 |
| Ring plane to Ph-O | 6.42 | 1.51 | 12.32 | 6.96 |
| O-C-C=O | 88.16 | 28.25 | 98.55 | 32.75 |

Table 3. Energies, enthalpies, Gibbs free energies (at B3LYP/6-31+G(d) level in kJ/mol, lowest absolute energies in hartrees) of investigated conformers. The carboxyllic hydrogen vibrational data is also given as hydrogen bond detector

| | ΔE | ΔH | ΔG | Frequency | Intensity | Dipole moment |
|---|---|---|---|---|---|---|
| Fibric acid | | | | | | |
| A | -613.787086 | -613.773857 | -613.826981 | 3593 | 225.23 | 5.25 |
| B | 0.82 | 0.60 | 3.24 | 3683 | 65.50 | 0.60 |
| C | 2.46 | 2.26 | 4.06 | 3619 | 113.35 | 3.95 |
| D | 5.90 | 5.58 | 7.04 | 3673 | 61.30 | 2.49 |
| E | 6.21 | 5.43 | 5.56 | 3679 | 61.41 | 2.54 |
| F | 11.25 | 10.48 | 8.71 | 3683 | 64.14 | 1.93 |
| G | 14.37 | 13.57 | 13.14 | 3689 | 70.14 | 2.99 |
| H | 32.62 | 31.32 | 29.54 | 3741 | 47.02 | 4.49 |
| Bezafibrate | | | | | | |
| B1 | -1551.600088 | -1551.599144 | -1551.677736 | 3411 | 736.23 | 4.59 |
| B2 | 1.40 | 1.40 | 12.63 | 3673 | 55.83 | 3.97 |
| Ciprofibrate | | | | | | |
| Ci1 | -1649.610938 | -1649.609994 | -1649.677895 | 3598 | 247.20 | 4.75 |
| Ci2 | 1.03 | 1.03 | 1.13 | 3683 | 66.84 | 3.02 |
| Clofibric acid | | | | | | |
| C1 | -1073.377848 | -1073.376904 | -1073.433304 | 3601 | 230.18 | 3.29 |
| C2 | 1.12 | 1.12 | 0.89 | 3682 | 67.99 | 2.53 |
| Fenofibric acid | | | | | | |
| F1 | -1417.676120 | -1417.675176 | -1417.747816 | 3607 | 246.64 | 3.05 |
| F2 | 1.43 | 1.42 | 0.39 | 3672 | 70.34 | 5.11 |

Table 4: Proton affinities and average ALOGPS 2.1 solubilities (in most stable conformation, at B3LYP/6-31+g(d) level, in kJ/mol) of investigated substances

| | ΔH | pS |
|---|---|---|
| Fibric acid | 1410.10 | 1.79 |
| Clofibric acid | 1393.48 | 2.72 |
| Bezafibrate | 1338.02 | 4.21 |
| Ciprofibrate | 1399.86 | 4.20 |
| Fenofibric acid | 1383.11 | 4.55 |

Table 5: Enthalpies and free energies (at B3LYP/6-31+G(d) level in kJ/mol) of hydrolysis of estrified fibrates (pro-drugs)

| | ΔH | ΔG |
|---|---|---|
| Clofibrate | 6.34 | 4.05 |
| Fenofibrate | 9.12 | 1.05 |

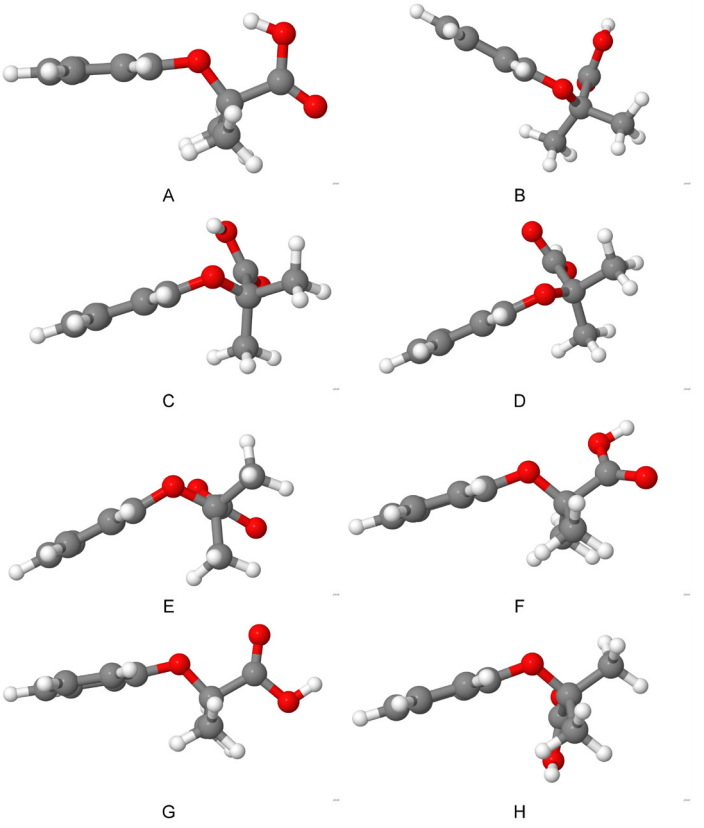


Fig. 1. The stable conformers of fibric acid, ordered by increasing energy. Structures A, G an H are symmetrical. The others can exist in two mirrored stereoconfigurations

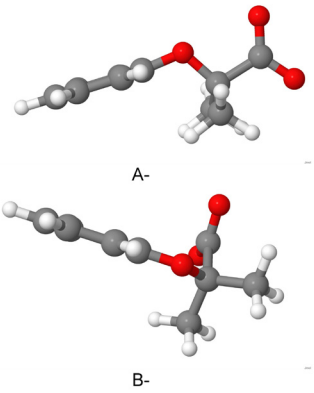


Fig. 2. The most stable conformers of fibric acid anion, ordered by increasing energy. Structure A is symmetrical. The second one can exist in two mirrored stereoconfigurations

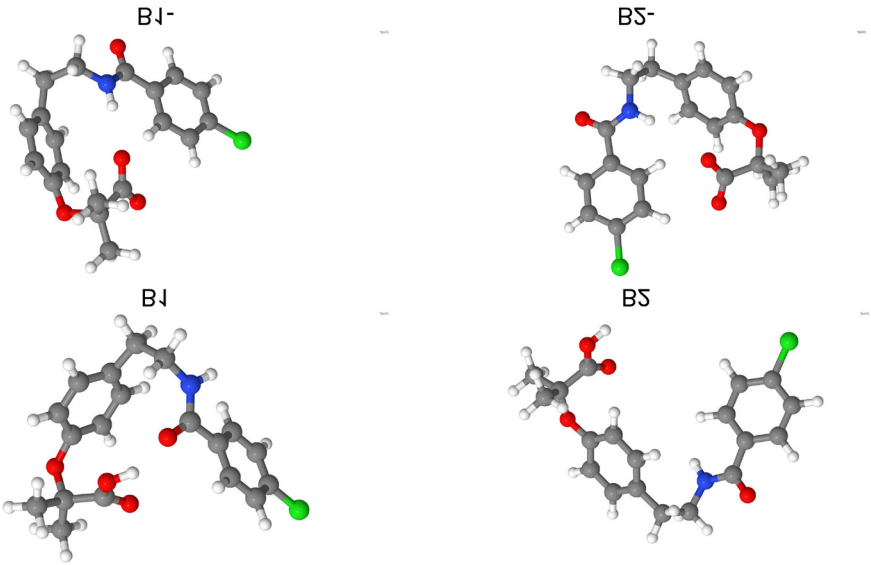

Fig. 3. The most stable conformers of bezafibrate and its anion

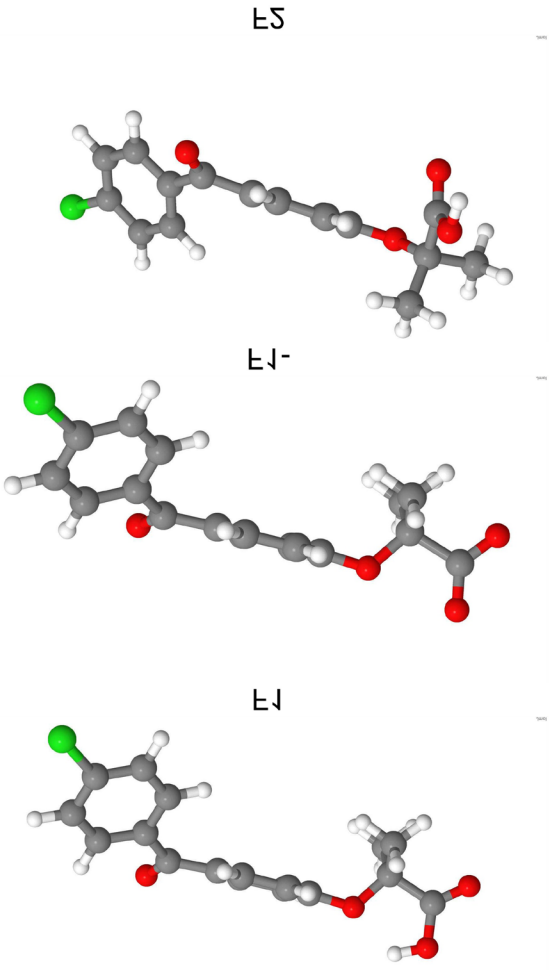

Fig. 4. The most stable conformers of fenofibric acid and its anion

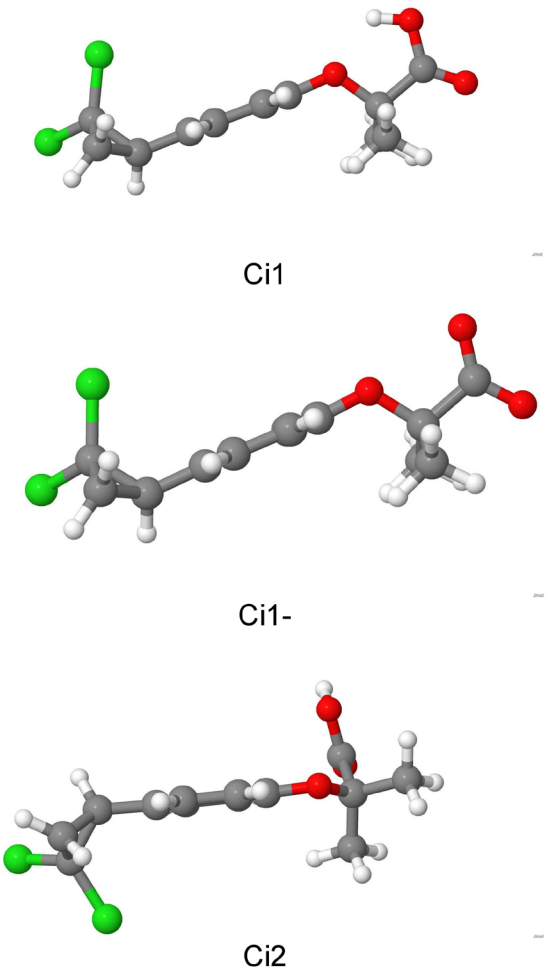


Fig. 5. The most stable conformers of ciprofibrate and its anion

## SUMMARY

A theoretical study on fibrate-type drugs in gas phase is presented. All stable conformations of fibric acid (as common and active moiety of these drugs) were identified and optimized at B3LYP/6-31+g(d) level. The lowest energy is observed in the case of symmetric conformer with intramolecular hydrogen bond between carboxyllic hydrogen and phenoxy oxygen. Similar energy is possessed by asymmetric conformation without any hydrogen bond, existing in two mirrored stereoconfigurations. The fibric anion can exist in two conformations only, also symmetrical and asymmetrical. Substituents present at para- position in clofibric acid, fenofibric acid and ciprofibrate

do not influence on the conformational behaviour of active fibric acid nor anion moiety. They have two rotational minima around benzene ring, one visibly deeper. However, the substituent influences geometry significantly in the case of bezafibrate, forming hydrogen bonds between amide hydrogen or second benzene ring hydrogens and carboxyllic oxygen. Bezafibrate anion possesses hydrogen bonds between carboxyllic oxygens and second benzene ring hydrogens. Although geometries of bezafibrate without any hydrogen bond can exist, they have much higher energy and they cannot be suspected in real life. Additionally, gas phase acidities (proton affinities) and hydrolysis enthalpies of clofibrate (to clofibric acid) and fenofibrate (to fenofibric acid) were calculated.

*Keywords:* fibrates, conformational analysis, hydrogen bonding

## STRESZCZENIE

W pracy przedstawiono badania obliczeniowe w fazie gazowej leków z grupy fibratów. Wszystkie stabilne konformacje kwasu fibrowego (jako aktywnej struktury wszystkich leków z tej grupy) zostały zoptymalizowane na poziomie B3LYP/6-31+g(d). Najniższą energię zaobserwowano w przypadku konformacji symetrycznej z wiązaniem wodorowym pomiędzy tlenem grupy fenoksylowej a wodorem grupy karboksylowej. Zbliżoną energię otrzymano dla asymetrycznego konformeru bez wiązania wodorowego, istniejącego w dwóch lustrzanych odbiciach. Anion kwasu fibrowego istnieje tylko w dwóch konformacjach – jednej symetrycznej i jednej asymetrycznej. Podstawniki w pozycji para- w kwasie klofibrowym, fenofibrowym i ciprofibracie nie mają wpływu na zachowanie konformacyjne aktywnego fragmentu. Podstawniki te mają dwa minima rotacji wokół wiązania z pierścieniem benzenowym, jedno o wyraźnie niższej energii. Natomiast w przypadku bezafibratu podstawnik ma istotny wpływ na konformacje, tworząc wiązania wodorowe między wodorem grupy amindowej lub wodorami drugiego pierścienia, a tlenem C=O grupy karboksylowej. Chociaż istnieją geometrie bezafibratu bez wiązań wodorowych, mają wyraźnie wyższą energię i ciężko się ich spodziewać doświadczalnie. Dodatkowo obliczono kwasowości w fazie gazowej i entalpie hydrolizy klofibratu i fenofibratu do odpowiednich kwasów.

*Słowa kluczowe:* fibraty, analiza konformacyjna, wiązanie wodorowe