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Study of the Stability, Solubility and Geometry of the Complex of Inclusion β-CD with the Nimesulide by Computer Chemistry Methods †

Ekaterina S. Barteneva [1,*], Pavel Y. Andreev [2] and Elena V. Grekhneva [1]and Kirill S. Efanov [3]

[1] Department of Chemistry, Kursk State University, Kursk 305000; grekhnyovaev@yandex.ru
[2] Department of Oncology, Federal State Budgetary Educational Institution of Higher Education "N.N. Burdenko Voronezh State Medical University" of the Ministry of Health of the Russian Federation, Voronezh 394036, Russia; pawelandrejew@yandex.ru
[3] Department of Thermophysics, Institute of Nuclear Physics and Technology, National Research Nuclear University MEPhI, Kashirskoe Highway 31, Moscow 115409, Russia; kir.efanoff@yandex.ru
* Correspondence: yekaterina.barteneva@bk.ru
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Abstract: During the study, a molecular system was modeled: nimesulide, β-cyclodextrin, inclusion complex. The use of the Gaussian 16W software package allowed to optimize geometry and determine the thermochemical characteristics of molecular systems without considering solvent. And also in water media, accounted for by the polarized continuum model (PCM). To confirm the accuracy of the geometry of the β-cyclodextrin molecule, a structural alignment of 46 β-cyclodextrin molecules, accessible by a corresponding search query in the RCSB database, was performed. The RSMD values of carbon and oxygen atom deviations, as well as the total number of atoms aligned were calculated. This calculation showed a complete conformational coincidence of the designed by us β-cyclodextrin structure with the RCSB database structures. This ensures the correct approach to subsequent calculations involving this structure. Quantum-mechanical modeling of the relationship was carried out in several stages with a gradual complexity of the basic set. Using the hybrid method of functional density B3LYP and 6-31G(d). At the end of the calculation stage, on the surface of the studied complex, the potential energy of several minimal elements is detected. This means that there are several conformational forms of the molecular system with different likely. The change in potential energies of the investigated compounds, caused by application to optimized in vacuum molecules of the PCM model, allowed to determine values of the solvatization energies. The greater magnitude of these values in the complex under consideration indicates its better solubility in water compared to nimesulide.

Keywords: cyclodextrins; conformations; inclusion complexes; solubility; computer modeling

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1. Introduction

The inclusion complexes are a little-known part of the sub-molecular chemistry. The importance of studying host-guest complexes is constantly increasing due to the need for improved delivery systems, and the development of new encapsulated forms of biologically active compounds. Most theoretical assumptions about complexation mechanisms are based on the results of quantum-chemical calculations. Recently, the study of these objects is gaining popularity in molecular dynamics methods. These approaches allow to get an idea of the course of the process of complexation, the presence of sterile difficulties, deformations of molecules in the course of action. Computational methods are currently extremely well-known, as they help to look at the usual experiment from a different angle

and find ways of creating new high-efficiency technologies. In turn, we designed the β-cyclodextrin (β-CD) and ni-mesulid (Nim), as well as the proposed inclusion complex (β-CD/Nim). Optimization of geometry of structures was carried out with the help of Gaussian16W program. Geometry of the RMSD-trajectory is confirmed by analysis of RMSD-trajectories [1–3]. The inclusion of the complex has been evaluated for its stability and solubility based on the PCM model. The water solubility of nimesulide is <0.02 mg/mL, which has a low bioavailability of the drug. The possibility of including nimesulide in the β-CD molecule will be assessed to identify methods for obtaining samples with improved permeability [4,5].

2. Computational Chemistry Methods Used

The modeling of the molecular systems under consideration was performed using the software package GAUSSIAN16W. Quantum-chemical calculation was performed using the hybrid method of B3LYP functional density in the base 6-31G(d). The validation of the β-CD structure was done with the PyMOL program and the RCSB database. Solubility is approached through the polarized continuum model (PCM)[6,7].

3. Results and Discussion

3.1. Optimization of the Geometry of the Carrier Molecule β-CD

Quantum-mechanical modelling of all connections was done in stages with gradual complexity of the base set to reduce the computer time and accuracy of results. Thus, the use of the hybrid method of B3LYP and 6-31G(d) basis at the end of the calculation stage resulted in the detection on the surface of the potential energy of the studied complex of two minimums, what it can say about the existence of several conformational forms of data of molecular systems, formed with different probabilities [8,9].

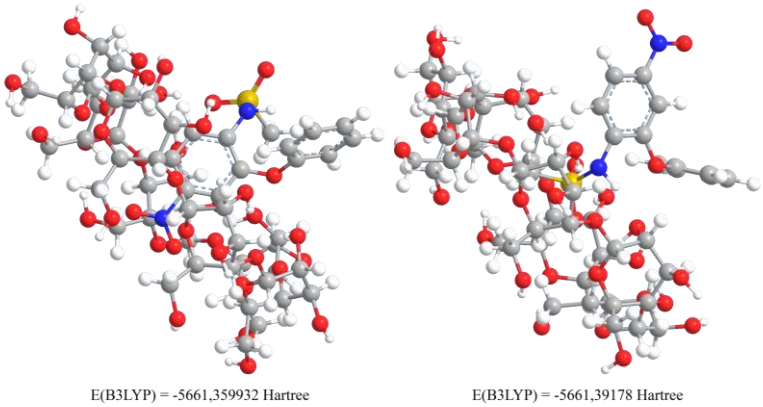

Figure 1. The conformational forms of the complex under consideration, corresponding to the two minima on the surface of the potential energy of the system, found during calculation/.

3.2. RMSD Trajectory Analysis

Using the RCSB database, 46 β-SD molecules were found.All structures, optically divided by X-ray diffraction and NMR spectroscopy, were aligned with the molecule obtained in our Gaussian 16W as a reference for comparison with experimental PBDs. RSMD values of carbon and oxygen atom deviations were calculated, as well as the total number of atoms levelled. Results are presented in Table 1.

Table 1. RSMD calculation of deviations.

№	PDB ID	Method	Resolution, Å	RMSD, Å (Atoms of 77)	Atoms Aligned of 77
1	1VFO	X-ray	2.81	0.768	73
2	2V8L	X-ray	1.8	0.767	73
3	2Z1K	X-ray	2.3	0.630	74
4	3CGT	X-ray	2.40	0.000	77
5	3JUV	X-ray	3.12	0.879	73
6	5E6Z	X-ray	1.878	0.759	73
7	6JEQ	X-ray	1.802	0.846	73

In the end, a structure with PDB ID 3CGT was found that has full conformity with the standard. This structure shows complete absence of atom aberration (RMSD = 0.0), with all atoms aligned (77 atoms to 77 atoms of the reference). Three more structures (PDB IDs: 2Z1K, 5E6Z and 2V8L) have RMSD 0.630–0.767Å and alignment 73–74 out of 77 atoms (Figure 2).

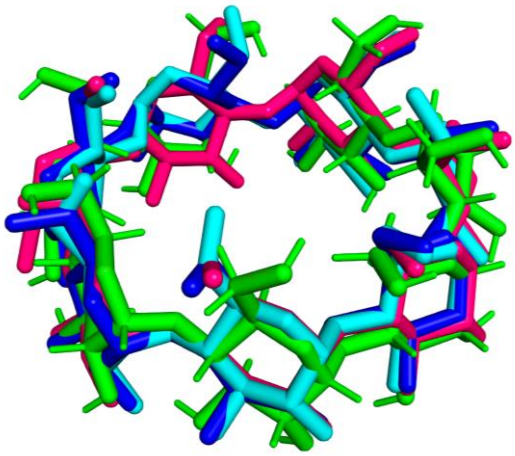

Figure 2. Alignment of the geometry of the β-CD molecule. Color highlighted: green—the pattern obtained in Gaussian, blue—5E6Z, pink—2Z1K, blue—yem-2V8L, orange—3CGT (not visible as it corresponds fully to the pattern obtained in Gaussian).

The data obtained show that the β-cyclodostrin geometry from Gaussian is correct, corresponding to structures defined expressively.

3.3. Taking into Account the Effects of the Concatenation

The use of the Gaussian 16 software package has allowed to optimize geometry and determine the thermochemical characteristics of molecular systems both without the solvent, and in water media accounted for by polarized continuum model (PCM). The change in potential energies of the studied compounds caused by application to optimized in vacuum molecules of the PCM model allowed to determine values of the covalent energies, the larger size of which in the complexes under consideration indicates their better solubility in water compared to the neissulide [10].

Table 2. Results of calculation in the program Gaussian 16W.

Element Name	Solvation Accounting	S, kcal/mol*K	Sum of Electronic and Thermal Free Energies, Hartree/Particle	Sum of Electronic and Thermal Enthalpies, Hartree/Particle	E(B3LYP), Hartree	Solvatation Energy, Hartree
β-CD	-	383.432	−4273.99089	−4273.80871	−4275.10458	0.0696683
	PCM	386.579	−4274.06354	−4273.87986	−4275.17425	
Nim	-	143.736	−1386.05638	−1385.98809	−1386.2509	0.01683559
	PCM	144.997	−1386.07425	−1386.00536	−1386.26774	
Complex №1	-	491.886	−5660.034603	−5659.800892	−5661.359932	0.08395511
	PCM	498.4	−5660.12313	−5659.88632	−5661.44389	
Complex №2	-	488.694	−5660.06363	−5659.83143	−5661.39178	0.08010679
	PCM	501.576	−5660.15194	−5659.91363	−5661.47189	

The solvent-based free energy value of Gibbs per-sectional molecular systems still confirms their thermodynamic possibility

4. Conclusions

Recent advances of chemical sciences open up new promising opportunities, including modelling molecular systems by computer software with further investigations beyond a wet lab. Among a broad range of computational approaches, quantum-mechanical calculations provide a better understanding of geomagneic structure, solvatization energies and thermodynamic features of interest compounds.

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