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КОНФОРМАЦИОННОЕ ПОВЕДЕНИЕ ГИДРАЗОНА, ПРОИЗВОДНОГО ПИРИДОКСАЛЬ-5-ФОСФАТА И ИЗОНИАЗИДА

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Гидразоны, производные пиридоксаля либо пиридоксаль-5-фосфата или гетероциклических гидразидов, представляют интерес, благодаря своей потенциальной биологической активности и возможности использования в качестве сенсоров на ионы металлов. Эти свойства гидразонов могут зависеть от конформационных равновесий молекулы, поскольку наиболее стабильный конформер может отличаться от формы с наибольшим сродством к биомолекуле либо иону металла. В настоящей работе депротонированный гидразон, производный пиридоксаль-5-фосфата и изониазида (PLP-INH^{3-}), исследован методами квантовой химии. Для этого гидразона возможны 3 различных вращения, приводящих к 8 конформерам, однако 4 из них, полученные при вращении пиридинового кольца остатка изониазида, являются вырожденными. С использованием теории функционала плотности (B3LYP/6-311++G(d,p)) были оптимизированы геометрические характеристики различных невырожденных конформеров вращения данного гидразона (различающихся взаимной ориентацией карбонильной группы остатка изониазида и атома кислорода в положении 3 остатка PLP), а также оценены активационные барьеры переходов между ними. Обсуждаются изменения в энергии и строении конформеров, а также переходных состояний. Количественный QTAIM (Quantum Theory of Atoms in Molecules) анализ был проведен с целью проверки наличия внутримолекулярных водородных связей. Формы гидразона, способные образовывать комплекс с ионами металлов, отличаются от наиболее устойчивых (по величинам полной энергии) конформеров. Была проведена предварительная оценка биологической активности гидразона PLP-INH^{3-}, а также молекулярный докинг для гидразона и киназы G-белок сопряженного рецептора. Определена предпочтительная конформация для связывания лиганда с активным сайтом киназы.

Ключевые слова: пиридоксаль-5-фосфат, изониазид, гидразон, конформер, активационный барьер

CONFORMATIONAL BEHAVIOR OF HYDRAZONE DERIVED FROM PYRIDOXAL 5'-PHOSPHATE AND ISONIAZID

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The hydrazones derived from pyridoxal or pyridoxal 5'-phosphate and heterocyclic hydrazides are of interest due to their potential biological activity and metal sensing properties. These characteristics of hydrazones could be dependent on the conformation equilibria of molecule since the most stable conformer could differ from the one with the highest affinity towards biomolecule or metal ion. In the present contribution, deprotonated hydrazone formed by pyridoxal 5'-phosphate and isoniazid (PLP-INH^{3-}) was studied by means of quantum chemistry. Three rotations leading to eight conformers are possible for this hydrazone; however, four of those species obtained by rotation of pyridine ring of isoniazid residue are degenerated. The geometry of different non-degenerated rotation conformers of the hydrazine (differing by the mutual arrangement of carbonyl group of the isoniazid residue and oxygen in 3'-site of PLP moiety) was optimized using density functional theory (B3LYP/6-311++G(d,p)). Activation barriers were evaluated. Changes in energy and geometry of conformers as well as transition states are discussed. Quantitative QTAIM (Quantum Theory of Atoms in Molecules) analysis was performed in order to check the intermolecular hydrogen bonding existence. The species capable of forming the complex with the metal ions differs from the most stable (according to the total energy values) conformer. The preliminary prediction of biological activity of PLP-INH^{3-} hydrazone and the docking for the hydrazone and G-protein-coupled receptor kinase were performed and the preferable conformation for ligand binding to the kinase active site was found.

Key words: pyridoxal 5'-phosphate, isoniazid, hydrazone, conformer, activation barrier

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INTRODUCTION

Hydrazones of different composition and structure are of great interest for researchers due to the wide range of their possible applications. They could be used in analytical chemistry as sensors for anions and metal ions [1, 2], antibacterial and antifungal agents [2, 3], catalysts [3], molecular machines brakes and switches [1], which are sensitive to the changes in pH and UV-irradiation. Hydrazone derived from pyridoxal 5'-phosphate and isoniazid (PLP-INH) is the closest analog of pyridoxal isonicotinoyl hydrazone, the low-toxic chemical, which has been found to possess the membranotropic [4], antioxidant [5], demetalling towards iron [6], copper [7, 8] properties. PLP-INH hydrazone has been previously found to bind cobalt(II,III), nickel(II) ions [9] as well as to inhibit the copper(II)-mediated oxidation of ascorbate [10].

Either coordination behavior or biological activity of hydrazone may depend on the conformation equilibria in the solution since the species may differ significantly in total energy and capability of binding the metal ions or biomolecules. Conformation free-

dom for the studied hydrazone is associated with the different molecular fragments ability to rotate around single (or partially double) bonds (Fig. 1).

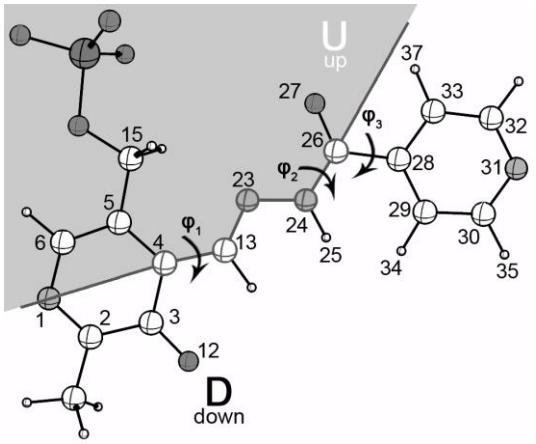

Fig. 1. Structure of PLP-INH^{3-} (DU conformer). Arrows show possible rotations leading to the different conformers
Рис. 1. Структура PLP-INH^{3-}. Стрелки указывают возможные направления вращения, приводящие к разным конформерам

The φ_3 rotation (Fig. 1) could possibly make the same structure, however, it has to be confirmed. Mutual arrangement of 12 oxygen in the site 3 of pyridoxal 5'-phosphate residue and carbonyl group of isoniazid residue relative to the conditional line passing through the hydrazone molecule is used for the different conformers naming (Fig. 1). For example, in the scheme of the DU conformer (Fig. 1), atom O_{12} is located below (D – down) the chain C_{13}-N_{23}-N_{24}-C_{26} and atom O_{27} is located above (U – up) the chain. Other possible structures are DD, UD, UU.

Therefore, the aim of the present contribution is to study the different conformers of PLP-INH formed as a result of the rotation φ_1, φ_2, φ_3. Quantum chemical calculations (DFT) were chosen as the method of preliminar study since it would allow finding the differences between conformers, which, in turn, could help to chose the experimental method for further investigations. The fully deprotonated hydrazone (PLP-INH^{3-}) was studied only since these species could be predominant in the biological fluids basing on the lg K_a values [11]. *E*-isomer has been considered only.

CALCULATIONS METHODS

The quantum chemical calculations were performed using Gaussian09 software [12] within the framework of density functional theory. The functional of B3LYP and basis set of 6-311G++(d,p) [13] were employed in order to optimize the geometry of different PLP-INH^{3-} species and transition states. The suggested ground and transition states were verified by frequency analysis after optimization. The solvent (water) was set within the framework of CPCM approach [14] in all cases. In order to study the internal rotations φ_1, φ_2, φ_3, potential energy surface (PES) scan was done using changing of dihedral angles N_{23}-C_{13}-C_4-C_5 (φ_1), N_{23}-N_{24}-C_{26}-O_{27} (φ_2), N_{24}-C_{26}-C_{28}-C_{29} (φ_3, Fig. 1) from -180° to 180° with the step of 10°. Quantitative QTAIM (Quantum Theory of Atoms in Molecules) analysis was performed using AIMAll software package [15].

RESULTS AND DISCUSSION

The example of the pathway of the PLP residue rotation (φ_1) is given (Fig. 2). Relative values of the dihedral N_{23}-C_{13}-C_4-C_5 in the transition states are close to (±)100°. The PLP moiety in the DU(-33) ground state could possibly freely oscillate in the range of dihedral values of (-20°÷20°) since the energy required for these variation do not exceed 2.5 kJ mol^{-1} (kN_AT, when T = 298.15 K).

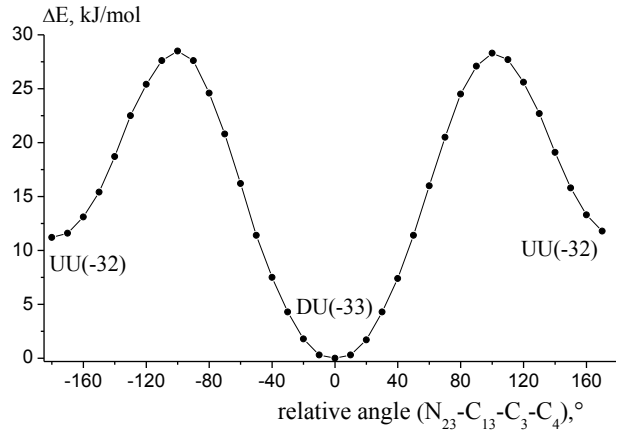

Fig. 2. Potential energy function of φ_1 rotation in the PLP-INH^{3-} hydrazone
Рис. 2. Функция потенциальной энергии вращения φ_1 в гидразоне PLP-INH^{3-}

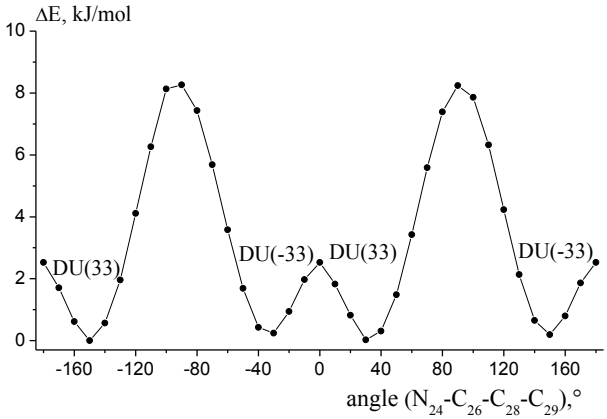

Fig. 3. Potential energy function of φ_3 rotation in the PLP-INH^{3-} hydrazone
Рис. 3. Функция потенциальной энергии вращения φ_3 в гидразоне PLP-INH^{3-}

The rotation of pyridine residue of isoniazid (φ_3) could occur via two different transition states. The lesser one (*ca*. 2.5 kJ mol^{-1}) is characterized by relative angle of N_{24}-C_{26}-C_{28}-C_{29} close to 0°; pyridine ring of INH moiety is almost perpendicular towards the rest of the hydrazone molecule in the another one (*ca*. 8.2 kJ mol^{-1}). Therefore, the preferable pathway is through the planar transition state.

During the DU↔DD and UU↔UD (φ_2) rotations, the search for the transition states is complicated. First, the inversion of partly sp^3 hybridized N_{23} atom occurs. Another issue is the simultaneous φ_3 value alteration during scanning the φ_2 dihedral angle. Therefore, DU↔DD and UU↔UD processes pathways could probably include more than one transitions state.

The results of quantum chemical calculations including optimized geometries and total energies related towards the most stable structure are given (Fig. 4).

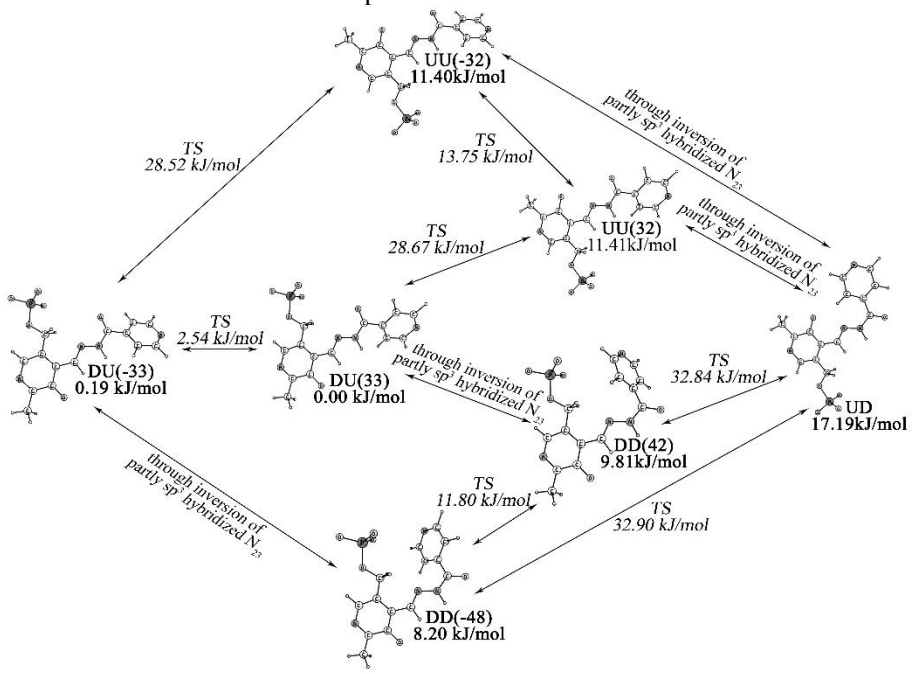

Fig. 4. Conformation equilibria of PLP-INH^{3-} hydrazone. Energies of ground states (bold) and changes in total energies of activations of the transfer between species (TS, italic) are related towards the most stable conformer

Рис. 4. Конформационные равновесия гидразона PLP-INH^{3-}. Энергии основных состояний (полужирный) и изменения полной энергии активации конформационных переходов (TS, курсив) приведены по отношению к наиболее устойчивому конформеру

Table

Key parameters of the different conformers of PLP-INH^{3-} hydrazone

***Таблица 1.* Основные параметры различных конформеров гидразона PLP-INH^{3-}**

Parameter	DU (-33)	DU (33)	UU (-32)	UU (32)	DD (-48)	DD (42)	UD
ΔE* (kJ mol^{-1})	0.19	0.00	11.40	11.41	8.20	9.81	17.19
ΔG* (kJ mol^{-1})	0.00	1.07	11.04	11.12	5.85	11.52	19.43
Bond lengths, Å							
C_4-C_{13}	1.443	1.443	1.444	1.444	1.445	1.444	1.445
C_{13}-N_{23}	1.295	1.295	1.297	1.297	1.294	1.295	1.294
N_{23}-N_{24}	1.376	1.376	1.378	1.378	1.382	1.383	1.370
N_{24}-C_{26}	1.360	1.360	1.359	1.359	1.356	1.357	1.361
C_{26}-O_{27}	1.229	1.229	1.230	1.230	1.235	1.236	1.238
C_{26}-C_{28}	1.506	1.506	1.506	1.506	1.502	1.501	1.511
Dihedral angles,°							
φ_1	-179.0	-179.5	-0.2	-0.7	170.3	172.3	0
φ_2	179.0	-178.2	178.6	-178.3	-11.6	8.6	-180.0
φ_3	-33.0	32.5	-32.2	32.3	-47.8	42.0	0

* - related towards the total or free energy of the most stable conformer

* - по отношению к полной либо свободной энергии наиболее устойчивого конформера

DU species (see Fig. 1 for naming principle) are the most stable among all possible ones. The molecule of DU form is non-planar due to the steric repulsion between hydrogens of pyridine ring of isoniazid residue (H_{34}) and –NH- group (H_{25}). Therefore, two stable structures are possible differing by φ_3 value; they are marked as DU(φ_3) (See Fig. 4). These species are equal in energy; the geometry of the molecular fragment between two pyridine moieties is also the same (Table 1). Activation barrier of DU(-33)↔DU(33) transition is low (ΔE = ~2.5 kJ/mol) allowing quick exchange.

Analogously, UU species are also capable of forming two structures with different φ_3 value. The rotation of the PLP residue around C_3-C_{13} bond (conformational transition DU→UU) leads to the decreasing of the distance between methylene and –CH= group protons (4.0 Å vs. 2.2 Å) which could be responsible for the slightly increased total energy compared with DU structures. Geometry parameters of the hydrazone central fragment differ insignificantly in the DU and UU species (Table 1).

Activation barrier for the UU(-32)↔UU(32) transition is similar to that of DU φ_3 rotation since both cases the molecule goes through the planar structure with the same distance between protons of pyridine residue and –NH- group (1.953 Å).

In the DD species, pyridine ring of isoniazid residue is close to the methylene phosphate moiety of PLP fragment. It results in more strong steric repulsion and, thus, bigger non-planar distortion ($|\varphi_3|$>40°). Besides, due to the fact that –CH_2- group does not lie exactly within the same plane with pyridine residue of pyridoxal 5'-phosphate, the conformers differing by φ_3 value become non-equivalent energetically in relatively significant degree (ΔE 8.20 *vs.* 9.81; ΔG 5.85 *vs.* 11.52 kJ mol^{-1}). It also increases the rotation barrier of the DD(-48)↔DD(42) transition, since the angle C_{26}-C_{28}-C_{29} has to be increased in the transition state compared with ground states (~126.0 *vs.* ~123.0).

The DD species geometry of the central part of hydrazone molecules changes somewhat more significantly (Table 1, compare DU and UU *vs.* DU and DD).

Finally, UD structure is the least stable among all studied species and form no conformers due to φ_3 rotation. Though planar, it is not completely free from steric hindrance. The interaction between methylene and –CH= as well as –CH= and –NH- protons could probably increase its total and free energy (see Table 1). The shortening of the N_{23}-N_{24} bond as well as the lengthening of the C_{26}-C_{28} bond are notable changes in the geometry of hydrazone comparing with DU structures (Table 1). According AIM calculations the charge q(H_{34}) in UD structure is increased as compared with other conformers (UD>DD>UU≈DU: +0.15→+0.07→ +0.05→+0.05). In case of UD conformer we found the bond critical points (BCPs) corresponding to hydrogen bonds $N_{23}\cdots H_{34}$ and $O_{12}\cdots H_{34}$. The values of electron density $\rho(r)$ in BCPs are 0.022 ($N_{23}\cdots H_{34}$) and 0.010 ($O_{12}\cdots H_{34}$) a.u. The values of Laplacian of electron density $\nabla\rho(r)$ are 0.081 ($N_{23}\cdots H_{34}$) and 0.033 ($O_{12}\cdots H_{34}$) a.u. For hydrogen bonds values of $\rho(r)$ and $\nabla\rho(r)$ in BCP should lie in the range from 0.002 to 0.035 a.u. and from 0.024 to 0.139 a.u., respectively [16].

The transitions between φ_1 and φ_2 conformers could be concluded to occur relatively fast since the values of rotation barriers are low (20-30 kJ mol^{-1}). The barriers of φ_3 rotations do not exceed 10 kJ mol^{-1}.

The analysis of conformational behavior of hydrazones is related to their coordination properties. The X-ray diffraction study of Cu(II) and Fe(III) complexes with pyridoxal isonicotinoyl hydrazone ans 2-hydroxy-1-naphtaldehyde isonicotinoyl hydrazone [7] have shown these ligands to be tridentate. They interact with metal ions through the oxygen atoms of carbonyl and hydroxyl groups as well as nitrogen of –CH=N- group. The complexes of ML and ML_2 composition could be formed this way.

Therefore, all the groups coordinating the metal ion should be oriented 'up' in order to make the complex formation possible. Among the studied conformers, the UU species are the only ones capable of metal binding. However, they are relatively unstable structures in the solution as it follows from the total energies calculations (Fig. 2). Thus, the PLP-INH^{3-} hydrazone should exist predominantly as a mixture of DU species in the solution. There are the costs of the energy required for the DU↔UU transition. Alteration of the aromatic substituents structure on either end of central chain (C_{13}-N_{23}-N_{24}-C_{26}) may reduce or increase the contribution of conformation change and, thus, influence the stability of metal-hydrazone complex.

The studies on the conformational behavior of the hydrazone relate also to its binding ability towards the protein molecule. The preliminary prediction of biological activity of PLP-INH hydrazone performed using PASS Online [17, 18] has shown it being the potential inhibitor of the G-protein-coupled receptor kinase (GRK) inhibitor with P_a = 0.975; P_i = 0.001 (P_a – probability of being active, P_i – probability of being inactive). This property of hydrazone is important since the inhibition of adrenergic receptors kinase is recognized by some authors as promising strategy of heart failure treatment [19]. The 4-pyridinyl hydrazone moiety is known to act by competitive inhibition of ATP, binding to the kinase active site [20].

In order to figure out, which conformation could probably exist in the complex with protein, we have performed docking using the optimized geometries of different conformers of hydrazone (as ligand) and crystal structure of GRK (as macromolecule) taken from [20] as input data. The scanning area was set to include the following amino acids residues, Phe202, Lys220, Asp335, and Met274 since they are the part of the kinase active site [20]. The AutoDock Vina software was used for docking [21].

The results are similar for all seven initial conformers. Each of them can form nine binding modes with the binding affinity varying within the range of (-32)÷(-27) kJ mol^{-1}. The calculated structure of the most stable complex is given (Fig. 5).

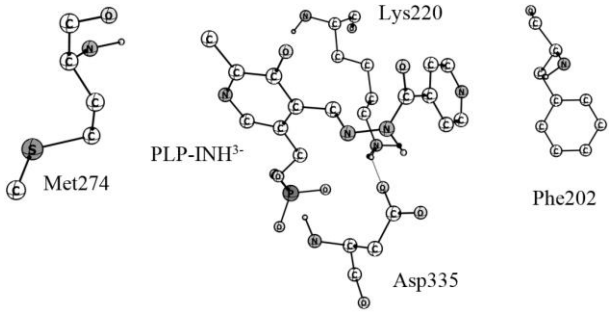

Fig. 5. Calculated structure of the complex of PLP-INH^{3-} hydrazone and active site of GRK2

Рис. 5. Расчетная структура комплекса гидразона PLP-INH^{3-} и активного сайта GRK2

The hydrazone mode with the most binding affinity (Fig. 5) is close to the UU conformer. However, it is additionally twisted as it is follows from the dihedral angles values of this conformer (φ_1 = 101.8°; φ_2 = 25.4°; φ_3 = -29.6°) when compared to those of UU (Table 1). The ligand could be also concluded to be too short to bind efficiently, since the distances between PLP-INH^{3-} and Met274 and Phe202 are about 4 Å. Probably, spacers insertion is in order.

CONCLUSIONS

The geometry of different conformers of the hydrazone derived from pyridoxal 5'-phosphate and isoniazid was optimized by means of quantum chemical calculations (DFT, B3LYP/6-311++G(d,p)). Conformers differ one from another by the dihedral angles values of N_{23}-C_{13}-C_4-C_5, N_{23}-N_{24}-C_{26}-O_{27} and N_{24}-C_{26}-C_{28}-C_{29}. Most of the studied species, except for UD structure, are non-planar due to the steric repulsion between hydrogen atoms of methylene, methyne or –NH- groups. The stability of conformers evaluated from their total energy values decreases in the following sequence: DU>DD(-48)> DD(42)>UU>UD.

The transitional states geometry referring to the φ_1, φ_2, φ_3 rotation was optimized as well and the values of activation barriers were estimated. The conformation equilibria are fast since the largest $\Delta G^{\ddagger}$ does not exceed 30 kJ mol^{-1}.

The most stable conformer is incapable of complexating the metal ions. The positive change in the total energy between it and the species forming the complex (namely, UU) contributes into the complexation thermodynamics.

The docking performed for PLP-INH^{3-} hydrazone and G-protein-coupled receptor kinase revealed that the conformation of ligand bound to the active site is close to UU. However, it is additionally twisted in relation to the UU conformer, e.g. in terms of φ_1 dihedral angle values (101.8° *vs.* ~0-1°).

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