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GEOMETRIC AND ELECTRONIC STRUCTEURE OF SUBSTITUTED PYRIRDINE N-OXIDES

Introduction:

Heterocyclic compounds containing N-oxide group have attracted great interest because of their **biological activity**. According to numerous studies, the biochemical activity of N-oxides is due to complexation with the metalloporphyrins in living organisms. In addition, some substituted pyridine N-oxides have antiviral activity, including against various types of **coronaviruses** (SARS-CoV, MERS-CoV, FIPV), as well as **HIV-1** and **HIV-2**, however, at the moment there is no explicit structure-activity correlation for these compounds [1-3].

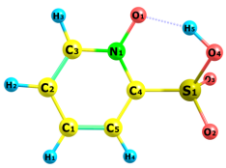
High ability of N-oxides to form complexes is usually considered as the result of **donor properties of the N→O group** and its spatial accessibility. The properties of the chemically interesting polar N–O bond may vary due to the **different substituents** in the ring [4].

Quantum-chemical calculations are widely used for detailed study of the electronic and geometric structure of molecules.

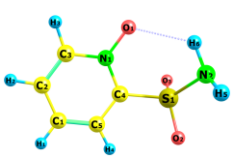
Research methods:

- Quantum-chemical calculation – **DFT**
- Functional – **B3LYP**
- Basis set – **cc-pvTZ**
- **NBO** analysis
- Program – **Gaussian09**
- Visualization – **ChemCraft**

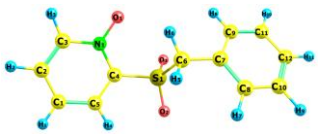
Molecules are objects of research:



N-oxide-2-pyridine sulfonic acid
(A)



N-oxide-2-aminosulfonylpyridine
(B)



N-oxide-2-phenylmethylsulfonylpyridine
(C)

Results of research:

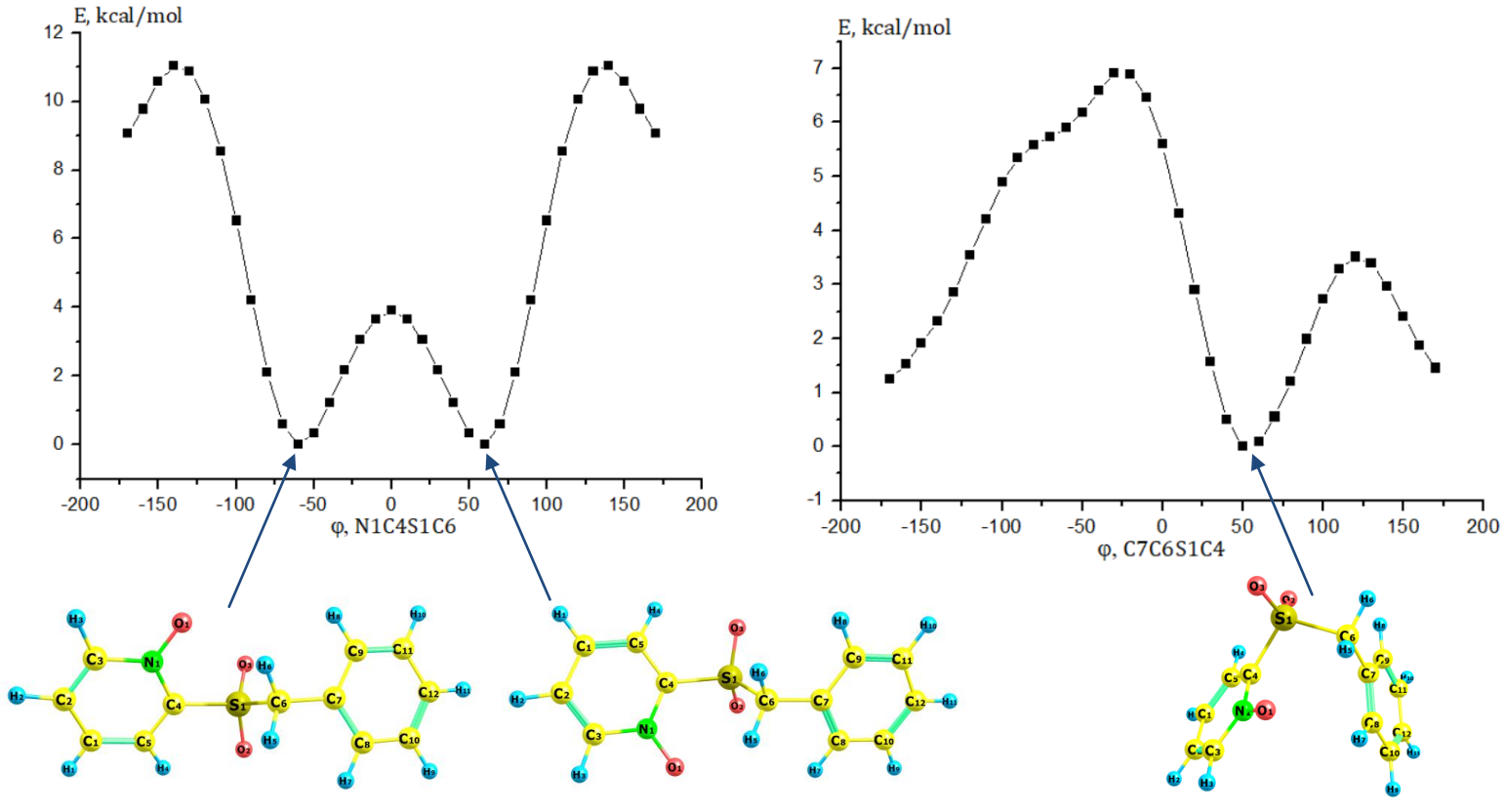
Geometric optimization and NBO analysis of the electron density distribution was performed. Bond lengths N→O (r, Å) and charges on oxygen and nitrogen atoms (q) were determined, as well as lengths and energies of intramolecular hydrogen bond ($r_{(H\cdots O)}$, Å; E_{DA}, kcal/mol) for molecules **A** and **B**. The comparison of the calculated parameters with the unsubstituted pyridine-N-oxide [5] is shown in the Table 1.

Possible conformations were found for molecule **C** using the analysis of potential internal rotation functions (Fig. 1).

Table 1. N-O bond length, charges on nitrogen and oxygen atoms and energy of intramolecular hydrogen bond.

	r(N-O), Å	q(N)	q(O)	$r_{(H\cdots O)}$, Å	E_{DA}, kcal/mol
Pyidine-N-oxide	1.271	0.112	-0.510	–	–
A	1.299	0.085	-0.544	1.601	38.4
B	1.274	0.104	-0.517	2.105	3.72

Figure 1. Potential internal rotation functions and conformations of molecule **C**.



(C1) φ, N1C4S1C6 ≈ -60° **(C2)** φ, N1C4S1C6 ≈ 60° **(C3)** φ, C7C6S1C4 ≈ 50°

Conclusions:

I. In molecule **A** there is a strong intramolecular hydrogen bond of type O–H···O ($r_{(H\cdots O)}$ = 1.601 Å, E_{DA}(LP(O)→σ*(OH))= 38.4 kcal/mol). A less strong hydrogen bond of type O–H···O occurs in the molecule **B** ($r_{(H\cdots O)}$ = 2.105 Å, E_{DA}(LP(O)→σ*(NH))= 3.72 kcal/mol).

The **presence of intramolecular hydrogen bonds** in these molecules leads to increased electron-properties of groups –SO2-X and increase the negative charge on the oxygen atom semipolar N→O, which in turn leads to **increased electron-donor properties** of N-oxides of pyridine.

II. **Conformational flexibility** is one of the most important parameters for antiviral drugs, which is **responsible for the drug's** access to the target and **modifications due to mutations**.

Analysis of potential internal rotation functions for molecule **C** showed that this molecule has **three stable conformers**, two of which differ in the position of the pyridine N-oxide fragment relative to the C4–S1 bond (**C1** and **C2**, Fig. 1), and the third has an arcuate structure due to the rotation of the phenylmethyl fragment around the C6-S1 bond (**C3**, Fig. 1).

Scientific adviser: *Doctor of Chemical Sciences, Prof. N. I. Giricheva.*

List of references:

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