

Theoretical Study about the Reactivity of Formyl Groups in Heterocyclic Derivatives

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The conformational minima of 2-formylazoles (2-formyl-imidazole, respectively 2-formyl-thiazole) have been computed using ab initio methods at HF/6-31G(d) level. The transition state structures for the addition of the hydroxyl ion at imidazole-2-carboxaldehyde, respectively thiazole-2-carboxaldehyde and the most favorable trajectories of the nucleophilic attack were determined.

Keywords: transition state, azole-2-carboxaldehyde, nucleophilic addition

The reactivity of derivatives containing formyl group has known some argued models to explain and predict the nucleophilic attack at the double bond C=O.

One of the first models is proposed by Cram (1952) (Figure 1) [1] which supposed that, in the nucleophilic addition reaction prevails the diastereoisomer formed through the nucleophilic attack on the least sterically hindered side of the carbonyl bond, the double bond being intercalated between the two smaller groups of the asymmetric adjacent center.

The nucleophilic attack trajectory is considered to be perpendicular on the carbonyl group C=O, and the possible steric repulsions are not considered.

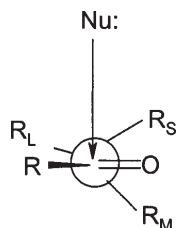


Fig. 1. Cram model for the nucleophilic addition (R_L , R_M , R_S – large, medium, respectively small substituents)

In 1967 Karabatsos proposes another model (fig. 2) [2], based on the most stable ground state conformation. The trajectory of the nucleophilic attack is also considered to be perpendicular on the carbonyl group, and the transition state is “reactant-like”. There are also considered the interactions that can appear between the bulky substituents (R_M and R_L) and the oxygen atom from the carbonyl group.

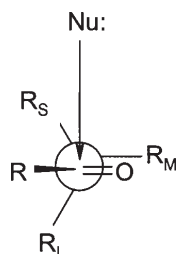


Fig. 2. Karabatsos model for the nucleophilic addition (R_L , R_M , R_S – large, medium, respectively small substituents)

The Felkin model (fig. 3) [3], proposed in 1968, may be characterized by a “reactant-like” transition state, the major product being the one with the completely staggered conformation.

The Felkin model gives good results for ketones, but fails for aldehydes because it neglects the steric interactions.

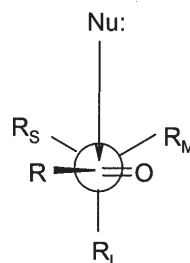


Fig. 3. Felkin model for the nucleophilic addition reaction (R_L , R_M , R_S – large, medium, respectively small substituents)

Anh's improvements to the Felkin model led to the most known and used prediction model of the nucleophilic addition reaction, the Felkin-Anh model (fig. 4) [4]. The nucleophilic attack is no longer considered to occur under a 90° angle, including the Burgi-Dunitz trajectory in which the angle of the nucleophilic attack allows the maximum overlap of HOMO- π^* orbitals. The nucleophilic attack occurs on the least sterically hindered side and does not depend on the ground-state conformers' stability.

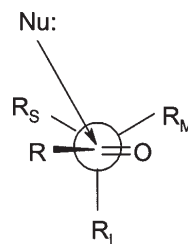
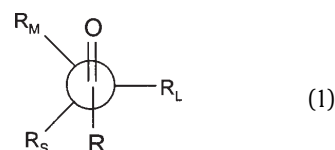


Fig. 4. Felkin-Anh model for the nucleophilic addition (R_L , R_M , R_S – large, medium, respectively small substituents)

The Burgi-Dunitz trajectory was determined through crystal structure data and varies in the range $105^\circ \pm 5^\circ$ for different types of nucleophiles. The experimental results and the theoretical calculations led to the most accepted value of 107° [5].

Most of the literature's data regarding nucleophilic addition reaction at a carbonyl group refer to the acyclic aldehydes, with an asymmetric adjacent center:

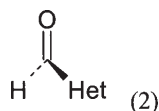


(1)

General formula of an acyclic aldehyde

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In the present paper we propose the study of a nucleophilic addition to an aldehyde in which the formyl group is bound on a heterocyclic skeleton:



General formula of a heterocyclic aldehyde

A possible example is represented by the nucleophilic addition of the hydroxyl ion to heterocyclic aldehydes.



Nucleophilic addition reaction of hydroxyl ion to heterocyclic aldehydes

Based on their reactivity towards the hydroxyl ion, the heterocyclic aldehydes may be divided in two groups:

- five-membered aldehydes with an excess of π -electrons (carbonylic compounds of furan, thiophene, N-substituted pyrrole), in which addition of the hydroxyl ion occurs similar to benzaldehydes
- five- or six-membered aldehydes with π -electron deficiency (carbonylic compounds of thiazole, imidazole and pyridine), which exist in aqueous solution in a considerable percent as the hydrated form [6].

We choose to study the nucleophilic addition of the hydroxyl ion at the aldehydes with π -electron deficiency, in this case 2-formyl azoles (thiazole, imidazole or oxazole). The experimental data (NMR) [6] confirm that these heterocyclic aldehydes dissociate to a geminal diol. In aqueous solutions these heterocyclic aldehydes exist in hydrated form in a 70-90%.

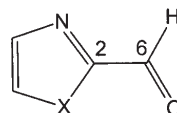
As one can see, the proposed models imply different conformations of the substituents at the formyl group [7, 8]. Therefore a conformational behaviour of the system should be also analyzed.

To analyze the possible influence of the most stable conformer in the reaction course, in the transition state and in the final products, we studied the conformational behaviour of these compounds [9].

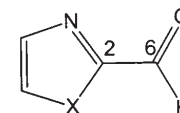
The energetic barriers appearing in the organic compounds during the internal rotation around a simple bond are determined by the electronic and steric interactions. Thus, the conformational analysis provides data regarding the stability of the conformers and correlates their conformations with their properties.

In the literature, there are a number of experimental and theoretical data regarding the conformational analysis of the carbonylic compounds of five-membered heterocycles with one heteroatom. The carbonylic compounds of azoles, which should behave somewhat between the five-membered heterocycles and pyridine, were less studied. One of the first and most complete study of the conformational analysis of 2-formyl azoles has been published in 1989 and it refers mainly on oxazole and thiazole [8].

The rotational profile and the transition states of the internal rotation process of the formyl group in the following compounds were determined in the present study:



X,O-cis



X,O-trans

X = NH, O, S (4)

2-Formyl-azoles

Methods

The geometry optimization of the different structures and the rotational profile were calculated using Gaussian 03 software package [10] with the 6-31G basis sets (Polak-Ribiere algorithm, with termination condition of RMS gradient = 0.01 kcal/(Åmol). The transition states were determined by performing IRC calculations (semi-empirical method, RM1 level), using the MOPAC 2009 software [11]. The bond orders values were computed using Gaussian 03 software package [10], at HF/6-31G level of theory.

Results and discussions

Conformational analysis of 2-formyl azoles

The torsion angle, α , is the X-C₂-C₆-O dihedral; $\alpha = 0^\circ$ corresponds to the X,O-cis conformation. The rotation profile of the compounds was calculated by optimizing the geometry of 2-formyl azoles in steps of $\alpha = 30^\circ$, maintaining constant the value of the torsion angle and optimizing all the others parameters.

Analyzing the obtained results, in each of the three cases the most stable form corresponds to the value of $\alpha = 0^\circ$ (X, O-cis). The conformers have an almost planar structure that favors an extended π -conjugation, providing their stability. The coplanarity of the heterocyclic ring and the formyl group were also demonstrated by the solid-state

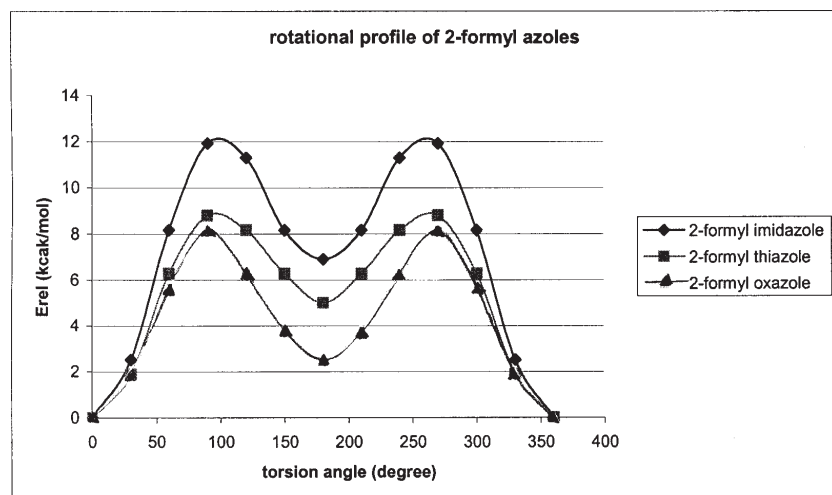


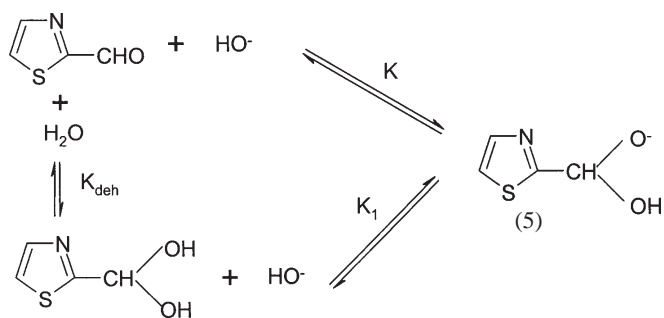
Fig. 5. The rotation profile of 2-formyl-azoles (*ab initio*, 6-31G, Gaussian 03)

heterocyclic compounds study (proton NMR spectroscopy) [12].

The energy barriers are influenced by the conjugation of the C=O with the heterocyclic ring, which is enhanced with the presumptive decrease of the aromatic character of the heterocyclic ring. The computed bond order values for the C2-C6 bond are 1.0269 for thiazole-2-carboxaldehyde and 1.0462 for imidazole-2-carboxaldehyde, respectively. The values are in good agreement with the bond order value of 1.0261 calculated for the C-C bond between the C atom of the carbonyl group and the C atom from the benzene moiety in benzaldehyde. The conclusions of the conformational analysis performed at HF/6-31G level with the Gaussian 03 program are in good agreement with the results of the study at 3-21G level [8].

Transition state study

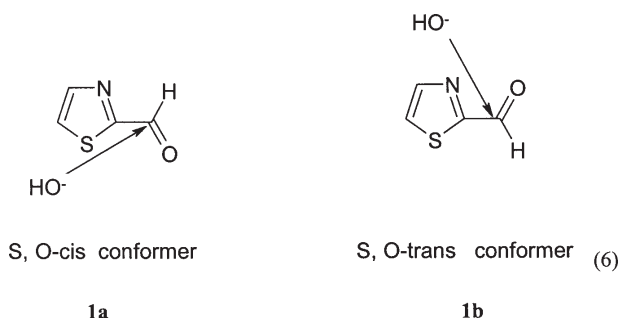
For the study on the transition state of the nucleophilic addition of the heterocyclic aldehydes, we choose as a model the transition state of the addition of the hydroxyl ion to the 2-thiazole-carboxaldehyde [6]:



Nucleophilic addition of the hydroxyl ion to the 2-thiazole-carboxaldehyde

The reaction-path method was used, starting from an approximated structure of the transition state. Reaction-path calculations involve the gradual variation of an internal coordinate (it can be an interatomic distance, an angle or a dihedral angle), all the other coordinates being optimized during the calculations. Once a possible transition state has been located, it must be confirmed by performing a vibration analysis in order to evidence the presence of exactly one negative (imaginary) frequency.

To build the approximate transition state we considered the approach angle of the nucleophile reagent to be at 107° (towards the C=O bond) and we start, as a result of the conformational analysis performed, from the most stable conformer S,O-cis. In order to see if the transition state structure is influenced by the relative energy of the conformers, a transition state search starting from the S,O-trans conformer was performed, maintaining the nucleophile trajectory to 107° .



The cis-trans conformers of 2-formylthiazole (6)

Both for the S,O-cis and S,O-trans conformers, the transition state has a very similar conformation (geometrical parameters of the transition state structures are given in table 1). For instance, the structure of the transition state of the nucleophilic addition of the hydroxyl ion to the thiazole-2-carboxaldehyde is presented in figure 6:

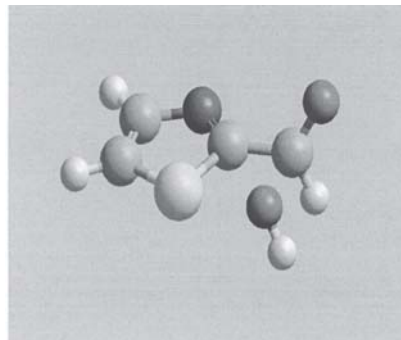


Fig. 6. Transition state obtained for the nucleophilic addition of the hydroxyl ion to the S,O-trans conformer of thiazole-2-carboxaldehyde

Following the same reaction-path calculation method, the transition state for the nucleophilic addition of the hydroxyl ion to 2-formyl-imidazole was determined.



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Nucleophilic addition of the hydroxyl ion to the 2-imidazole-carboxaldehyde (7)

To elaborate an approximate transition state, we consider a number of possible trajectories of the nucleophilic attack in the range $100-110^\circ$, maintaining the angle value constant, and, in the following steps, allowing it to optimize. We obtained a possible geometry of the transition state (a single negative vibration frequency) only when the attack angle was optimized at 100.66° .

The structure of the transition state is very similar to that obtained in the case of the addition of the hydroxyl ion to the thiazole-2-carboxaldehyde.

Based on these results, one may conclude that in the case of the nucleophilic addition of the hydroxyl ion at the azole-2-carboxaldehyde, the nucleophilic attack is influenced only by the steric factors, being preferred a trajectory of the hydroxyl ion which does not have steric hindrances, even though the conformer is not the most stable one. This is also supported by the Curtin-Hammett principle: the selectivity of the reaction does not depend on the relative energy of the reactants.

The very similar transition state structures obtained in both addition reactions may be explained by the antiperiplanar effect [12]: the interactions between the C=N bond and forming of the bond C-O will stabilize the transition state (the geometry corresponding from this point of view, the HO⁻ and the C=N bond being in different planes).

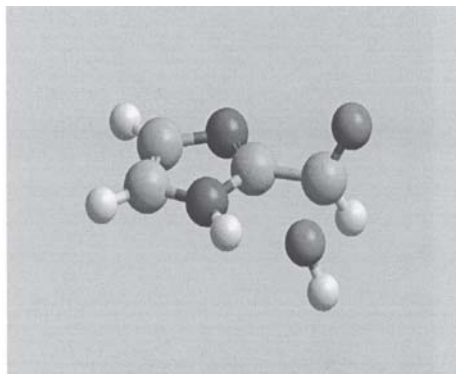


Fig. 7. The transition state structure obtained for the nucleophilic addition of the hydroxyl ion to the NH,O-cis conformer of imidazole-2-carboxaldehyde

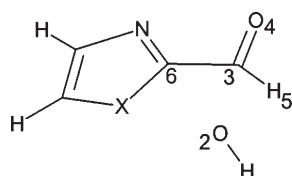


Fig. 8. General structure of the transition states obtained for the nucleophilic addition of the hydroxyl ion to the X,O-cis and X,O-trans conformers of azole-2-carboxaldehyde

Table 1
GEOMETRICAL PARAMETERS OF THE TRANSITION STATE (TS) STRUCTURES OF THE NUCLEOPHILIC ADDITION OF THE HYDROXYL ION TO THIAZOLE-, RESPECTIVELY IMIDAZOLE-2-CARBOXALDEHYDE

TS	d(C-O) (Å)	O ₂ -C ₃ -O ₄ (°)	N-C ₆ -C ₃ -O ₂ (°)	X-C ₆ -C ₃ -O ₄ (°)	X-C ₆ -C ₃ -H ₅ (°)
1a	1.976	107°	184°	257°	93.4°
1b	1.905	107°	178°	250°	92.7°
2a	1.823	100.6°	186°	260°	108°
2b	1.823	100.6°	186°	260°	108.1°

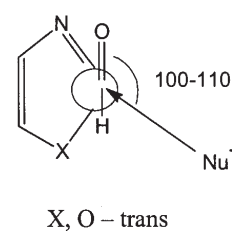
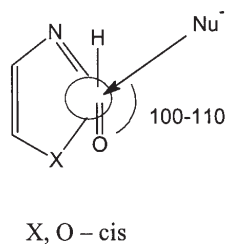


Fig.9. Trajectories of the nucleophilic attack of the hydroxyl ion to azole-2-carboxaldehydes

Conclusions

Considering the previously presented theoretical models for the nucleophilic addition reaction, the most favorable trajectories of the nucleophilic attack of the hydroxyl ion at the azole-2-carboxaldehydes are according to figure 9.

These assumptions were the starting point for the transition state searching and the results confirm our suppositions. First of all, in both cases the nucleophilic attack occurs on the least steric hindered side, next to the H atom, which agrees the Felkin-Anh model.

Secondly, the nucleophile approach angle is 107° (when the substrate is 2-formyl-thiazole), respectively ~101° (when the substrate is 2-formyl-imidazole), according to the Burgi-Dunitz trajectory.

Finally, the geometry of the transition state may be explained by the antiperiplanar effect, according to the Cieplak model [13]: best electron-donor (in this case, C=N) is aligned *anti* to the incoming nucleophile in order to stabilize the σ^* orbital of the forming bond, fact which can be observed from the N-C₆-C₃-O₂ angle values.

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