Reaction of $N$-allenyl-$1H$-pyrrole-$2$-yl-carbaldehyde with hydroxylamine: a quantum-chemical model

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Abstract. The mechanism of the reaction between hydroxylamine and $N$-allenylpyrrole-$2$-carbaldehyde has been studied using quantum-chemical methods ($B2PLYP$-$D2/6-311+G**/B3LYP/6-31+G*$). It is shown that the calculations should take into account the solvent molecules. Solvent molecules provide both proton transfer and adequate reproduction of activation barriers. It is found that two solvent molecules are necessary for modeling oximation reaction, whereas only one solvent molecule is sufficient for the cyclization step.

1. Introduction

The study of the chemical properties of biologically active compounds is one of the most urgent challenges in modern chemistry. In particular, the pyrrole structural motif is frequently met in many drugs with anti-tuberculosis, antibiotic, anti-cancer activity [1–3]. The pyrrole core is a part of optically active compounds, chemosensors, and semiconductors. The compounds containing an allene fragment are also biologically active. There are a number of natural and synthetic antibiotics containing an allene fragment: mycomycin, marasmin, nemotin, etc. [4]. The compounds bearing one or more isonitroso groups (oximes) also draw research interest. They exhibit various biological activities [5–8]. For example, oxime derivatives of a number of heterocyclic compounds are recommended for use in agriculture and pharmaceuticals [5].

The well-known reaction of oximes with alkyl- or aryl-halides leads to the formation of a valuable class of organic compounds, nitrones. They are used successfully in organic synthesis as building blocks for assembling complex molecular structures. More recently, an attempt to combine pyrrole, alleny and oxide structural fragments in one compound afforded the cyclic nitrones. A one-pot synthesis of pyrrolypyrazine oxides from $N$-allenyl-pyrrole-$2$-carbaldehydes and hydroxylamine in ethanol (Scheme 1) [9] was implemented.

$$
\text{R} = \text{Ph- (76%), p-Cl-Ph- (89%), p-H_3C-Ph- (81%), thiophenyl (86%), naphthyl (70%), p-(CH}_3O-\text{-Ph- (87%)} \nonumber
$$

Scheme 1. The formation of 3-methylpyrrolo[1,2-a]pyrazine-2-oxides.
It has been experimentally established that the reaction proceeds through the intermediate \(N\)-allenlypyrrol-2-yl-oxime. There are two nucleophilic centers (nitrogen and oxygen atoms of the oxime group) and two probable routes of the nucleophile attack at the alleny1 group (terminal and internal atoms). Since no products of the \(Z\)-oxime cyclization (\(O\)-nucleophile attack) were found experimentally, we considered the competition in the addition of the nitrogen atom to the terminal and internal atoms of the allene substituent yielding 3-methylpyrrolo[1,2-a]pyrazine-2-oxide (A) and 3\(H\)-pyrrolo[1,2-a]1,4-diazepine-2-oxide (B).

![Scheme 2. Formation of possible cyclization products.](image)

### 2. Computational details

#### 2.1. Method

In this work, we have chosen the combined approach B2PLYP-D2/6-311+G**//B3LYP/6-31+G*. Geometries optimization in the gas phase and calculation of vibrational corrections were performed using the B3LYP method with the 6-31+G* basis set. The energy was refined and the dispersion correction was calculated using the B2PLYP-D2 method with the 6-311+G** basis set. This approach has already been successfully applied for the theoretical study of the mechanisms of allene reactions and showed good agreement with the high-precision method CCSD(T)/6-311+G**//CCSD/6-31+G* [10,11]. Connection of the transition states and local minima proved descent along the reaction coordinate using the LQA algorithm [12]. The solvent effects were studied within the framework of the cluster-continuum model. The specific solvation was considered by the inclusion the solvent molecules into the calculation, and non-specific interactions were taken into account within IEFPCM method. All calculations were carried out in the Gaussian 09 software package [13].

#### 2.2. Wertz entropy correction for ethanol solutions

Wertz [14] approach suggests that all solutes lose the same fraction of entropy when dissolved in water. Abraham [15] have shown that it takes place for other solvents. Wertz also argues that the same amount of entropy is lost when the ions are solvated. This allows one to introduce appropriate corrections for an arbitrary solvent. Previously, we used this method for a DMSO solution[16].

Wertz method for ethanol solutions comprises several steps. In the first stage a solute is treated as an ideal gas and compressed from 1 atm to a hypothetical ideal gas state with the concentration equal to that of the liquid state (\(d=0.789\ g/ml, 298\ K, 17.126\ M\)). This entropy change can be estimated as

\[
\Delta S_1 = -R \ln \frac{P_2}{P_1} = -R \ln (22.4 \cdot 17.126) = -49.47 \frac{J}{mol \cdot K}
\]

The next step is the conversion of this hypothetical state to the final liquid state. The fraction of entropy lost in second step is defined as a coefficient, \(\alpha\).

\[
\alpha = \frac{\Delta S_2}{S_g} = \frac{S_g - S_0^0}{S_0^0} = \frac{\Delta S_4 + \Delta S_1}{S_0^0} = \alpha S_g = \alpha S_0^0 + \alpha \Delta S_1
\]

The entropy of liquid ethanol \(S_0^0 = 159.86 \frac{J}{mol \cdot K}\) (standard state)[17]. The entropy of vaporization can be estimated from the normal heat of vaporization (42.3 kJ/mol) and boiling temperature (351.5 K at 1 atm) as \(\Delta S_{vap}^0 = 280.20 \frac{J}{mol \cdot K}\), \(S_g = S_0^0 + \Delta S_1 = 230.73 \frac{J}{mol \cdot K}\), and \(\alpha = 0.307\).

The entropy change from the gas state of any given molecule \(M\) in standard state to its 1 M state in ethanol is composed of three steps. The first is the compression of ideal M gas in standard state to a
hypothetical ideal gas state with the concentration equal to that of the solvent liquid state (17.126 M) that gives the same $\Delta S_1 = -49.47 \frac{J}{mol \cdot K}$. Conversion of the hypothetical ideal gas state to a hypothetical liquid state brings $\Delta S_2 = aS_g^0 + a\Delta S_1$. The fraction of entropy lost in this step is assumed to be equal to $\alpha$. Finally, expansion of the hypothetical liquid state to the 1M state in ethanol results in $\Delta S_3 = R \ln(17.126) = 23.62 \frac{J}{mol \cdot K}$. The calculated gas phase entropy of M in standard state is then converted to the corresponding entropy in its 1 M state in ethanol according to the following equation:

$$S_f^0 = S_g^0 + \Delta S_1 - \Delta S_2 + \Delta S_3 = 0.69 \times S_g^0 - 10.52 \frac{J}{mol \cdot K}.$$ 

For a bimolecular reaction it results in changing $T\Delta S_i = 0.69 \times T\Delta S_e - 0.75 \text{ kcal/mol}$.

### 3. Results and discussion

#### 3.1. Choice of a compound for proton transport

Due to the addition of hydroxylamine hydrochloride into the reaction mixture at the initial stage (Scheme 1), the medium becomes acidic. To neutralize hydrochloric acid, sodium bicarbonate was employed that resulted in water formation. Being protic solvents both water and ethanol can transfer protons. First, we needed to solve the issue about the proton carrier in such a water-alcohol system. In addition, it was necessary to determine number of these molecules to adequate describe proton transport at each stage.

Obviously, a stronger acid compound in a mixture of two substances should realize protons transport. It is known [18] that measuring acidity in the alcohol-water system is difficult. First, the pH of an aqueous solution of alcohol is actually measured, and after a certain moment, when the concentration of alcohol exceeds the concentration of water, the pH of the alcohol solution of water is measured. At this point, the pH measurement scale changes. It is known [18] that alcohol in an alcoholic solution is a stronger acid than water in the same solution. In addition, the number of solvent molecules in the system under study significantly exceeds the number of water molecules dissolved in it (by about 5.4 times). So, solvent molecules with a high probability act as a proton carrier.

#### 3.2. The issue of choosing the solvate cluster size and modeling the reaction of N-allenylpyrrole-2-carboxaldehyde with hydroxylamine

The next step of the investigation was to determine the solvation cluster size, sufficient for the most complete description of the solvent effects. This and others methodological issues are expedient to study using a model molecule without a substituent in the 5 position of the pyrrole ring. It is connected with the economy of computing resources.

The total energy of the starting molecules is adopted for reference point: N-allenylpyrrole-2-carboxaldehyde, hydroxylamine and ethanol. The formation of pre-reaction complex 1a from these three molecules increases the Gibbs free energy by $\Delta G = 4.8 \text{ kcal/mol}$.

The hydroxylamine addition to the carbonyl group (TS1a→2a, figure 1) occurs with the synchronous protons transfer from the hydroxylamine nitrogen atom to the oxygen atom of the carbonyl group through an ethanol molecule. This process is accompanied by an activation barrier $\Delta G^1 = 23.2 \text{ kcal/mol}$ with dispersion correction or $28.6 \text{ kcal/mol}$ without it. Further, we will use such notation: $\Delta G^2 = 23.2 (28.6) \text{ kcal/mol}$, where the value without dispersion correction is indicated in parentheses.
\[ \Delta G = 4.8 \ (8.1) \]

\[ \Delta G^\ddagger = 23.2 \ (28.6) \]

\[ \Delta G = 3.9 \ (8.7) \]

Figure 1. The hydroxylamine addition to N-allenylpyrrole-2-carbaldehyde involving one ethanol molecule (\( \Delta G, \Delta G^\ddagger \) kcal/mol).

The inclusion of the second solvent molecule into the transition state of hydroxylamine addition (TS\(_{1b-2b}\), figure 2) decreases the activation energy by \( \Delta \Delta G^\ddagger = 8.3 \ (5.2) \) kcal/mol. In this case, the activation is estimated to be \( \Delta G^\ddagger = 14.9 \ (23.4) \) kcal/mol. The protons transfer is also carried out synchronously, but already through two ethanol molecules.

\[ \Delta G = 12.3 \ (19.7) \]

\[ \Delta G^\ddagger = 14.9 \ (23.4) \]

\[ \Delta G = 0.9 \ (8.1) \]

Figure 2. The hydroxylamine addition to N-allenylpyrrole-2-carbaldehyde involving two ethanol molecules (\( \Delta G, \Delta G^\ddagger \) kcal/mol).
The subsequent abstraction of a water molecule can lead to two isomers of E- and Z-oximes (3E and 3Z, respectively). This depends on the conformation of the formed (hydroxyamino)(1-propadienyl-1H-pyrrol-2-yl)methanol (2c and 2d). If one solvent molecule is taken into account in the calculation, the activation barriers are $\Delta G^i = 28.6$ (33.6) kcal/mol for the E-oxime and $\Delta G^i = 26.5$ (30.9) kcal/mol for the Z-oxime. The ratio of these two barriers indicates the preferable formation of the Z-oxime, which disagree with the experimental data [19] about a higher yield of the E-oxime in similar reactions with N-vinylpyrrole-2-carbaldehydes.

At the same time, an enlargement of the solvation cluster up to two ethanol molecules decreases the activation energies. The transition state $\text{TS}_{2c-3E}$ (figure 3) of a water molecule elimination with the 3E formation has an activation barrier $\Delta G^i = 20.0$ (27.0) kcal/mol. Oxime 3Z is formed through the $\text{TS}_{2d-3Z}$ overcoming the activation barrier $\Delta G^i = 21.3$ (29.5) kcal/mol. Such values of activation barriers are adequate for experimental conditions. So, it should take into account not less two ethanol molecules at the stage of oximation.

Figures 3. Formation of N-allenylpyrrole-2-E-/Z-oximes ($\Delta G$, $\Delta G^i$ kcal/mol).
Neither the Z-oxime nor the products of its transformations were found experimentally. Thus, further we have investigated the mechanism of only E-oxime transformations. The E-oxime is able to cyclize yielding two isomeric products: 3-methylpyrrolo[1,2-a]pyrazine-2-oxide (addition to the internal allenyl carbon atom) and 3H-pyrrolo[1,2-a][1,4]diazepine-2-oxide (addition to the terminal atom).

3-Methylpyrrolo[1,2-a]pyrazine-2-oxide 6 (figure 4) is formed through the intramolecular nucleophilic addition of an oxime nitrogen atom to an internal allenyl atom. The transition state $\text{TS}_{3Ea\rightarrow 4}$ is characterized by an activation barrier $\Delta G^i = 21.7$ (24.5) kcal/mol. Contrary to our expectations, proton transfer from the hydroxyl group to the formed carbanion does not occur during the descent along the reaction coordinate. At the same time, according to the calculations, proton transfer proceeds without an activation barrier at the next step. It should be noted that the smoothing of the activation barrier takes place already at the stage of taking into account the vibrational corrections in $\text{TS}_{4\rightarrow 5}$. Formation of 6 is accompanied by a thermal effect equal to $\Delta G = -46.1$ (-45.3) kcal/mol.

![Figure 4. Formation of 3-methylpyrrolo[1,2-a]pyrazine-2-oxide ($\Delta G$, $\Delta G^i$ kcal/mol).](image)

3H-pyrrolo[1,2-a][1,4]diazepine-2-oxide 9 is formed through the intramolecular nucleophilic addition of the nitrogen atom of the oxime group to the terminal atom of the allenyl group (figure 5). The transition state $\text{TS}_{3Eb\rightarrow 7a}$ is characterized by an activation barrier $\Delta G^i = 30.1$ (32.5) kcal/mol. Then, the molecule undergoes a conformational transition, when the carbon atom leaves the formed plane ring structure. Transition state of this transformation ($\text{TS}_{7a\rightarrow 7b}$) is higher than $\text{TS}_{3Eb\rightarrow 7a}$, therefore the resulting barrier of 8 formation is $\Delta G = 32.6$ (35.4) kcal/mol. After that, a barrier-free proton migration from the hydroxyl group to the formed carbanion occurs to give 8. Formation of 9 is accompanied by a thermal effect equal to $\Delta G = -31.8$ (-30.1) kcal/mol.

It is shown that the formation of 6 is much more preferable than that of 9, both kinetically $\Delta \Delta G^i = 10.9$ (10.9) kcal/mol and thermodynamically $\Delta \Delta G = 14.3$ (15.2) kcal/mol. The addition of the second solvent molecule slightly decreases the activation barriers $\Delta \Delta G^i = 0.9$ (0.8) kcal/mol, therefore, it can be considered sufficient to take into account only one solvent molecule in an explicit form at the intramolecular cyclization stage.
4. Conclusions
The quantum-chemical calculations have revealed that the formation of pyrazine-2-oxide from Nallenylpyrrole-2-carbaldehyde and hydroxylamine in ethanol is most preferable. The rate-determining stage of the reaction is an intramolecular cyclization. It is established that for an adequate description of the oximation reaction in ethanol, it is necessary to explicitly take into account two solvent molecules. However, it is sufficient to take into consideration only one molecule to simulate the intramolecular cyclization reaction.

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