Effect of the anionic center hydration on the activation barrier of intramolecular nucleophilic addition in αβ-unsaturated oximes

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Abstract. The mechanism of intramolecular nucleophilic addition in αβ-unsaturated oximes, as well as the effect of the anionic center hydration with one and two water molecules on the activation barriers of intramolecular cyclization, was studied using the B2PLYP-D2/6-31+G**//B3LYP(D)/6-31+G* method with the solvation effects included within the SMD model. The activation barrier for nucleophilic addition of the anionic center of the oxime group to the carbon skeleton of 3-ethyl-N-hydroxy-5-phenylpenten-3-imine-2 is about 21 kcal/mol. During the hydration of the anionic center with one water molecule, a strong complex is formed, which increases the activation barrier by ~ 6 kcal / mol. The addition of a second water molecule leads to an even higher activation barrier (ΔG‡ = 28 kcal/mol), but promotes the binding of the leaving hydroxide ion.

1. Introduction

Due to its biologically important antiviral [1], antimicrobial [2], and antitumor [3] properties, the isoxazoline structural motif is met in numerous important drugs. Isoxazolines are also widely used in organic synthesis as building blocks and intermediates. The stability of the ring as well as lability of the N – O bond allows the ring to be introduced into the system and, if needed, to open this ring by selecting the appropriate conditions, which ensures the synthesis of poly-substituted organic compounds.

Intramolecular cyclization of allyloximes is currently considered one of the most promising approaches to the synthesis of 2-isoxazolines. [4]. Most often, such cyclization is carried out via radical mechanism, but there are also examples of the formation of 2-isoxazolines from allyloximes under the action of bases [5]. In particular, ring-closure in the presence of the superbasic KOH/DMSO system is proposed as one of the stages of the recently developed one-pot method for the preparation of 2-isoxazolines from ketones, arylacetylenes, and hydroxylamine [6]. Intramolecular nucleophilic addition of the O-anionic center of the oxime to the multiple bond followed by protonation of the C4 position of the ring is preceded by prototropic rearrangement (Scheme 1).

Formation of 5-benzyl-4-ethyl-3-methyl-4,5-dihydro-1,2-oxazole is the simplest example given in the experimental work [6]. Its precursor, 3-ethyl-N-hydroxy-5-phenylpenten-3-imine-2 (1), can exist in four isomeric forms, namely, (2Z,3E), (2Z,3Z), (2E,3E) and (2E,3Z). However, only the 2Z-form of the oxime group can enter into the intramolecular cyclization reaction. Here we have estimated the
activation energy of the closure of the \((2Z,3E)\) and \((2Z,3Z)\)-anions of oxime 1 and the effect of water present in the system on value of this energy.

**Scheme 1.** Prototropic rearrangement of allyloxime and subsequent intramolecular cyclization

### 2. Computational details

In this work, all quantum chemical calculations were performed within the framework of the density functional theory (DFT). The geometry optimization and the calculation of vibrational corrections were carried out using the hybrid functional B3LYP [7] with the valence-split 6-31+G* basis set. The energy characteristics of the system were estimated using the double-hybrid functional B2PLYP [8] with an extended 6-311+G** basis set and empirical dispersion correction D2 included. The effects of solvation in dimethyl sulfoxide (DMSO) were taken into account using the polarizable continuum model SMD/6-31+G* (Solvation Model based on Density) [9]. The effect of the solvent on the entropy was estimated using a scheme based on Wertz's idea [10, 11], according to which the entropy in a DMSO solution can be obtained based on the entropy \(S_{\text{harm}}\) found in the harmonic approximation for an ideal gas, as \(S_{\text{sol}} = 0.74 \cdot S_{\text{harm}} – 3.21\) [12]. Calculations were performed using the Gaussian-09 program [13].

### 3. Results and discussion

#### 3.1. Intramolecular cyclization of 3-ethyl-N-hydroxy-5-phenylpenten-3-imine-2 with the participation of one water molecule

The O-anionic center of isolated \((2Z,3Z)\)-3-ethyl-N-hydroxy-5-phenylpenten-3-imine-2 could attack the double bond to form the isoxazoline ring through the transition state \(\text{TS}1\text{a}\) (see figure 1a) with an imaginary frequency \(\nu_{\text{im}} = -458.02\) cm\(^{-1}\) and requires overcoming the activation barrier of \(\Delta G^\ddagger = 20.89\) kcal/mol. However, in the experimental conditions [6], the cyclization reaction proceeds in the basic medium, the \((2Z, 3Z)\)-oximate ion forms a strong complex 2 with water bound by \(\Delta G = 8.23\) kcal/mol.

The transition state \(\text{TS}1\text{b}\) (\(\nu_{\text{im}} = -467.98\) cm\(^{-1}\)) found on the PES of the cyclization of \((2Z,3Z)\)-3-ethyl-N-hydroxy-5-phenylpenten-3-imine-2 in a complex with a water molecule (figure 1b) is structurally similar to the \(\text{TS}1\text{a}\) of the closure of the free \((2Z,3Z)\) oxime ion (see figure 1b). However, the free activation energy of such cyclization increases to \(\Delta G^\ddagger = 26.63\) kcal/mol.

**Figure 1.** Transition states of ring-closure of free \((2Z,3Z)\)-oximate-ion \(\text{TS}1\text{a}\) (a) and its complex with water molecule \(\text{TS}1\text{b}\) (b)
The transition state of the ring-closure with an imaginary frequency \( \nu_{\text{im}} = -446.91 \text{ cm}^{-1} \) was also found for the complex of the (2Z,3E)-oximate ion with water. However, this transition state is by 1.4 kcal/mol higher in energy than that of the (2Z,3Z)-complex and also leads to a thermodynamically less stable (by 2.04 kcal / mol) cyclization product. Therefore, below we will only discuss the closure of the (2Z,3Z) isomer of the oximate ion.

Upon completion of the ring formation the water molecule remains bound to the resulting 5-benzyl-4-ethyl-3-methyl-4,5-dihydro-1,2-oxazolid-4-ion; this complex 3a is stable against decomposition at \( \Delta G = 2.90 \text{ kcal/mol} \) (see figure 2).

**Figure 2.** Complex of 5-benzyl-4-ethyl-3-methyl-4,5-dihydro-1,2-oxazolid-4-ion with a water molecule (3a)

During the closure of the cycle in the presence of a water molecule, the free energy increases by 12.86 kcal/mol. The migration of a water molecule to the C4 position of the ring (4a), which is required for subsequent protonation, augments the energy of the system by 2.04 kcal/mol. Overcoming the activation barrier for protonation (\( \Delta G^\ddagger = 2.47 \text{ kcal/mol} \)) gives the final 5-benzyl-4-ethyl-3-methyl-4,5-dihydro-1,2-oxazole (6) and returns the hydroxide ion to the system with a decrease in energy by 7.92 kcal/mol. Notably, such an energy decrease does not compensate for the increase in free energy at the ring closure stage. Therefore, according to the computation results, the reaction should stop at the stage of the oximate ion formation.

This reasoning misses one important circumstance, namely the presence in the system of an equivalent amount of water, which forms a stable complex \( \text{H}_2\text{O} \cdot \text{HO}^- \) with the leaving hydroxide ion, the binding energy of this complex being \( \Delta G = 10.08 \text{ kcal/mol} \).

Taking this circumstance into account, the intramolecular cyclization of the hydrated oximate ion is generally accompanied by a decrease in free energy by 5.14 kcal/mol.

The presence of an additional water molecule in the reaction system requires consideration of an alternative transformation path with the participation of two water molecules at all stages of the ring-closure.

### 3.2. Intramolecular cyclization of 3-ethyl-N-hydroxy-5-phenylpenten-3-imine-2 with the participation of two water molecules

The (2Z,3Z) oximate ion forms a stable complex 2c bound by \( \Delta G = 9.81 \text{ kcal/mol} \). For this complex, a transition state TS1c with an imaginary frequency \( \nu_{\text{im}} = -482.22 \text{ cm}^{-1} \) was found on the PES. This TS corresponds to the bond formation between the oxygen atom of the oxime group and the C4 carbon atom of the (2Z,3Z)-3-ethyl-N-hydroxy-5-phenylpenten-3-imine-2 (see figure 3).

Due to the hydration of the anionic center by two water molecules, the activation barrier of such cyclization increases to \( \Delta G^\ddagger = 27.93 \text{ kcal/mol} \). Descending along the reaction coordinate leads to complex 3c of the cyclic anion with two water molecules, the decomposition of which is accompanied by an increase in energy by \( \Delta G = 3.68 \text{ kcal/mol} \) (see figure 4).

The migration of one water molecule to the C4-carbanion center (4b) of the cycle decreases the energy of the system by 0.63 kcal / mol. The second water molecule remains bound to the nitrogen atom by the formed hydrogen bond (1.77Å). Then the cycle is protonated with an activation barrier \( \Delta G^\ddagger = 5.35 \text{ kcal/mol} \). The formation of intermediate complex 5 with subsequent decomposition into 5-benzyl-4-ethyl-3-methyl-4,5-dihydro-1,2-oxazole (6) and a complex of water with a hydroxide ion...
leads to a total decrease in free energy relative to the initial oximate ion complex with two water molecules by 1.53 kcal/mol. The final 5-benzyl-4-ethyl-3-methyl-4,5-dihydro-1,2-oxazole is formed as the (4R,5S)-isomer, energy of which is by 3.5 kcal/mol lower than that of the (4R,5R) one.

Additionally, using this stage as an example, we have estimated the effect of taking into account the dispersion correction at the stage of geometry optimization. Comparison of the results of calculations of energy parameters using the B2PLYP-D2/6-311+G**//B3LYP/6-31+G* and B2PLYP-D2/6-311+G**// B3LYP-D2/6-31+G* methods shows that both methods give comparable results. Thus, the total energy of the complex of the (2Z,3Z)-oximate ion with two water molecules increases by 0.31 kcal/mol, and the energy of (4R,5S)-5-benzyl-4-ethyl-3-methyl-4,5-dihydro-1,2-oxazole decreases by 1.25 kcal/mol. In general, the relative energies and activation barriers change within 2 kcal/mol. Thus, the inclusion of the dispersion correction at the stage of geometry optimization does not make a large contribution to the value of the absolute and relative energies of molecules, but could increase the total number of optimization steps.

4. Conclusions
The mechanism of intramolecular cyclization of 3-ethyl-N-hydroxy-5-phenylpenten-3-imine-2 into (4R,5S)-5-benzyl-4-ethyl-3-methyl-4,5-dihydro-1,2-oxazole is studied within a DFT approach. Hydration of the anionic center of an oxime decreases its activity and, consequently, increases the activation barrier of intramolecular nucleophilic addition to a multiple bond. Taking into account the dispersion correction D2 at the stage of geometry optimization has little effect on the absolute and relative energies of the molecules under study.

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References
[1] Rashad A A, El-Sabbagh O I, Baraka M M, Ibrahim S M, Pannecouque C, Andrei G, Snoeck R, Balzarini J and Mostafa A 2010 Design, synthesis and preliminary antiviral screening of new N-phenylpyrazole and dihydroisoxazole derivatives Med. Chem. Res. 19 1025–35
[2] Varshney V, Mishra N N, Shukla P K and Sahu D P 2009 Synthesis and antibacterial evaluation of isoxazolinyl oxazolidinones: Search for potent antibacterial Bioorg. Med. Chem. Lett. 19 3573–6
[3] Kaur K, Kumar V, Sharma A K and Gupta G K 2014 Isoxazoline containing natural products as anticancer agents: A review Eur. J. Med. Chem. 77 121–33
[4] Liao J, Ouyang L, Jin Q, Zhang J and Luo R 2020 Recent advances in the oxime-participating synthesis of isoxazolines *Org. Biomol. Chem.* **18** 4709–16

[5] Norman A L, Shurrush K A, Calleroz A T and Mosher M D 2007 A tandem oximation-cyclization route to Δ2-isoxazolines *Tetrahedron Lett.* **48** 6849–51

[6] Schmidt E Y, Tatarinova I V., Ivanova E V., Zorina N V., Ushakov I A and Trofimov B A 2013 A one-pot approach to Δ2-isoxazolines from ketones and arylacetylenes *Org. Lett.* **15** 104–7

[7] Becke A D 1988 Density-functional exchange-energy approximation with correct asymptotic behavior *Phys. Rev. A* **38** 3098–100; Lee C, Yang W and Parr R G 1988 Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density *Phys. Rev. B* **37** 785–9

[8] Grimme S 2006 Semiempirical GGA-type density functional constructed with a long-range dispersion correction *J. Comput. Chem.* **27** 1787–99

[9] Marenich A V., Cramer C J and Truhlar D G 2009 Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions *J. Phys. Chem. B* **113** 6378–96

[10] Wertz D H 1980 Relationship between the gas-phase entropies of molecules and their entropies of solvation in water and 1-octanol *J. Am. Chem. Soc.* **102** 5316–22

[11] Cooper J and Ziegler T 2002 A Density Functional Study of S N 2 Substitution at Square-Planar Platinum(II) Complexes *Inorg. Chem.* **41** 6614–22

[12] Vitkovskaya N M, Kobychev V B, Bobkov A S, Orel V B, Schmidt E Y and Trofimov B A 2017 Nucleophilic Addition of Ketones To Acetylenes and Allenes: A Quantum-Chemical Insight *J. Org. Chem.* **82** 12467–76

[13] Frisch M J, Trucks G W, Schlegel H B, Scuseria G E, Robb M A, Cheeseman J R, Scalmani G, Barone V, Petersson G A, Nakatsuji H, et al 1916 Gaussian 09, Revision C.01