Assembly of 1H-pyrrole from cyclopentanone oxime and acetylene: a quantum-chemical model

A S Bobkov\textsuperscript{1,2} and N M Vitkovskaya\textsuperscript{1}

\textsuperscript{1} Laboratory of Quantum Chemical Modeling of Molecular Systems, Irkutsk State University, 664003, 1 Karl Marx St, Irkutsk, Russia
\textsuperscript{2} A.E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033, 1 Favorsky St, Irkutsk, Russia

E-mail: alex.bobkov@isu.ru

Abstract. Quantum-chemical modeling of the mechanism of 1,4,5,6-tetrahydrocyclopenta[b]pyrrole assembly from cyclopentanone oxime and acetylene has been carried out. The kinetic and thermodynamic characteristics of all reaction stages are calculated. The computation results have revealed a fundamental possibility of 1,4,5,6-tetrahydrocyclopenta[b]pyrrole formation via the Trofimov reaction.

1. Introduction
The base-promoted Trofimov reaction (scheme 1) opened a direct and effective way to the synthesis of various 1H-pyrroles and N-vinylpyrroles. The mechanism of this reaction was not only confirmed experimentally \cite{1}, but also recently studied in detail using quantum-chemical methods \cite{2}.

\begin{center}
\textbf{Scheme 1.} Trofimov reaction.
\end{center}

The literature covers the syntheses of various 1H-pyrroles condensed with saturated carbocycles: 4,5,6,7-tetrahydro-1H-indole (figure 1, A) \cite{3}, 1,4,5,6,7,8-hexahydrocyclohepta[b]pyrrole (figure 1, B) \cite{4}, 1,4,5,6,7,8,9-heptahydrocycloocta[b]pyrrole (figure 1, C) \cite{4} and even 1,4,5,6,7,8,9,10,11,12,13-undecahydrocyclocodeca[b]pyrrole (figure 1, D) \cite{4}. However, there is no mention on the synthesis of 1,4,5,6- tetrahydrocyclopenta[b]pyrrole by the Trofimov reaction (figure 1, E) (it was only noted that such a compound was not found \cite{4}).

\begin{center}
\textbf{Figure 1.} 1H-pyrroles structures.
\end{center}

Aubert et al. \cite{5} reported on the synthesis of tetrahydrocyclopenta[b]pyrroles by the reaction of 2-azidocyclopent-1-en-1-carbaldehyde with aliphatic ethers (scheme 2).
i. LDA, THF, -78°C

ii. RCH₂CO₂R' 

iii. POC₁₃, pyridine, benzene, 0°C

iv. PPh₃, toluene, room temp.

\[ R = H, R' = Et \]

Scheme 2. Tetrahydrocyclopenta[b]pyrroles synthesis by Aubert’s protocol.

Relatively recently, Yoshida and colleagues [6] have synthesized the substituted tetrahydrocyclopenta[b]pyrroles from 2-alkynyl-1-azaspiro[2.3]hexanes using platinum dichloride (scheme 3).

\[ 10\text{ mol } \% \text{ PtCl}_2 \]

\[ 100^\circ C \]

Scheme 3. Tetrahydrocyclopenta[b]pyrroles synthesis by Yoshida’s protocol.

These methods of obtaining pyrroles are laborious and expensive. Therefore, the issue of the fundamental possibility of the 1,4,5,6-tetrahydrocyclopenta[b]pyrrole synthesis by the Trofimov reaction becomes urgent. The issue can be addressed using high-level quantum chemical calculations.

2. Computational details

The geometries of the complexes and transition states were obtained using anionic model, with the geometry optimizations being performed in solution (DMSO) using the continuum solvent model IEFPCM [7] and the B3LYP/6-31+G* method. The vibrational corrections to enthalpies and Gibbs free energies were calculated at a standard temperature of 298.15 K. The energies were refined with the double-hybrid B2PLYP method and the 6-311++G** basis set. Effects of nonspecific solvation were additionally estimated using a solvation free energy correction within the IEFPCM model. The combined approach B2PLYP//B3LYP has already been successfully applied for the mechanistic study of the reaction in superbasic media and has shown good agreement with the high-precision CCSD(T)/6-311++G**//CCSD/6-31+G* method [8].

The connection of the transition states with the corresponding minima on the potential energy surface (PES) was proved with the reaction coordinate following, performed using the local quadratic approximation algorithm (LQA) [9]. To describe the kinetic and thermodynamic characteristics of the reactions, thermal effects \( \Delta H \) and free activation energies \( \Delta G^\ddagger \) were used.

To estimate changes of entropy in solution, we used Wertz approach [10,11] applied for a solution of dimethyl sulfoxide [12]. According to this approach the entropy in solution \( S_{\text{sol}} \) can be evaluated as follows: \( S_{\text{sol}} = 0.74S_{\text{harm}} - 3.21 \text{cal} \cdot \text{mol}^{-1} \cdot \text{K}^{-1} \), where \( S_{\text{harm}} \) is entropy of the ideal gas obtained within the harmonic approximation.

All calculations were carried out using the Gaussian 09 program package [13].

3. Results and discussion

The mechanism of the Trofimov reaction comprises the following key steps: vinylation of oxime by acetylene; 1,3-prototropic rearrangement of O-vinlyloxime into O-vinylhydroxylamine; [3,3]-sigmatropic shift in O-vinylhydroxylamine; intramolecular cyclization of iminoaldehyde; transformation of 5-hydroxypyrroline to 3H-pyrrole; rearrangement of 3H-pyrrole into 1H-pyrrole. All stages will be discussed in detail in the sections below.

3.1. O-vinlyloxime formation

The pyrrole assembly by the Trofimov reaction mechanism begins with the stage, which is classical for the base-promoted reactions. This is the formation of a nucleophile. The proton abstraction from cyclopentanone oxime 1 occurs with no activation barrier yielding a stable complex 2 of the oximate.
ion and a water molecule ($\Delta G = -11.5 \text{ kcal/mol}$). After introducing acetylene, nucleophilic addition of the oximate ion to the C≡C bond occurs with an activation barrier $\Delta G^\ddagger = 22.4 \text{ kcal/mol}$ (figure 2). The resulting carbanion is barrier-free protonated by a water molecule to form a complex 5 of O-vinyl oxime and hydroxide ion. It should be noted that in the case of cyclohexanone oxime, the vinylation stage was rate-determining with an activation barrier $\Delta G^\ddagger = 25.0 \text{ kcal/mol}$.

Figure 2. Reaction profile of oxime vinylation.

3.2. 1,3-Prototropic rearrangement and [3,3]-sigmatropic shift

The $\alpha$-carbon atom deprotonation occurs with an activation barrier $\Delta G^\ddagger = 7.8 \text{ kcal/mol}$ (figure 3) and leads to the formation of complex 6 with an increase in the system free energy by $\Delta G = 4.7 \text{ kcal/mol}$. The migration of a water molecule from a carbon atom to a nitrogen one gives more stable complex 7 ($\Delta G_0 = -12.4 \text{ kcal/mol}$). The protonation of the nitrogen atom affords complex 8 of O-vinylhydroxylamine and hydroxide anion and increases the energy to $\Delta G_0 = -7.1 \text{ kcal/mol}$. The next stage of the mechanism is [3,3]-sigmatropic shift. In the transition state, N−O bond is cleaved and the C−C bond between the second carbon atom of the cyclopentene ring and the $\beta$-carbon atom of the vinyl fragment is formed, yielding C=O and C=N bonds. The transition state of [3,3]-sigmatropic shift is higher than that of 1,3-prototropic rearrangement. Thus, the resulting activation barrier of two these stages is $\Delta G^\ddagger_{\Sigma} = 18.3 \text{ kcal/mol}$. The decrease in the system energy relative to the initial compounds in complex 9 of iminoaldehyde with hydroxide anion is $\Delta G_0 = -62.4 \text{ kcal/mol}$.

Figure 3. Reaction profile of 1,3-prototropic rearrangement and [3,3]-sigmatropic shift.
3.3. IntraMolecular cyclization of iminoaldehyde and 5-hydroxypyrroline vinylation

The iminoaldehyde conformation in complex 9 does not allow closing it into a cycle. Its change is carried out by a slight activation barrier $\Delta G^\ddagger = 1.8$ kcal/mol and leads to a more stable complex 10 ($\Delta G_0 = -63.1$ kcal/mol). Then, carbon atom of carbonyl group undergoes a nucleophilic attack by a nitrogen electron pair with an activation barrier $\Delta G^\ddagger = 6.6$ kcal/mol (figure 4). The proton of imino group migrates to hydroxide ion during descent from the transition state yielding complex 11 of the 5-hydroxypyrroline anion with a water molecule. The migration of a water molecule to the $O$-anion results in a more stable complex 12.

It was previously shown that 5-hydroxypyrroline vinylation is one of the key steps in the reaction mechanism [2]. Nucleophilic addition of the 5-hydroxypyrroline anion to acetylene occurs with an activation barrier $\Delta G^\ddagger = 24.3$ kcal/mol to afford complex 12 of 5-vinyloxypyrroline and hydroxide ion.

3.4. Formation of 3H-pyrrole and rearrangement to 1H-pyrrole

We have previously considered various ways of obtaining 3H-pyrrole [2]. The most promising way is realized through a series of transformations, which starts with a hydroxide ion addition to the C=N bond of 5-vinylxopyrroline.

The addition of the hydroxide ion to the C=N carbon atom is carried out with an activation barrier $\Delta G^\ddagger = 15.4$ kcal/mol. This process is accompanied by the simultaneous elimination of the vinyl alcohol anion (figure 5). The addition of a hydroxide ion to neutral azolin-2-ol leads to the abstraction of a proton from position 4 of the cycle with a barrier $\Delta G^\ddagger = 13.6$ kcal/mol. The elimination of the hydroxy group from the intermediate anion with the formation of 3H-pyrrole corresponds to the barrier $\Delta G^\ddagger = 11.3$ kcal/mol.

Rearrangement of 3H-pyrrole to 1H-pyrrole takes place with no activation barrier, and system energy decreases significantly. The formed 1H-pyrrole anion is much more favorable than the neutral form. It is consistent with the high acidity of pyrroles in dimethyl sulfoxide.
3.5. Comparison of the activation barriers

So, all thermodynamic characteristics of the main stages of the 1,4,5,6-tetrahydrocyclopenta[b]pyrrole assembly had been obtained. Next, they can be compared with characteristics for 4,5,6,7-tetrahydro-1H-indole. It allows to evaluate the possibility of 1,4,5,6-tetrahydrocyclopenta[b]pyrrole synthesis via the Trofimov reaction. Values of the activation barriers are presented in table 1.

Table 1. Activation barriers for the assembly stages of 4,5,6,7-tetrahydro-1H-indole and 1,4,5,6-tetrahydrocyclopenta[b]pyrrole.

| Stage                                      | Oxime vinylation | 1,3-Prototropic rearrangement and [3,3]-sigmatropic shift | Intramolecular cyclization | 5-Hydroxypyrroline vinylation | Azolin-2-ol formation | Azolin-2-ol deprotonation | 3H-pyrrole formation | 1H-pyrrole formation |
|--------------------------------------------|------------------|-----------------------------------------------------------|--------------------------|-------------------------------|-----------------------|-------------------------|-----------------------|----------------------|
| ![Pyrrole Reaction Profile](image.png)     | 24.9             | 17.3                                                      | 6.9                      | 24.3                          | 16.7                  | 13.7                    | 8.1                   | —                    |
| ![Pyrrole Reaction Profile](image.png)     | 22.4             | 18.3                                                      | 6.6                      | 24.3                          | 15.4                  | 13.6                    | 11.3                  | —                    |
| ![Pyrrole Reaction Profile](image.png)     |                  | 1.0                                                       | –0.3                     | 0.0                           | –1.3                  | –0.1                    | –3.2                  | –                    |
| ![Pyrrole Reaction Profile](image.png)     |                  | –2.5                                                      | –0.3                     | 0.0                           | –1.3                  | –0.1                    | –3.2                  | –                    |

First of all, it should be noted that the rate-determining step of 4,5,6,7-tetrahydro-1H-indole formation is the O-vinylation of oxime, while the vinylation of 5-hydroxypyrroline represent such a stage for 1,4,5,6-tetrahydrocyclopenta[b]pyrrole. However, the difference in these limiting barriers is insignificant (\(\Delta\Delta G^2 = 0.6\) kcal/mol), and in the case of 1,4,5,6-tetrahydrocyclopenta[b]pyrrole activation barrier is actually lower. Only at the stage of 3H-pyrrole formation, the activation barrier turns out to be higher by 3.2 kcal/mol for 1,4,5,6-tetrahydrocyclopenta[b]pyrrole, although it is still insignificant in comparison with the barrier of the rate-determining stage.
4. Conclusion

A quantum-chemical modeling of 1,4,5,6-tetrahydrocyclopentab[1]pyrrole assembly from cyclopentanone oxime and acetylene in superbasic medium has been carried out. It is shown that the activation barriers of the rate-determining stages of 4,5,6,7-tetrahydro-1H-indole and 1,4,5,6-tetrahydrocyclopentab[1]pyrrole formation are similar. So, 1,4,5,6-tetrahydrocyclopentab[1]pyrrole formation is theoretically possible under conditions similar to those for obtaining pyrrole from cyclohexanone oxime (~100°C, 1 atm.). However, 1,4,5,6-tetrahydrocyclopentab[1]pyrrole was not experimentally obtained by the Trofimov reaction. Most likely, this is due to various side processes of hydrolysis and condensation, which are characteristic of the basic media. The investigations in this field are under way.

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