The addition of ethylhydrazine to $\alpha,\beta$- and $\beta,\gamma$-unsaturated ketones: a quantum-chemical modeling

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Abstract. The reactivity of $\alpha,\beta$- and $\beta,\gamma$-unsaturated ketones with respect to the nucleophilic attack by ethylhydrazine in one of the key stages of the formation of 4,5-dihydropyrazole has been studied. It is shown that the addition of the terminal nitrogen atom of ethylhydrazine to the carbonyl group of $\beta,\gamma$- and $\alpha,\beta$-unsaturated ketones with the formation of $\beta,\gamma$- and $\alpha,\beta$-unsaturated hydrazones is energetically preferable with the participation of two water molecules. At the same time, the addition of the internal nitrogen of ethylhydrazine to the double C=C bond of the $\alpha,\beta$-unsaturated ketone (which is preferable in the presence of one water molecule) to give $\beta$-ethylhydrazinyl ketone occurs with a lower activation barrier and is thermodynamically more favorable than the addition to the C=O bond.

1. Introduction

It was experimentally shown [1] that the interaction of arylketones and phenylacetylenes in a superbasic medium (KOH/DMSO) followed by the addition of hydrochloric acid and alkylhydrazines afforded 4,5-dihydropyrazoles in a mixture with small amounts of benzylpyrazoles (figure 1).

![Figure 1. Formation of 4,5-dihydropyrazoles from phenylacetylenes, arylketones and alkylhydrazines.](image)

This reaction is of practical importance, since the structure of 4,5-dihydropyrazole is frequently met in various drugs exhibiting antitumor [2-4], antibacterial [5-6], antiviral [7], and antifungal [8] activities. However, the mechanism of 4,5-dihydropyrazoles formation is not fully understood.

Among the key intermediates of this reaction are $\beta,\gamma$- and $\alpha,\beta$-unsaturated ketones, which are formed via the C-vinylation of the starting ketones with phenylacetylene. Unsaturated ketones have two electrophilic centers: the carbonyl C=O bond and the double C=C bond. At the same time, $\alpha,\beta$-
unsaturated ketones possess more expressed electrophilic properties than β,γ-unsaturated ketones due to the π-conjugated structure, which activates β-carbon of the double C=C bond.

In this work, we have studied the reactivity of the carbonyl group of 1,4-diphenylbut-3-en-1-one and two electrophilic centers (C=O and C=C) of 1,4-diphenylbut-2-en-1-one (hereinafter β,γ- and α,β-unsaturated ketones, respectively) with respect to nucleophilic attack by ethylhydrazine. The addition of ethylhydrazine terminal nitrogen atom to the carbonyl group of unsaturated ketones delivers the corresponding unsaturated hydrazones, while the addition of an internal nitrogen atom to the double C=C bond of the α,β-unsaturated ketone gives β-ethylhydrazinyl ketone (figure 2).

![Figure 2](image_url)

**Figure 2.** Possible reaction products of the interaction of ethylhydrazine with α,β- and β,γ-unsaturated ketones.

The formation of any of these intermediates requires the participation of proton transfer molecules. In the reaction system, such molecules can be water, which is labile in the DMSO solution and is contained in the initial hydrochloric acid (36%) and potassium hydroxide (KOH·0.5H₂O), as well as is formed via the ketone deprotonation. The study of the reactions of addition of ethylhydrazine to the C=O and C=C bonds is carried out with the participation of one and two water molecules.

2. Computational details

All calculations were carried out using the GAUSSIAN 09 program package [9].

The structures of all studied systems were optimized using density functional theory (DFT), employing the B3LYP functional [10, 11] in combination with the 6-31+G* basis set. The correction of the solvation energy were calculated at the same level of theory (B3LYP/6-31+G*) using the IEFPCM [12] continuum model. The energies at the stationary points were refined by using the double-hybrid functional B2PLYP [13] in combination with the extended 6-311+G** basis set and taking into account the dispersion D2 Grimme correction [14] for improved accuracy.

For all stationary points the number of negative eigenvalues of the Hessian matrix was analyzed; the connection of the transition states with the corresponding potential energy surface (PES) minima was proved by the reaction coordinate following, using the local quadratic approximation algorithm (LQA) [15].

3. Results and discussion

3.1. Addition of terminal nitrogen atom of ethylhydrazine to the carbonyl group of β,γ-unsaturated ketones

The mechanism of hydrazine addition to the carbonyl group of ketones was previously considered in [16] by the example of hydrazine addition to acetone in an aqueous medium with the direct participation of water molecules. We have studied the nucleophilic addition of ethylhydrazine terminal nitrogen atom to the carbonyl group of β,γ-unsaturated ketone 1a involving one and two water molecules (figure 3). All stationary points on potential energy surface (PES) are located relative to the starting reagents: ketone 1a, ethylhydrazine, and the corresponding number of water molecules (one or two).
Figure 3. The mechanism of nucleophilic addition of ethylhydrazine terminal nitrogen atom to the carbonyl group of β,γ-unsaturated ketone 1a.

The interaction of 1a with ethylhydrazine with the participation of water molecules (n = 1, 2) through the transition state TS_{1a-2a} leads to intermediate 2a with an increase of the system energy by ΔG_{H2O} = 5.8 kcal/mol, n=1 (ΔG_{2H2O} = 5.8 kcal/mol, n=2). In this case, a proton is transferred from the terminal nitrogen atom to the oxygen of the carbonyl group through a sequence of hydrogen bonds of water molecules with the simultaneous formation of a C-N bond. The activation barrier TS_{1a-2a} is ΔG^{‡}_{H2O} = 21.2 kcal/mol (ΔG^{‡}_{2H2O} = 18.4 kcal/mol) relative to isolated 1a, ethylhydrazine, and water molecules (n=1, 2). Further, complex 2a rearranges into complex 3a due to a change in the conformation of 2a and location of water molecules (figure 4).

With the participation of one water molecule the complex 5a, consisting of β,γ-unsaturated hydrazone and two water molecules is formed through the transition state TS_{3a-5a}(H2O) with the decrease of the system energy to ΔG_{H2O} = −5.9 kcal/mol.

Figure 4. Reaction profile of the formation of β,γ-unsaturated hydrazone 6a with the participation of one and two water molecules from ethylhydrazine and β,γ-unsaturated ketone 1a and structures of the transition states. The dashed red line on transition state structures denotes the cleaved bond, and the dashed blue line denotes the formed bond. Hereinafter, all the values of ΔG are given in kcal/mol relative to the starting reagents (0.0).

With the participation of two water molecules the complex 4a (ΔG_{H2O} = 16.7 kcal/mol), consisting of a positively charged substrate, two molecules of water and a hydroxide anion is form through the transition state TS_{3a-4a}(2H2O). These transformations occur due to the simultaneous cleavage of C-OH bond and the proton transfer from neighboring water molecule to the hydroxyl group. Unstable
complex $4a$ without an activation barrier transforms into a complex of $\beta,\gamma$-unsaturated hydrazone and three water molecules $5a$, with a decrease of the system energy to $\Delta G = -3.9 \text{ kcal/mol}$. In this case, a proton is transferred from the terminal nitrogen atom to the hydroxide anion through one water molecule. Dissociation of complex $5a$ leads to isolated $\beta,\gamma$-unsaturated hydrazone $6a$ with a decrease in the energy of the system by $\Delta G = -8.2 \text{ kcal/mol}$ relative to $1a$ and ethylhydrazine.

Since at the first stage of the interaction of $1a$ with ethylhydrazine, a thermodynamically unfavorable complex $2a$ is formed, and the free energy of the $TS_{3a-2a}$ (2H$_2$O) and $TS_{3a-5a}$ (H$_2$O) transition states is higher than that of $TS_{1a-2a}$ (figure 4), the total activation energy is determined relative to the initial $1a$, ethylhydrazine, and water molecules. Thus, the activation barrier $TS_{3a-5a}$ (H$_2$O) is $\Delta G^\ddagger_{\text{H2O}} = 28.8 \text{ kcal/mol}$, and the activation barrier $TS_{3a-4a}$ (2H$_2$O) is $\Delta G^\ddagger_{\text{2H2O}} = 24.2 \text{ kcal/mol}$. The activation barrier of the rate-determining stage of this reaction with the participation of two water molecules is by 4.6 kcal/mol lower than that with the participation of one water molecule, therefore the addition of ethylhydrazine to $\beta,\gamma$-unsaturated ketone is kinetically more favorable with the participation of two water molecules.

3.2. Addition of terminal nitrogen atom of ethylhydrazine to the carbonyl group of $\alpha,\beta$-unsaturated ketones

Nucleophilic addition of terminal nitrogen atom of ethylhydrazine to the carbonyl group of $\alpha,\beta$-unsaturated ketone $1b$ has also been (figure 5) with the participation of one and two water molecules. All stationary points on the PES are calculated relative to the starting reagents: $1b$, ethylhydrazine, and the corresponding number of water molecules ($n=1, 2$).

**Figure 5.** The mechanism of nucleophilic addition of ethylhydrazine terminal nitrogen atom to the carbonyl group of $\alpha,\beta$-unsaturated ketone $1b$.

At the first stage, intermediate $2b$ is formed through the transition state $TS_{1b-2b}$ with an increase of the system energy by $\Delta G_{\text{H2O}} = 10.1 \text{ kcal/mol}$ ($\Delta G_{\text{2H2O}} = 9.3 \text{ kcal/mol}$). The activation barrier $TS_{1b-2b}$ is $\Delta G^\ddagger_{\text{H2O}} = 25.1 \text{ kcal/mol}$, $\Delta G^\ddagger_{\text{2H2O}} = 20.9 \text{ kcal/mol}$. Then complex $2b$ rearranges into complex $3b$ due to a change in the conformation of complex $2b$ and location of water molecules in the complex (figure 6).
Figure 6. Reaction profile of the formation of $\alpha,\beta$-unsaturated hydrazone $6b$ with the participation of one and two water molecules from ethylhydrazine and $\alpha,\beta$-unsaturated ketone $1b$ and structures of the transition states. The dashed red line on transition state structures denotes the cleaved bond, and the dashed blue line denotes the forming bond.

With the participation of one water molecule, like with $1a$, through the transition state $TS_{3b-5b}(H_2O)$, water is eliminated with the formation of the dihydrate complex $5b$ and with a decrease in the energy of the system by $\Delta G_{H2O} = -6.0$ kcal/mol relative to $1b$, ethylhydrazine, and one water molecules. With the participation of two water molecules through the transition state $TS_{3b-4b}(2H_2O)$, the hydroxyl group is eliminated with the formation of complex $4b$ ($\Delta G_{2H2O} = 13.5$ kcal/mol). Further, proton transfer from the terminal NH-group to the hydroxide ion through the one water molecule occurs without an activation barrier. In this case, complex $5b$ is formed with a decrease in the energy of the system by $\Delta G_{2H2O} = -4.4$ kcal/mol relative to $1b$, ethylhydrazine, and two water molecules.

Dissociation of complex $5b$ gives the isolated $\alpha,\beta$-unsaturated hydrazone $6b$ with a decrease in the energy of the system by $\Delta G = -8.1$ kcal/mol. The activation barrier $TS_{3b-5b}(H_2O)$ is $\Delta G^\dagger_{H2O} = 27.9$ kcal/mol, and the activation barrier $TS_{3b-4b}(2H_2O)$ is $\Delta G^\dagger_{2H2O} = 22.2$ kcal/mol (figure 6). These barriers are limiting for the formation of $\alpha,\beta$-unsaturated hydrazone $6b$. The activation barrier of the rate-determining stage of this reaction with the participation of two water molecules is by 5.7 kcal/mol lower than that with the participation of one water molecule. This means that the addition of ethylhydrazine to an $\alpha,\beta$-unsaturated ketone with the participation of two water molecules is preferable, as in the case of $\beta,\gamma$-unsaturated ketone.

3.3. Addition of internal nitrogen atom of ethylhydrazine to the double C=C bond of $\alpha,\beta$-unsaturated ketones

The mechanism of the addition of ethylhydrazine internal nitrogen atom to the $\beta$-carbon of the double C=C bond of the $\alpha,\beta$-unsaturated ketone $1b$ has been studied (figure 7). All points on the PES are represented relative to the starting reagents: $1b$, ethylhydrazine, and the corresponding number of water molecules ($n=1, 2$).
The mechanism of addition of ethylhydrazine internal nitrogen atom to the double C=C bond of α,β-unsaturated ketone 1b with the participation of one and two water molecules.

At the first stage, through the TS$_{1b-2c}$ transition state with an activation barrier $\Delta G^\ddagger = 14.7$ kcal/mol, a proton is transferred from the internal nitrogen atom to the oxygen of the carbonyl group without the participation of water molecules with the simultaneous formation of the C-N$_{inter}$ bond. This transformation leads to the intermediate 2c with an insignificant increase in the energy of the system by $\Delta G = 0.1$ kcal/mol (figure 8).

At the second stage, proton of the hydroxyl group is transferred to the internal nitrogen atom, through the transition state TS$_{2c-3c}$ with the participation of water molecules (figure 9). This transformation gives complex 3c with an increase in the energy of the system by $\Delta G_{H_2O} = 12.7$ kcal/mol ($\Delta G_{2H_2O} = 9.7$ kcal/mol).

Figure 7. The mechanism of addition of ethylhydrazine internal nitrogen atom to the double C=C bond of α,β-unsaturated ketone 1b with the participation of one and two water molecules.

Figure 8. Reaction profile of the formation of β-ethylhydrazinylketone 6c with the participation of one and two water molecules from α,β-unsaturated ketone 1b and ethylhydrazine.

Figure 9. Structures of transition states of the reaction of addition of ethylhydrazine to the double C=C bond of α,β-unsaturated ketone 1b. The dashed red line on transition state structures denotes the cleaved bond, and the dashed blue line denotes the formed bond.
The activation barrier $\text{TS}_{2c-3c}$ is $\Delta G^{i}_{\text{H}_2\text{O}} = 12.9$ kcal/mol ($\Delta G^{i}_{2\text{H}_2\text{O}} = 16.5$ kcal/mol). Next, complex $3c$ undergoes conformational transformation to complex $4c$ with an increase in the energy of the system by $\Delta G_{\text{H}_2\text{O}} = 12.1$ kcal/mol ($\Delta G_{2\text{H}_2\text{O}} = 12.6$ kcal/mol). Through the transition state $\text{TS}_{4c-5c}$ with the participation of water molecules (figure 8), a proton is transferred from the internal nitrogen atom to $\alpha$-carbon with the formation of complex $5c$ and a decrease in the energy of the system by $\Delta G_{\text{H}_2\text{O}} = -5.4$ kcal/mol ($\Delta G_{2\text{H}_2\text{O}} = -2.2$ kcal/mol). Upon the dissociation of complex $5c$, isolated $\beta$-ethylhydrazinylketone $6c$ is formed with a decrease in the energy of the system by $\Delta G = -9.5$ kcal/mol.

Since after the first and second stages of interaction of $1b$ with ethylhydrazine, a thermodynamically unfavorable complex $3c$ is formed, and the free energy of the transition state of $\text{TS}_{4c-5c}$ is higher than that of $\text{TS}_{1b-2c}$ and $\text{TS}_{2c-3c}$ (figure 8), the activation energy of $\text{TS}_{4c-5c}$ is determined relative to the initial $1b$, ethylhydrazine and water molecules (one or two). Thus, the activation barrier of $\text{TS}_{4c-5c}$ with the participation of one water molecule is $\Delta G^{i}_{\text{H}_2\text{O}} = 19.5$ kcal/mol, which is by 1.2 kcal/mol higher than activation barrier in case of two water molecules ($\Delta G^{i}_{2\text{H}_2\text{O}} = 20.7$ kcal/mol). Therefore, the addition of ethylhydrazine internal nitrogen atom to the $\beta$-carbon of the double C=C of $\alpha,\beta$-unsaturated ketone is kinetically more favorable with the participation of one water molecule. Moreover the addition of ethylhydrazine internal nitrogen atom to the C=O bond of the $\alpha,\beta$-unsaturated ketone $1b$ with the participation of one water molecule and with the formation of intermediate $6c$ is kinetically and thermodynamically more preferable than the addition to the C=O bonds of $1a$ and $1b$ (Table 1).

**Table 1.** Activation barriers ($\Delta G^i$, kcal/mol) and Gibbs free energy ($\Delta G$, kcal/mol) of the addition of ethylhydrazine terminal nitrogen atom to the C=O group $\beta,\gamma$- ($1a$) and $\alpha,\beta$- ($1b$) unsaturated ketones and internal nitrogen atom to the C=C bond of $\alpha,\beta$-unsaturated ketone $1b$.

| Reaction | $\Delta G^i$, kcal/mol | $\Delta G$, kcal/mol |
|----------|------------------------|---------------------|
| $1a$ $\xrightarrow{\text{H}_2\text{O}}$ $6a$ | 24.2 | -8.2 |
| $1b$ $\xrightarrow{\text{H}_2\text{O}}$ $6b$ | 22.2 | -8.1 |
| $1b$ $\xrightarrow{\text{H}_2\text{O}}$ $6c$ | 19.5 | -9.5 |

4. Conclusions
In this work we have shown that:
- The nucleophilic addition of ethylhydrazine can occur both to the carbonyl group of $\beta,\gamma$- and $\alpha,\beta$-unsaturated ketones, and to the C=C bond of $\alpha,\beta$-unsaturated ketone;
- The addition of ethylhydrazine to the carbonyl group of $\beta,\gamma$- and $\alpha,\beta$-unsaturated ketone occurs preferably with the participation of two water molecules and leads to the formation of $\beta,\gamma$- and $\alpha,\beta$-unsaturated hydrazones, respectively;
- The addition of ethylhydrazine to the double C=C bond of an $\alpha,\beta$-unsaturated ketone is more favorable with the participation of one water molecule to give $\beta$-ethylhydrazinyl ketone;
The addition of ethylhydrazine internal nitrogen atom to the C=C bond of the α,β-unsaturated ketone is kinetically and thermodynamically preferable than the addition to the C=O bonds of the both unsaturated ketones;

The assembly of 4,5-dihydropyrazole from ethylhydrazine and unsaturated ketones occurs mainly through the formation of an intermediate β-ethylhydrazinyl ketone.

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