Acetylene vs ketones on the route to base-promoted assembly of furans or 6,8-dioxabicyclo[3.2.1]octanes and cyclopentenols: a quantum-chemical study

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Abstract. The electronic characteristics of substrates (\(\alpha,\beta\)-unsaturated ketones) and reagents (carbanions of ketones and ethynide ions), as well as thermodynamic and kinetic characteristics both their interaction and the formation of final products have been evaluated using the B2PLYP/6-311++G**//B3LYP/6-31+G* and B3LYP/6-311++G**//B3LYP/6-31+G* quantum-chemical approaches. Reactivity indices that adequately describe the electrophilic and nucleophilic properties of the substrates and reagents are proposed. It has been shown that, regardless of the nature of substrates and reagents, the formation of cyclopentenols and furans is thermodynamically favorable, while the presence of bulky substituents leads to an increase in energy during the formation of 6,8-dioxabicyclo[3.2.1]octanes and explains in this case their absence in products. The calculated activation barriers of the competing reactions of the nucleophilic addition of ethynide ions and ketone carbanions to the double C=C bond of \(\alpha,\beta\)-unsaturated ketones are correlated with the observed reaction direction and the proposed reactivity indices.

1. Introduction

Recently, it has been shown that ketones in the presence of superbases at elevated temperatures react with acetylenes not to form tertiary alcohols (the Favorsky reaction), but are added to the triple carbon-carbon bond as C-nucleophiles to afford unsaturated ketones:

\[
\begin{align*}
\text{R}_1\text{O}\text{R}_2 + \text{R}_3 & \xrightleftharpoons[100 \degree C, 30-60 \text{ min}]{\text{MOH/DMSO}} \text{R}_1\text{O}\text{R}_2\text{R}_3 \\
\end{align*}
\]

This reaction tolerates aliphatic, cycloaliphatic, and alkylaromatic ketones, and both acetylene itself and its aryl and hetaryl derivatives can act as the acetylene component [1].

The formed unsaturated ketones can further interact with the molecules of ketones and acetylenes that have not yet reacted. In various combinations, these interactions lead, depending on the nature of the reagents and reaction conditions, to various carbocyclic (hexahydroazulenones and cyclopentenols) or heterocyclic (furans, benzoxepines, dioxabicyclooctanes, etc.) compounds [1]. One of the branching points arises as a result of competition between initially formed in the superbasic system ethynide ion and ketone carbanion for the nucleophilic addition at the C\(\beta\)-atom of the double
C=C bond of the α,β-unsaturated ketone. Thus, under slightly different conditions [1], in the reaction with the ketone carbanion (interaction I), 1,5-diketones, precursors of dioxabicyclooctanes and cyclopentenols, are selectively formed, while substituted furans are selectively obtained in the reaction with the ethynide ion (interaction II):

\[
\begin{array}{c}
\text{I} \quad \text{R}_1 \text{C} = \text{C} / \text{H}_2\text{O} \quad \text{II} \quad \text{R}_1 \text{C} = \text{C} / \text{H}_2\text{O}
\end{array}
\]

Until now, however, the factors that determine the preference of I or II direction of the reaction, and which final product (furan, bicyclooctane or cyclopentenol) will be formed, depending on the nature of the reagents, have not been established. It was experimentally established [2] only that the formation of the furan ring is observed when bulky substituents are present in the initial ketone at the carbonyl group (for example, \(R_1 = \text{Mes}\)) or at the α-carbon atom (for example, \(R_2 = \text{Ph, Bn}\)). Using the methods of quantum-chemical modeling, in order to establish the factors influencing these transformations, the electronic properties of substrates (α,β-unsaturated ketones) and reagents (ketone carbanions and ethynide ions), differing in substituents \(R_1\) and \(R_2\), have been estimated. Thermodynamic and kinetic characteristics have been calculated both in the path of interaction of substrates and reagents, and in the path of formation of final products.

2. Computational details
Quantum-chemical calculations were carried out within the anionic model ANION\(_{\text{GAS}}\) [3], which neglects the presence of the cation and considers isolated ketone carbanions and ethynide ions with solvent only as a polarizable continuum. The recent use of this model to calculate activation barriers of this reaction has allowed us to successfully estimate the competition between ethynide ions and ketone carbanions for the nucleophilic addition to the C=C bond of α,β-unsaturated ketone [3]. The structural parameters, vibrational corrections to enthalpies and Gibbs free energies of the studied systems were calculated using B3LYP/6-31+G* approach [4,5]. Further, for the calculations of electronic properties of initial α,β-unsaturated ketones, ethynide ions and ketone carbanions the energies at the stationary points were refined using the same B3LYP method with an extended basis 6-311++G**, whereas for the calculations of thermodynamic and kinetic properties the double-hybrid functional B2PLYP/6-311+G** [6] was used. The last one was successfully used in the study of nucleophilic addition to the C=C bond of α,β-unsaturated ketone [3]. Solvation energy in DMSO was computed additionally by the polarizable dielectric model using the IEFPCM [7]. To estimate activation free energy in the solution we have used approach, which is based upon results by Wertz [8] suggested in article [9] and applied us to dimethyl sulfoxide solutions [10]. All calculations have been carried out using the GAUSSIAN 09 program package [11].

3. Results and discussions
3.1. Estimations of the free energies of formation of furans, 6,8-dioxabicyclo[3.2.1]octanes and cyclopentenols
One of the important characteristics of the reaction is the changes in Gibbs free energy during the process (\(\Delta G\)), which determines the possibility of its implementation at constant pressure and temperature. At the first stage of the study, the change in Gibbs free energy during the formation of various substituted furans (\(\Delta G_{\text{FUR}}\)), 7-methylene-6,8-dioxabicyclo[3.2.1]octanes (\(\Delta G_{\text{BCO}}\)) and cyclopentenols (\(\Delta G_{\text{CP}}\)) was estimated for the reactions:
α,β-unsaturated ketone molecule was chosen as the initial substrate, but its anionic form (dieneolate ion), which is more stable in a superbasic medium [3]. The values of the relative free energies (table 1) indicate, according to the calculations, that only the formation of furans and cyclopentenols (at R₂ = H [12]) is always thermodynamically favorable.

Table 1. Relative free energies of formation of some 7-methylene-6,8-dioxabicyclo[3.2.1]octanes (ΔG\textsubscript{BCO}), cyclopentenols (ΔG\textsubscript{CP}) and substituted furans (ΔG\textsubscript{FUR}), kcal/mol.

| R₁  | R₂  | ΔG\textsubscript{BCO} | ΔG\textsubscript{CP} | ΔG\textsubscript{FUR} |
|-----|-----|----------------------|----------------------|----------------------|
| Ph  | H   | −4.9                 | −18.6                | −31.0                |
| Mes | H   | 10.0                 | −7.9                 | −29.7                |
| Th  | Me  | −1.7                 | −34.6                | −33.8                |
| Ph  | Bn  | 2.0                  | −                   | −                   |

The formation of 6,8-dioxabicyclo[3.2.1]octanes is accompanied by a decrease in free energy only at R₁ = Ph, R₂ = H and R₁ = Th, R₂ = Me, but in the case of bulky substituents (R₁ = Mes or R₂ = Bn), the free energy increases by 10.0 and 2.0 kcal/mol, respectively. Thus, the presence of bulky substituents at the carbonyl group or at the α-carbon atom leads to thermodynamic instability of 6,8-dioxabicyclo[3.2.1]octanes relative to the starting alkylaryl ketones and acetylene. For such α-substituted ketones, the only possible products are furans, and for α-unsubstituted ketones are also cyclopentenols.

When the formation of 6,8-dioxabicyclo[3.2.1]octanes is thermodynamically allowed (table 1), the direction of the reaction is determined by the competition between the ethylnide ion and the ketone carbanion for nucleophilic addition to the double C=C bond of the α,β-unsaturated ketone. Further, the preference for the interactions of an unsaturated ketone with a ketone carbanion and an unsaturated ketone with an ethylnide ion was evaluated based on the electrophilic properties of α,β-unsaturated ketones and the nucleophilic properties of ketone carbanions and ethylnide ion.

3.2. Electronic characteristics of substrates (α,β-unsaturated ketones) and reagents (carbanions of ketones and ethylnide ions)

To estimate the electrophilic and nucleophilic properties, a large variety of different reactivity indices have been proposed, and some of them have been successfully used to determine the preference of one or another interaction, including in reactions of nucleophilic addition to the C=C bond of unsaturated ketones [13]. Let us consider the main ones. In the R. Parr work [14], the total electrophilicity of the system ω is determined through its chemical potential μ and chemical hardness η:

$$\omega = \frac{\mu^2}{2\eta}.$$  \hspace{1cm} (1)
This index indicates the decrease in the system energy when electrons arrive from the outside and the ability of the system to accept donor electrons. In turn, the global characteristics $\mu$ and $\eta$, determined through the first and second derivatives of energy with respect to the number of electrons in the system [14,15], can be approximated through the vertical ionization potential $I$ and the electron affinity energy $A$:

$$-\mu = \left( \frac{\partial E}{\partial N} \right) \approx \frac{(I + A)}{2} = \chi,$$

where $\chi$ is Mulliken electronegativity and

$$\eta = \frac{1}{2} \left( \frac{\partial^2 E}{\partial N^2} \right) = \frac{1}{2} \left( \frac{\partial \mu}{\partial N} \right) \approx \frac{I - A}{2}.$$

Often, to estimate $\mu$ and $\eta$, instead of the $I$ and $A$, the energies of the highest occupied MO and the lowest unoccupied MO are used; however, within the density functional theory, such an approach can lead to gross errors [16]; therefore, we have employed a different approach called $\Delta$SCF (self-consistent field), assuming

$$I = E_{N-1} - E_N,$$
$$A = -(E_{N+1} - E_N),$$

where $E_N$ are the energies of neutral systems, and $E_{N+1}$ and $E_{N-1}$ are the energies of systems with an additional and removed electrons.

The electrophilicity indices were evaluated both for $\alpha,\beta$-unsaturated ketones reacting with ketone carbanions (1-3) and for those reacting with ethynide ion (4-6). The values obtained range from 2.26 to 2.71 eV (table 2), which allows for both cases to classify the considered unsaturated ketones as strong ($\omega > 1.5$ eV) electrophiles [17].

Table 2. Ionization potentials $I$ (eV), electron affinities $A$ (eV), electronic chemical potentials $\mu$ (eV), chemical hardness $\eta$ (eV), and global electrophilicities $\omega$ (eV) of $\alpha,\beta$-unsaturated ketones $R_1-(CO)-CR_2=C-CH_3$.

| No | $R_1$ | $R_2$ | $I$ | $A$ | $\mu$ | $\eta$ | $\omega$ |
|----|------|------|-----|-----|-------|-------|-------|
| 1  | Th   | H    | 8.79| 0.63| -4.71 | 4.08  | 2.71  |
| 2  | Ph   | H    | 8.84| 0.53| -4.69 | 4.15  | 2.64  |
| 3  | Th   | Me   | 8.53| 0.46| -4.49 | 4.04  | 2.50  |
| 4  | Th   | Ph   | 8.16| 0.61| -4.39 | 3.77  | 2.55  |
| 5  | Ph   | Bn   | 8.21| 0.38| -4.29 | 3.92  | 2.35  |
| 6  | Mes  | H    | 8.21| 0.26| -4.24 | 3.97  | 2.26  |

However, a significant contribution to their overall electrophilicity, in addition to the C$^\beta$-carbon atom, is made by the carbonyl carbon atom, therefore, it is necessary to consider the local electrophilicity of only C$^\beta$-carbon atom $\omega^+$ [18] (table 3), which is defined as:

$$\omega^+ = \omega \cdot f^+,$$

where $f^+$ is Fukui function [19] for nucleophilic attack

$$f^+_k = q_k(N+1) - q_k(N).$$

To find the atomic charges $q_k$ included in (6), we used the Hirschfeld scheme [20].
Table 3. Fukui functions $f^*$, local electrophilicities $\omega^+$ (eV), charges on the C$^\beta$-atom $q(\beta)$ (a.u.) of $\alpha,\beta$-unsaturated ketones $R_1$–(CO)–CR$_2$=C–CH$_3$, activation barriers of ethynide ion addition $\Delta G^1_{et}$ (kcal/mol) to C=C bond of them, and yields of furans (%).

| No | R$_1$ | R$_2$ | $f^*$ | $\omega^+$ | $q(\beta)$ | $q(\beta)\times\omega$ | $\Delta G^1_{et}$ | Yield |
|----|-------|-------|-------|-----------|-----------|-----------------|-----------------|-------|
| 1  | Th    | H     | 0.0963| 0.2616    | 0.0547    | 0.1487          | 12.2            | –     |
| 2  | Ph    | H     | 0.1017| 0.2689    | 0.0545    | 0.1441          | 12.9            | –     |
| 3  | Th    | Me    | 0.0744| 0.1860    | 0.0283    | 0.0708          | 16.0            | –     |
| 4  | Th    | Ph    | 0.0762| 0.1944    | 0.0388    | 0.0991          | 13.9            | 62    |
| 5  | Ph    | Bn    | 0.0814| 0.1915    | 0.0268    | 0.0631          | 16.6            | 53    |
| 6  | Mes   | H     | 0.1169| 0.2639    | 0.0542    | 0.1222          | 14.4            | 73    |

Unfortunately, the local electrophilicities $\omega^+$ of $\alpha,\beta$-unsaturated ketones are poorly correlated ($R^2 = 0.60$) with the calculated activation barriers for the addition of ethynide ions. This may be due to the high hardness of the compact ethynide ion, the behavior of which should be characterized in addition to the orbital factor, determined by Fukui functions, also by the charge on C$^\beta$-atom. In this regard, we proposed the multiplication of the global electrophilicity $\omega$ and the value of the charge (according to Hirschfeld scheme [20]) on the attacked C$^\beta$-atom of the substrate as reactivity index (table 3). To our knowledge, such a combined index has never been used before us. It agrees well with both the yields of the final reaction products (table 3) and the activation energies of ethynide ion addition to the C=C bond of $\alpha,\beta$-unsaturated ketones (figure 1).

![Figure 1](image)

**Figure 1.** Relation between the free activation energy of the ethynide ion addition to the double C=C bond and combined index $q(\beta)\times\omega$.

The interaction of $\alpha,\beta$-unsaturated ketones with ketone carbanions is influenced not only by the electrophilicity of the substrate, but also by the nucleophilicity of the carbanion. In this work, the multiphilic index:

$$\Delta \omega_k = \left[ \omega_k^+ - \omega_k^- \right] = \omega \left[ f_k^+ - f_k^- \right],$$

(7)
where $\omega$ is electrophilicity index, $f^\pm_k$ are corresponding Fukui functions (table 4), introduced by the authors of [21] was used to characterize nucleophilicity. This index indicates the ability of the $k$ atom to show more nucleophilic ($\Delta \omega_k < 0$) or electrophilic properties ($\Delta \omega_k > 0$). The estimations obtained predict a significantly greater nucleophilicity of ketone carbanions, which really win the competition with ethynide ion for the addition to the C=C bond of $\alpha,\beta$-unsaturated ketones (table 4, entry 1-3).

Table 4. Global electrophilicities ($\omega$, eV), total Fukui functions ($f^+$ and $f^-$, a.u.), multiphlicity ($\Delta \omega_k$, eV) of ketone carbanions and ethynide ion, combined index in reaction with ketone carbanions ($\omega^+ \times \Delta \omega_k$, eV$^2$) and in reaction with ethynide ion ($q(\beta)\times \omega^+ \times \Delta \omega_k$, eV$^2$) total yields of 7-methylene-6,8-dioxabicyclo[3.2.1]octanes and cyclopentenols (Yield$_{BCO\&CP}$, %) and yields of substituted furans (Yield$_{FUR}$, %).

| No | R$_1$ | R$_2$ | $\omega$ | $f^+$ | $f^-$ | $\Delta \omega_k \times 10^3$ | $\omega^+ \times \Delta \omega_k \times 10^3$ | Yield$_{BCO\&CP}$ | $q(\beta)\times \omega^+ \times \Delta \omega_k \times 10^3$ | Yield$_{FUR}$ |
|----|------|------|---------|------|------|-----------------|-----------------|-------------|-----------------|----------|
| 1  | Th   | H    | 0.0238  | 0.0249| 0.2601| -5.6            | -1.490          | 72          | -1.472          | -        |
| 2  | Ph   | H    | 0.0260  | 0.0234| 0.2646| -6.3            | -1.694          | 98          | -1.427          | -        |
| 3  | Th   | Me   | 0.0415  | 0.0191| 0.1971| -7.4            | -1.376          | 41          | -0.701          | -        |
| 4  | Th   | Ph   | 0.0026  | 0.0061| 0.1425| -0.4            | -0.078          | -           | -0.981          | 62       |
| 5  | Ph   | Bn   | 0.0033  | 0.0032| 0.1937| -0.6            | -0.115          | -           | -0.625          | 53       |
| 6  | Mes  | H    | 0.0122  | 0.0117| 0.2658| -3.1            | -0.818          | -           | -1.210          | 73       |
| HCC|      |      | 0.0230  | 0.1561| 0.5852| -9.9            | -              | -           | -                |         |

Finally, the collective effect of the electrophilic properties of the substrate and the nucleophilic properties of reagents is presented in this study as the multiplication of the multiplicity index $\Delta \omega_k$ of nucleophiles and local electrophilicity of $\alpha,\beta$-unsaturated ketones $\omega^+$ (in the reaction with ketone carbanions), or the combined index $q(\beta)\times \omega$ (in the reaction with ethynide ion). The obtained index values are in good agreement with the experimentally observed formation of bicyclooctanes and cyclopentenols in cases of 1-3 and substituted furans in cases of 4-6, and also agree with the yields of these products (table 4).

Thus, the preferences in the nucleophilic addition of ketone carbanion to $\alpha,\beta$-unsaturated ketones are well predicted based on the multiplication of the indices of the local electrophilicity $\omega^+$ of the substrate and the multiplicity $\Delta \omega_k$ of the ketone carbanion, whereas the preferences in the nucleophilic addition of ethynide ion are well predicted based on both the combined index $q(\beta)\times \omega$ and its multiplication with multiplicity index $\Delta \omega_k$ of ethynide ion. It should be noted that the absence of a universal index for these competing reactions is expected, since in quantum mechanics there is no operator corresponding to such chemical characteristics of molecules as electrophilicity and nucleophilicity, and for each type of interaction it is often necessary to select its own indices.

3.3. Kinetic characteristics of the reactions of addition of the ethynide ion and ketone carbanions to the C=C bond of $\alpha,\beta$-unsaturated ketones

The applicability of the proposed indices for predicting the preference for nucleophilic addition of ethynide ion or ketone carbanion to the C=C bond of $\alpha,\beta$-unsaturated ketones was verified by calculating the activation barriers for some of these competing reactions (table 5). The lowest activation barriers were obtained for the interaction of unsaturated ketone/ketone carbanion pairs with $R_1 = Ph, R_2 = H; R_1 = Th, R_2 = Me$. The index proposed for them also predicts the greatest preference for this interaction, and indeed in these cases the formation of cyclopentenols and 6,8-dioxabicyclo[3.2.1]octanes is observed experimentally.
On the contrary, the addition of the ethynide ion to the α,β-unsaturated ketone with $R_1 = \text{Mes}$, $R_2 = \text{H}$ is associated with a lower barrier, which agrees with the indices obtained for these substrate/reagent pairs and the experimentally observed formation of substituted furans. The preference for interaction with the ethynide ion is also characterized by the indices for the case with $R_1 = \text{Ph}$, $R_2 = \text{Bn}$; however, the barriers to competing reactions are very close. Nevertheless, as previously was shown in Section 3.1, exclusive formation of substituted furans in this case is associated with the thermodynamically unfavorable formation of 7-methylene-6,8-dioxa[3.2.1]bicyclooctanes.

These results demonstrate that the proposed indices describe well the competing interactions of the ethynide ion and ketone carbanions with α,β-unsaturated ketones and can be used to predict the preferred direction of the reaction.

4. Conclusion
It was shown that the absence of 7-methylene-6,8-dioxa[3.2.1]bicyclooctanes (reaction products of unsaturated ketones and ketone carbanions) in cases with bulky substituents at the carbonyl group or at the α-carbon atom of ketones is due to the fact that their formation is thermodynamically unfavorable. On the contrary, the formation of furans, the products of the competitive reaction of unsaturated ketones with the ethynide ion, and cyclopentenols, other products of the reaction of unsaturated ketones with ketone carbanions, regardless of the nature of ketones, is thermodynamically favorable. If both reactions are thermodynamically favorable, the preferred direction is determined by the activation barriers at the stage of addition of ketone carbanions or ethynide ions to the C≡C double bond of the unsaturated ketone. The reactivity indices, which we have proposed for the reactions with ketone carbanions, as the product of the local electrophilicity $\omega^*$ of the substrate and the multiplicity $\Delta \omega_k$ of the ketone carbanion, and for reactions with ethynide ions as the product of the combined index $q(\beta)\times\omega$ substrate and multiplicity $\Delta \omega_k$ of the ethynide ion, are able to predict the direction of the reaction.

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