The effect of the reagents nature on nucleophilic addition of acetylenes to the C=N bond of aldimines: a quantum-chemical investigation

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Abstract. A quantum-chemical simulation of the mechanism of ethynylation of aldimines with substituted acetylenes was carried out. Kinetic and thermodynamic characteristics of this reaction for various reacting pairs were estimated by the B2PLYPD/6-31++G**//B3LYP/6-31+G * method. It was shown that in the reaction with N-alkylaldimines, the ethynylation barrier was significantly higher than in the reaction with N-arylaldimines. The change in the substituents at acetylene has no effect on the ethynylation barriers.

1. Introduction

Acetylenes play an important role in modern organic chemistry, especially in the synthesis of various heteroatomic (including heterocyclic) compounds with potentially high biological activity [1-4]. The advantages of acetylenes are their availability and ability to exhibit both electrophilic and nucleophilic properties. The use of superbasic system in acetylene chemistry allows the reactions to be carried out under milder conditions. This has resulted in discovery of new types of reactions that are implemented without transition metal catalytic systems [5].

An example of such reactions is the recently disclosed E-stereoselective reaction of the formation of 1-azadienes from aldimines and acetylenes [6]. It is carried out under mild conditions (14°C, 1 h) under the action of superbasic system KOBu/DMSO to give the target product in a yield of up to 72%. It is noted that when the temperature increases to 17°C and the reaction time grows to 2 hours, the yield decreases to 39%. This is due to the ability of 1-azadiene to polymerize under the reaction conditions. At the same time, the yield of this polymer drops by 30% when the synthesis duration is reduced to 1 hour [6]. It is possible to involve aldimines with different aryl substituents in the reaction at C=N bond, and the yield of the products varies between 33% and 72%, while in the case of the n-butyl substituent at the nitrogen atom the product is not detected. Similar regularities are also observed in the case of variable substituents at the triple C≡C acetylene bond [6]. Until now, however, the factors influencing the yield of 1-azadienes have not been experimentally established.

The proposed reaction mechanism involves the formation of an ethynide ion with the participation of KOBu/DMSO, followed by the addition of an ethynide ion by the C=N bond and isomerization of propargylamine to 1-azadiene (figure 1). In addition, it has been experimentally shown that in the
reaction of benzaldimine with phenylacetylene the conversion of propargylamines to 1-azadienes is a fast stage; therefore, ethynylation is apparently a rate-determining process.

![Figure 1. Mechanism of formation of 1-azadienes from aldimes and acetylenes.](image)

In this work, the effects of the substituent at the nitrogen atom of aldimes (R²) and at acetylene (R³) on the thermodynamic and kinetic characteristics of the aldime ethynylation have been established using quantum-chemical simulation. The mechanism of this interaction is studied for the following reaction pairs: benzaldimine/phenylacetylene (a); (E)-N,1-diphenylmethanimine/1-ethynyl-3-methylbenzene (b); (E)-N,1-diphenylmethanimine/1-ethynyl-4-methylbenzene (c); (E)-N,1-diphenylmethanimine/2-ethynyl-1,4-dimethylbenzene (d); (E)-N,1-diphenylmethanimine/3,3-dimethylbut-1-yne (e); (E)-N-butyl-1-phenylmethanimine/phenylacetylene (f).

![Figure 2. Ethynylation of aldimine (1→3) and the reaction products](image)

2. Computational details

In superbasic systems MOR/DMSO (M = Na, K; OR = OH, OBu') type due to specific solvent (DMSO) binding with alkali metal cation, the transformations can be described within the framework of the anionic model, neglecting the presence of remote cation and considering anion solvation only in the polarizable continuum as a correction for energy (ANION_GAS model) [7].

Basis sets with diffuse functions were used to describe anion systems as the electronic density of anions is located far away from the cores and these remote areas of space require accounting. We have chosen the base set 6-31+G*, combined with the B3LYP density functional method [8, 9]. This approach provides a fairly good description of the equilibrium geometry and is effective in calculating
vibrational corrections. Solvation energy was calculated using the same approach within the IEFPCM model [10]. To calculate the energy, a more accurate double-hybrid function B2PLYP [11] was used with an extended basis of 6-311+G** and taking into account the dispersion correction D2 [12]. We have shown that the use of such a combined B2PLYP//B3LYP approach to describe the reactions of acetylenes by superbasic demonstrates an accuracy comparable to that achieved by the precision methods CCSD(T)/6-311+G**//CCSD/6-31+G* and CBS-Q//B3 [7]. All calculations were performed using the Gaussian 09 software package [13].

3. Results and discussions

The ethynylation reaction for all studied systems is carried out through the transition state TS$_{1\rightarrow2}$ of the nucleophilic addition of ethynide ion to the C≡N bond (figure 3). The distance between atoms of the formed bond in transition states is 1.94-2.33 Å. For aryl substituents (R$^2$ and R$^3$), this distance is 2.21-2.22 Å (figure 3a). When N-butyldimine is involved in the reaction, it is reduced to 1.94 Å (figure 3b), and with t-butylicetylene the distance is increased to 2.33 Å (figure 3c).

![Figure 3](image)

**Figure 3.** The structure of the transition states TS$_{1\rightarrow2}$ of ethynylation: (a) – phenylacetylene with benzaldimine, (b) – (E)-N-butyl-1-phenylmethanimine with phenylacetylene and (c) – (E)-N,1-diphenylmethanimine with 3,3-dimethylbut-1-yne

Structural similarity of the transitional states is also confirmed by the close values of activation barriers. Thus, for aldmines with R$^2$ = Ph (table 1, a-e), the difference in ethynylation barriers does not exceed 1 kcal/mol. Significantly different values of activation energy is observed in the ethynylation of (E)-N-butyl-1-phenylmethanimine with phenylacetylene (table 1, f). In addition, for this reaction alone, the formation of butyl(1,3-diphenylprop-2-yn-1-yl)azanide (2f) followed by barrier-free generation of propargylamine N-(1,3-diphenylprop-2-yn-1-yl)butan-1-amine (3f) are associated with an increase in free energy of the system by 17.1 and 3.8 kcal/mol, respectively (table 1).

**Table 1.** Activation barriers of ethynylation ($\Delta G^\dagger_{1\rightarrow2}$, kcal/mol) and relative free energy of anion 2 ($\Delta G_{1\rightarrow2}$, kcal/mol), propargylamines 3 ($\Delta G_{1\rightarrow3}$, kcal/mol), and 1-azadienes 4 ($\Delta G_{1\rightarrow4}$ kcal/mol) and yields of 1-azadienes (%)

|     | $\Delta G^\dagger_{1\rightarrow2}$ | $\Delta G_{1\rightarrow2}$ | $\Delta G_{1\rightarrow3}$ | $\Delta G_{1\rightarrow4}$ | yield |
|-----|-----------------------------------|---------------------------|---------------------------|---------------------------|-------|
| a   | 15.8                              | -3.5                      | 0.2                       | -22.0                     | 72    |
| b   | 15.3                              | -4.3                      | -1.2                      | -21.8                     | 64    |
| c   | 16.2                              | -4.0                      | -1.2                      | -22.7                     | 53    |
| d   | 15.2                              | -4.4                      | -1.1                      | -21.2                     | 31    |
| e   | 15.4                              | -7.0                      | -3.9                      | -24.8                     | 0     |
| f   | 24.8                              | 17.1                      | 3.8                       | -21.1                     | 0     |
For all other cases, the ethynylation reaction leads to thermodynamically stable anions 2 and propargylamines 3 (table 1). However, the formation of all 1-azadienes 4a-f is carried out with a reduction of the system enthalpy by 24.3 ± 32.8 kcal/mol and free energy of the system by 21.1 ± 24.8 kcal/mol. Thus, the formation of 1-azadienes 4f is possible, but not under the experimental conditions (14°C), but at a higher reaction temperature (~60°C). However, it is shown [6] that at high temperatures 1-azadiene 4f most likely immediately polymerizes.

The nature of acetylene substituents has practically no influence on the thermodynamic and kinetic characteristics of the ethynylation reaction (figure 4).

No correlations are observed between the yields of 4a-e and both kinetic and thermodynamic characteristics of the reaction (table 1, figure 5). Moreover, the formation of 1-azadiene 4e, which is not observed experimentally, is associated with the largest decrease in free energy of the system relative to the initial reagents 1.

![Figure 4](image-url)
Figure 4. The profile of benzaldimine ethynylation with substituted acetylenes

![Figure 5](image-url)
Figure 5. Correlations of yields with: a – activation barrier; b – thermodynamic stability of anion 2; c – thermodynamic stability of propargylamine 3; d – thermodynamic stability of 1-azadiene 4
4. Conclusions
The high activation barrier of the ethynylation of (E)-N-butyl-1-phenylmethanimine with phenylacetylene explains the absence of (1E,2E)-N-butyl-1,3-diphenylprop-2-en-1-imine (4f) under the experimental conditions. Its formation is possible at higher temperatures, but under these conditions, it is likely to be impeded by the polymerization reaction experimentally observed in case of 4a.

It has been shown that regardless of the acetylene involved in the reaction, the differences in the kinetic and thermodynamic characteristics of the ethynylation stage are insignificant. The influence of the nature of acetylenes on yield of the 1-azadienes at this stage of studying has not been found, which requires additional studies.

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