Quantum-chemical description of interactions in the PhNH$_2$/HCCH system in a superbasic medium

D Z Absalyamov$^{1,2}$ and N M Vitkovskaya$^1$

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

E-mail: vita@cc.isu.ru

Abstract. The B2PLYP/6-311+G**//B3LYP/6-31+G* approach was applied to study the superbase-activated interaction of aniline molecule with three molecules of acetylene. The mechanism of the new cascade assembly of N-phenyl-2,5-dimethylpyrrole has been investigated and presented. It is shown that the cascade competes with the experimentally observed reaction of acetylene polymerization due to the comparable activation barriers of the rate-determining stages.

1. Introduction
The superbase KOH(KOBut)/DMSO activated self-assembly reaction of acetylene with arylamine providing pyrroles under mild conditions in up to 63% yield has been recently discovered. The attractiveness of such cascade multimolecular assemblies is in the fact that they satisfy the requirements of green chemistry. Such pyrrole syntheses open up new possibilities in industry and medicine [1]. Pyrroles not only exhibit important pharmacological properties [2], but also are precursors for the synthesis of more complex natural molecules and heterocycles [3].

Experimental study of the pyrrole formation mechanisms is difficult due to their multi-step nature and high reactivity of compounds. There are no experimental facts confirming the mechanism of N-phenyl-2,5-dimethylpyrrole formation from aniline molecule and three acetylene molecules activated by the superbasic system KOH(KOBut)/DMSO [4], since any intermediates have not been isolated in the PhNH$_2$/HCCH system. Moreover, it is reported [1] that the presence of polymers reduces yields of the target product. In our previous works [4,5], the mechanisms of ketones and ketimines reactions with acetylenes were successfully investigated by the quantum-chemical methods, which allows us to expect reliable results also in the case of amines. In the present work, the possible routes of interaction in the PhNH$_2$/HCCH system were considered using the ANION$_{GAS}$ model with the B2PLYP/6-311+G**//B3LYP/6-31+G* + PCM method.

2. Computational details
In our previous work [4], we proposed a common description concept for superbases (MOH/DMSO and MOBu'/DMSO, M = Na, K) through the representation of the reaction center as an undissociated MOH or MOBu' molecule in combination with different levels of accounting for solvation. The earlier simulations of superbase-stimulated vinylation of O-, S-, and C-nucleophiles and ethynylation of ketones have shown that the main act of the reaction, involving the addition of the formed nucleophilic species to the double or triple bond, occurs at the periphery of the reaction system [4]. This finding has
prompted us to employ a simple anionic model (ANIONGAS). While the ANIONGAS model neglects the presence of a remote cation and considers the surrounding solvation only as a polarizable continuum, it is characterized by a reasonable ratio of accuracy and resource consumption of calculations.

Optimization of the structural parameters of the molecular species involved in the reaction was carried out both in the gas phase (hereinafter denoted with subscript GAS) and taking into account the solvent effects at the level of the polarization continuum model IEFPCM [6] (hereinafter denoted with subscript PCM). The electronic structure in the geometry optimization calculations was described throughout using density functional theory (DFT) with the B3LYP functional and 6-31+G* basis set [7,8]. The vibrational corrections were calculated at the same (B3LYP/6-31+G*) level for a standard temperature of 298.15 K. The types of the stationary points were determined from the corresponding Hessians. The connections of the transition states with the minima were verified using the standard procedure of descending along the intrinsic reaction coordinate (IRC), employing the local quadratic approximation algorithm (LQA) [9].

The energies of the stationary points were further refined using the double-hybrid functional B2PLYP[10] in combination with the 6-311+G** basis set. Modeling of the cavity was performed within the approach GEPOL [11] using the universal force field radii (UFF) and universal scaling factor for the solvent α = 1.1 [12]. For the calculation of the solvation energy, the disulfide diene constant ε = 46.8 was used.

To estimate the entropy in solution, we used the Wertz method [13] proposed in [14] which was successfully employed in our previous work [15]. According to, [14] the entropy in solution (Ssol) can be calculated from the entropy of the ideal gas within the harmonic approximation (Sharm):

\[ S_{sol} = 0.74S_{harm} - 3.21\text{cal} \cdot \text{mol}^{-1} \cdot \text{K}^{-1} \]  

(1)

Recently [4], we have shown that activation energies of superbase-promoted acetylene reactions, such as vinylation and ethynylation, calculated by the B2PLYP/6-311+G**//B3LYP/6-31+G* approach, also applied in this work, are close to those predicted by CBS-Q/B3 and CCSD(T)/6-311+G**//CCSD/6-31G* methods. This approach suits very well to modeling the cascade reactions of acetylenes, as well as the nucleophilic addition to the double C=C bond of α,β-unsaturated ketones (the Michael reaction) and 1,3-protonotropic shift.

All quantum-chemistry calculations here were performed using GAUSSIAN-09 [16].

3. Experimental section

Different mechanisms of N-phenyl-2,5-dimethylpyrrole formation in the KOH/DMSO superbasic medium have been proposed [1]. In the first case, a sequential addition of acetylene molecule occurs directly on the aniline molecule followed by cyclization to the desired pyrrole (figure 1a). This route is indirectly confirmed by the fact that the intermediate 3-arylamino-1-butyne A was previously isolated in the reaction of aniline with acetylene in the PhNHK/dioxane system (160°C, 2 hours) [1]. An alternative mechanism (figure 1b) involves the directed nucleophilic addition of the aniline anion to an acetylene trimer, hexa-1,5-dien-3-yne B. An acetylene trimer, hexa-2,4-diyne C, can also participate in the reaction with arylamines (figure 1b).

![Figure 1](image_url)

Figure 1. Mechanisms of pyrrole formation: (a) upon sequential addition of three acetylene molecules to aniline molecule, (b) upon interaction of acetylene trimers with aniline molecule

We have calculated and analyzed possible reaction routes in the system containing the aniline molecule and three acetylene molecules.
3.1. Sequential addition of three acetylene molecules to the aniline molecule

Under the action of a superbasic medium, aniline is deprotonated with the formation of an unstable aniline anion 1 (figures 2, 3). The addition of 1 to the acetylene triple C≡C-bond is carried out through the transition state TS$_{1\rightarrow2}$ with the activation barrier $\Delta G^\ddagger = 23.6$ kcal/mol. In this case, unstable phenylaminoethenide 2 is formed, which is reduced to stable N-vinylaniline 3. The enamine-imine tautomerisation of 3, which follows through the anionic structure 4, leads to the thermodynamically favorable imine 5. The latter is ethynylated at the double C=N bond by ethyndiene-ion through the TS$_{5\rightarrow6}$ with the activation barrier $\Delta G^\ddagger = 16.3$ kcal/mol. The value of this barrier is characteristic of ethynylation reactions at the double C=Het (Het = O, N) bonds [4]. Thermodynamically favorable 6 is formed, which is protonated with a slight increase in energy to N-but-3-yn-2-yl-aniline 7.

Ethynylation of compound 7 at the triple C≡C bond (TS$_{7\rightarrow8}$) requires high energy consumption, the activation barrier is $\Delta G^\ddagger = 24.9$ kcal/mol. Anion 8 is formed, which in superbasic systems is readily protonated to N-hex-3-en-5-yn-2-yl-aniline 9 with a decrease in the system energy. Deprotonation of the nitrogen atom provides its intramolecular cyclization, which occurs with a low activation barrier $\Delta G^\ddagger = 13.0$ kcal/mol through the TS$_{10\rightarrow11}$ with the formation of a cyclic structure 11. Migration of the protons, whose activation barriers usually range 12.0÷17.0 kcal/mol [4], is carried out through stable structures 12 and 13 to afford a stable product N-phenyl-2,5-dimethylpyrrole 14 (figures 2, 3). The estimations of the activation barriers reveal that the rate-determining stage of the pyrrole formation mechanism (figures 2, 3) is the ethynylation of propyne structure 7 through the TS$_{7\rightarrow8}$. The first stage of the interaction of aniline with acetylene through the TS$_{1\rightarrow2}$, which initiates the pyrrole self-assembly, is also high-energy, the activation energy being only slightly lower than that of the rate-determining stage ($\Delta \Delta G^\ddagger = 1.3$ kcal/mol).

![Reaction profile of pyrrole formation through the sequential addition of three acetylene molecules to the aniline molecule. The values of $\Delta G(\Delta H)$ in kcal/mol are indicated under each point](image-url)
Figure 3. Reaction scheme of pyrrole formation through the sequential addition of three acetylene molecules to the aniline molecule

The implementation of propyne-allene rearrangements in superbasic media opens up the possibility of a slightly different pathway for the pyrrole formation (figures 4, 5). The changes begin after the formation of 7 (figures 2, 3). Isomerization of 7 leads to N-buta-2,3-dien-2-yl-aniline 15.

Figure 4. Reaction profile of pyrrole formation through the sequential addition of three acetylene molecules to the aniline molecule including propyne-allene isomerization. The values of $\Delta G(\Delta H)$ in kcal/mol are indicated under each point
Further, 15 is ethynylated with a high activation barrier $\text{TS}_{15\rightarrow16}$, $\Delta G^\ddagger = 27.6$ kcal/mol to give anionic structure 16. Protonation of 16 leads to $N$-hexa-2-en-5-yn-2-yl-aniline 17. Intermediate 17, in turn, is transformed through the propyne-allene rearrangement to $N$-hexa-2,4,5-trien-2-yl-aniline 18. Deprotonation of the nitrogen atom with the formation of structure 19 decreases energy of the system. Next, compound 19 through the transition state $\text{TS}_{19\rightarrow20}$ easily undergoes the intramolecular cyclization by nitrogen-centered anion at the double C=C bond, $\Delta G^\ddagger = 9.3$ kcal/mol (figures 4, 5). According to this mechanism, to obtain product 14, it is only necessary to protonate the resulting anion 20. However, it should be noted that the limiting barrier $\text{TS}_{15\rightarrow16}$ of the allene group ethynylation is significantly higher than the activation barrier of the propyne group ethynylation $\text{TS}_{7\rightarrow8}$ by $\Delta \Delta G^\ddagger = 2.7$ kcal/mol and that of the triggering interaction of aniline with acetylene $\text{TS}_{1\rightarrow2}$ by $\Delta \Delta G^\ddagger = 4.0$ kcal/mol. Based on the considered mechanisms of pyrrole 14 formation, a mechanism that includes the following stages is more energetically preferable: $1\rightarrow2\rightarrow3\rightarrow4\rightarrow5\rightarrow6\rightarrow7\rightarrow9\rightarrow17\rightarrow18\rightarrow19\rightarrow20\rightarrow14$ (figure 6).

**Figure 5.** Reaction scheme of pyrrole formation through the sequential addition of three acetylene molecules to the aniline molecule including propyne-allene isomerization. The values of $\Delta G(\Delta H)$ in kcal/mol are indicated under each point.

**Figure 6.** The sequence of stages of the energetically preferred mechanism of pyrrole formation from acetylene and aniline, obtained from the results of calculations.

3.2. *Formation of acetylene trimers and their transformations into each other*
It is shown [17] that pyrrole 14 can be obtained by the copper-catalyzed reaction of hexa-2,4-diyn with aniline. The issue of the hexa-2,4-diyn formation in a superbasic medium remains obscure. We have investigated the formation of acetylene trimers, hexa-1,5-dien-3-yne (figure 7a) and dipropargyl (figure 7b), which, according to our assumptions, could lead to hexa-2,4-diyn by the proton transfer in a superbasic medium. Moreover, hexa-2,4-diyn C was synthesized by the action of an alcoholic alkali on dipropargyl by A.E. Favorsky [18]. The first stage of the formation of hexa-1,5-dien-3-yne and dipropargyl is identical: the addition of ethynide-ion 21 to the acetylene triple C≡C bond through the TS_{21→22} transition state with an activation barrier ΔG_‡^1 = 24.8 kcal/mol furnishes but-1-en-3-yn-1-ide 22 with decreasing energy of the system (figure 9). The activation barrier for this transformation is higher than that of the reaction of aniline with acetylene by ΔΔG = 1.2 kcal/mol and is comparable to the activation barrier of the rate-determining stage of the sequential addition of the acetylene to aniline – the propyne structure 7 ethynylation through TS_{7→8}, ΔΔG = 0.1 kcal/mol. Protonation of 22 gives the energetically favorable but-3-en-1-yne 23. Deprotonation of terminal atom of the propyne fragment of 23 produces but-3-en-1-yn-1-ide 24 and almost does not change the energy of the system. The addition of 24 to the acetylene triple C≡C bond (figures 7a, 9 – purple line) occurs with the activation barrier TS_{24→ý} ΔG_‡ = 25.0 kcal/mol, which is close to the addition of the ethynide-ion to the acetylene triple C≡C bond TS_{21→22} (ΔΔG = +0.2 kcal/mol). The product of these sequential steps is anion 25, which is readily protonated to the stable hexa-1,5-dien-3-yne 26.

![Figure 7. Reaction scheme of the formation of (a) hexa-1,5-dien-3-yne and (b) dipropargyl](image)

The considered mechanism (figures 8, 9) of the formation of hexa-2,4-diyn 30 from hexa-1,5-dien-3-yne 26 directly relates to the propyne-allene rearrangements. The presence of cumulene structures 27, 28, 29 implies an increase in the system energy. Indeed, a study of the thermodynamic characteristics of the intermediates shows that all structures are extremely unstable with respect to the original 26 (figures 8, 9 – purple line).

![Figure 8. Reaction scheme of the formation of hexa-2,4-diyn from hexa-1,5-dien-3-yne. The values of ΔG(ΔH) in kcal/mol are indicated under each point](image)

Moreover, hexa-2,4-diyn 30 is less stable as compared to 26 and its formation is unlikely. The formation of hexa-2,4-diyn 30 is also possible from dipropargyl (figures 9, 10). The first stages up to the formation of but-3-en-1-yne 23 are the same as in the formation of hexa-2,4-diyn 30.
Ethynylation of the but-3-en-1-yne 23 double C=C bond by ethynide-ion occurs through the TS\textsubscript{23→32} transition state with an activation barrier $\Delta G^\ddagger = 21.3$ kcal/mol. Anion 32 lowers the energy of the system, and the product of its protonation, dipropargyl 33, is even more stable.

$\Delta G (\Delta H), \text{kcal/mol}$

**Figure 9.** Reaction profile of the formation of hexa-2,4-diyne and octa-1,3,5-trien-7-yne from three and four acetylene molecules, respectively. The values of $\Delta G(\Delta H)$ in kcal/mol are indicated under each point.

The formation of hexa-2,4-diyne 30 from 33 is associated with the migration of two triple bonds. These migrations can occur either alternately (figures 9 – gray line, 10a) or simultaneously through the diallene structure (figures 9 – pink line, 10b).

**Figure 10.** Reaction scheme of the formation of hexa-2,4-diyne from dipropargyl: (a) – alternative triple bond migrations, (b) – simultaneous propyne-allene rearrangement of triple bonds. The values of $\Delta G(\Delta H)$ in kcal/mol are indicated under each point.

The thermodynamic characteristics of all intermediates shown in figure 10 are estimated. In a superbasic medium, all of them can be formed, since less stable anionic structures are easily transformed into thermodynamically more favorable neutral molecules (figure 9).
According to the results obtained, the formation of hexa-2,4-diyn 30 is energetically more favorable by $\Delta H = -14.0$ kcal/mol relative to 33 and is a supposed direction of the reaction under real conditions.

3.3. Pyrrole formation from hexa-2,4-diyn and aniline

The addition of aniline anion 31 to the second C-atom of hexa-2,4-diyn (figures 11, 12) through the $\text{TS}_{31\rightarrow44}$ transition state with an activation barrier $\Delta G^\ddagger = 24.5$ kcal/mol leads through a series of proton migrations to hex-2-en-4-yn-2-yl(phenyl)azanide 46, capable of intramolecular cyclization by an $N$-centered anion to the $C=C$ bond through the transition state $\text{TS}_{46\rightarrow47}$ ($\Delta G^\ddagger = 23.8$ kcal/mol). Protonation of the formed carbanion 47 gives pyrrole 14.

![Figure 11. Reaction profile of pyrrole formation through the interaction of hexa-2,4-diyn with aniline. The values of $\Delta G(\Delta H)$ in kcal/mol are indicated under each point](image)

The studied mechanism of pyrrole formation (figures 11, 12) can compete with the mechanism of addition of three acetylene molecules to aniline molecule, because the barriers of the rate-determining stages ($\text{TS}_{21\rightarrow22}$ and $\text{TS}_{7\rightarrow8}$ respectively) of these mechanisms are close, $\Delta \Delta G^\ddagger = 0.1$ kcal/mol.

3.4. Polyene chain formation

Stable compound 23, formed in the course of preparation of 33, can also take part in the tetramerization of acetylene to octa-1,3,5-trien-7-yne 53 (figures 9 – brown line, 13).

![Figure 12. Reaction scheme of pyrrole formation through the interaction of hexa-2,4-diyn with aniline](image)
Figure 13. Reaction scheme of the octa-1,3,5-trien-7-yne formation. The values of $\Delta G$ in kcal/mol are indicated under each point.

The addition of ethynide-ion to the triple $C\equiv C$ bond of 23 occurs through the TS$_{25-51}$ transition state with an activation barrier $\Delta G^\ddagger = 21.8$ kcal/mol. The protonated product of this transformation, hexa-1,3-dien-5-yne 50, appears to be stable. The next addition of the ethynide-ion to the triple $C\equiv C$ bond of trimer 50 occurs with an even lower barrier ($\Delta G^\ddagger = 18.3$ kcal/mol), and the neutral product, tetramer 53, turns out to be even more stable (figure 9 – brown line). The performed study of acetylene tetramerization to 53 (figures 9 – brown line, 13) demonstrates that its formation can also compete with all the processes described above.

4. Conclusion

The ANION$_{GAS}$ model study of interactions between aniline molecule and three acetylene molecules has allowed us to explain the mechanism of cascade self-assembly of $N$-phenyl-2,5-dimethylpyrrole and to determine its key stages. In particular, it is revealed that:

- the acetylene molecule triggers the reaction acting both an electrophile and a nucleophile;
- self-assembly of $N$-phenyl-2,5-dimethylpyrrole is possible –
  - through the sequential reaction of aniline molecule with three acetylene molecules (figure 1a), the rate-determining stage being the ethynylation of structure 7;
  - through interaction with hexa-2,4-diyn molecule (figure 1b), the rate-determining stage being the first addition of ethynide-ion to acetylene;
- the values of the limiting barriers of two different self-assembly pathways do not differ ($\Delta \Delta G^\ddagger = 0.1$ kcal/mol);
- acetylene oligomerization is a kinetically available and thermodynamically favorable reaction, which indicates its ability to compete with the reaction of pyrrole formation;
- according to quantum-chemical estimations, the impossibility of fixing intermediates during the $N$-phenyl-2,5-dimethylpyrrole formation is associated with their rapid cascade transformations due to low activation barriers;
- the previously obtained $N$-but-3-yn-2-yl-aniline could be isolated but under strictly controlled reaction conditions, which can reduce the yields of the target $N$-phenyl-2,5-dimethylpyrrole.

The results of calculations of various competitive reaction routes discussed in this work demonstrate the broad capabilities of the simple ANION$_{GAS}$ model when performing primary estimations of interactions of complex chemical compounds containing a large number of atoms. The ANION$_{GAS}$ model is characterized by a reasonable ratio of accuracy and resource consumption of computations and is useful in building a roadmap, so that, using the obtained stationary points, then, to evaluate interactions in strict quantum-chemical approaches.

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