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V.I. Minkin on his 80th anniversary

Quantum Chemical Study of Mechanisms of Organic Reactions: IV.* Nucleophilic Addition of Ethylene Glycol to 4-Hydroxybut-2-ynenitrile

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Received October 25, 2014

Abstract—A theoretical mechanism has been proposed for nucleophilic addition of ethylene glycol to 4-hydroxybut-2-ynenitrile on the basis of DFT quantum chemical calculations at the B3LYP/6-311++G(*d,p*) level of theory. The reaction catalyzed by alkali involves nucleophilic attack by 2-hydroxyethoxide ion on the β -carbon atom of the acetylenic alcohol with intermediate formation of vinylic carbanion which undergoes intramolecular cyclization with closure of 1,3-dioxolane ring.

DOI: 10.1134/S1070428015030045

Cyanoacetylenic alcohols and various nucleophiles (amines, azoles, alcohols, diols, thiols, cyanide and thiocyanate ions, nucleic bases, nucleosides, amino acids, urea derivatives, etc.) are promising starting compounds for the design of new functionalized heterocyclic systems and potential drug precursors. High electrophilicity of the triple bond in cyanoacetylenic alcohols strongly facilitates nucleophilic addition to that bond, and these reactions generally occur in the absence of a catalyst under biomimetic conditions (i.e., at physiological temperature and pH in aqueous medium or without a solvent). The main results of relevant studies were abstracted in [2], discussed in reviews [3–9], and reported in original papers [10–12].

The present article continues the series of our publications on the simulation of organic reactions by modern quantum chemical methods [1, 13, 14] and deals with the mechanism of nucleophilic addition of 1,2-diols to cyanoacetylenic alcohols. It was reported previously [15] that reactions of 1,2- and 1,3-diols with phenylcyanoacetylene and cyanoacetylenic alcohols in the presence of a catalytic amount of bases yields functionally substituted 1,3-dioxolanes. We have recently shown that 1,3-dioxolane ring is also formed in reactions of cyanoacetylenic alcohols with adenosine [10],

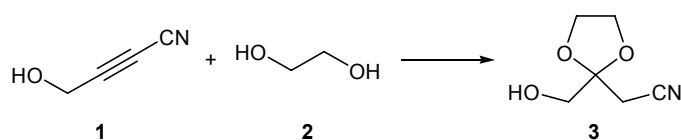
cytosine [11], and guanosine [12], which involve vicinal *cis*-2',3'-hydroxy groups in the ribose moiety. On the basis of the experimental data we presumed that 1,2-diols react with cyanoacetylenic alcohols via nucleophilic attack by one hydroxy group of the diol on the β -carbon atom of the acetylenic alcohol. The cyanoethylene adduct thus formed undergoes intramolecular cyclization as a result of nucleophilic attack by the second hydroxy group of the diol on the same β -carbon atom of the cyanoethylene fragment with closure of 1,3-dioxolane ring. However, intermediate cyanoethylene adduct was neither isolated nor detected by physicochemical methods [10–12].

In the present work we studied the mechanism of nucleophilic addition of ethylene glycol (**2**) to the simplest cyanoacetylenic alcohol, 4-hydroxybut-2-ynenitrile (**1**), with formation of 2-[2-(hydroxymethyl)-1,3-dioxolan-2-yl]acetonitrile (**3**) (Scheme 1) in terms of the density functional theory. Calculations were performed for the reaction of alcohol **1** with diol **2** as neutral species and for the reaction of neutral alcohol **1** with deprotonated ethylene glycol, 2-hydroxyethoxide ion **2a**.

The geometric parameters of the initial reactants and products were preliminary optimized, and intermediates and transition states were localized, at the DFT

* For communication III, see [1].

Scheme 1.



PBE/3z level of theory using PRIRODA 6.0 software package [16]. Transition states were identified by relaxed scans along the reaction coordinate and optimized using the Berny algorithm. All structures calculated in this work corresponded to stationary points on the potential energy surfaces, which was confirmed by analysis of theoretical vibrational spectra calculated from the Hessian matrices. In each case, the diagonalized Hessian matrices for minima on the PES contained only positive eigenvalues, while those calculated for transition states contained a single imaginary frequency (Fig. 1). The Gonzalez–Schlegel intrinsic reaction coordinate (IRC) following method [17] was used to confirm that the localized transition states lie on the corresponding reaction path. The final geometry optimization of all structures identified as stationary points and harmonic vibration analysis were performed with the aid of Gaussian 09 [18] at the DFT B3LYP/6-311++G(*d,p*) level. Solvent (diethyl ether) effects were included in terms of the Tomasi polarizable continuum model (IEF-PCM) [19]. Critical points on the Bader diagrams were calculated from the results of AIM analysis [20] using AIMAll [21].

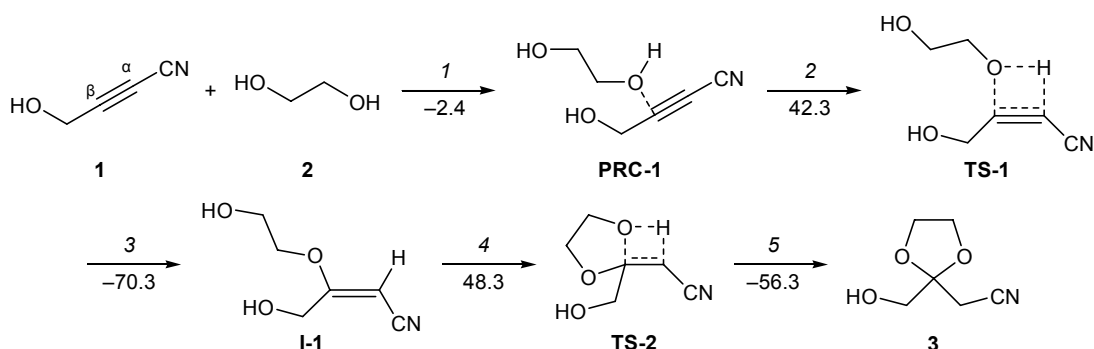
By analysis of the PES we localized stationary points corresponding to the ground states of initial reactants (**1**, **2**, **2a**), prereaction complexes (**PRC-1**, **PRC-1a**), cyanoethene intermediates (**I-1**, **I-1a**), final products (**3**, **3a**), and transition states (**TS-1**, **TS-1a**, **TS-2**, **TS-2a**) (Fig. 1). As shown by the Gonzalez–Schlegel IRC-following procedure [17], transition states **TS-1** and **TS-1a** actually correspond to the reaction paths connecting prereaction complexes **PRC-1** and **PRC-1a** with intermediates **I-1** and **I-1a**,

and **TS-2** and **TS-2a**, to the paths from **I-1** and **I-1a** to products **3** and **3a**, respectively. The energy profiles for the reactions **1** + **2** → **3** and **1** + **2a** → **3a** and imaginary frequencies of the transition states are given in Fig. 1, and Fig. 2 shows the structures of the prereaction complexes, intermediates, and transition states.

The results of our calculations allowed us to propose the following mechanism for the addition of neutral ethylene glycol molecule to acetylenic alcohol **1** (Scheme 2; heat effects of particular steps are given in kcal/mol under the arrows). The reaction begins with coordination of one oxygen atom of the diol **2** molecule to the β-carbon atom of alcohol **1** with formation of prereaction complex **PRC-1** which is more stable than the initial reactant system by 2.4 kcal/mol (step 1). Complex **PRC-1** is then transformed through a barrier of 42.3 kcal/mol into four-membered cyclic transition state **TS-1** (step 2) which is converted into cyanoethene intermediate **I-1** (step 3). The energy of the latter is lower than the energy of the initial reactant system by 30.4 kcal/mol. Intermediate **I-1** undergoes intramolecular cyclization via nucleophilic attack by the second oxygen atom of ethylene glycol on the same carbon atom of the cyanoethenyl fragment. The cyclization involves second four-membered cyclic transition state **TS-2** (energy barrier 48.3 kcal/mol; step 4) which is converted into final 1,3-dioxolane **3** (step 5). The overall heat effect is 38.4 kcal/mol.

It should be noted that the substrate and reagent molecules in prereaction complex **PRC-1** almost retain their geometric parameters though they are appreciably brought together due to coordination of the oxygen atom of ethylene glycol to the β-carbon atom of

Scheme 2.



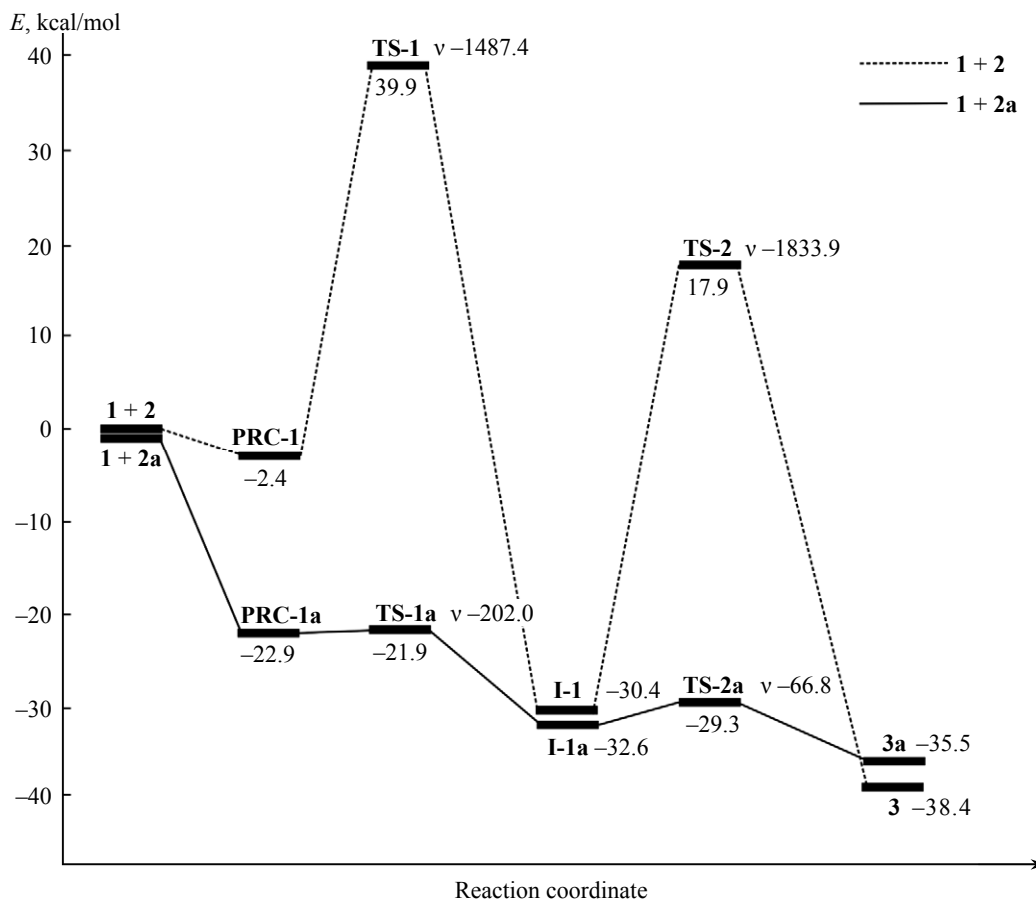
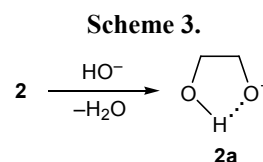


Fig. 1. Energy profiles of the reactions of 4-hydroxybut-2-ynenitrile (**1**) with ethylene glycol (**2**) and 2-hydroxyethoxide ion (**2a**). Imaginary frequencies in the theoretical vibrational spectra of the transition states are given (ν , cm^{-1}).

acetylenic alcohol **1** (Fig. 2). In particular, linear configuration of the $\text{C}\equiv\text{C}$ and $\text{C}\equiv\text{N}$ bonds in molecule **1** is conserved, which corresponds to ideal sp -hybridization of the triple-bonded carbon atoms. By contrast, the acetylenic fragment in **TS-1** is strongly bent as a result of formation of four-membered ring, so that the carbon atoms undergo rehybridization to sp^2 and the triple bond becomes essentially double (1.209 Å in **PRC-1** against 1.319 Å in **TS-1**; Fig. 2). The transformation of **TS-1** into intermediate **I-1** is completely stereoselective, and the resulting double bond has *transoid* configuration since alternative *cisoid* structure is impossible for steric reasons. In fact, all our attempts to scan the reaction coordinate toward the formation of cyanoethylene intermediate with *cisoid* configuration of the double bond were unsuccessful. In going to **TS-2**, the aforesaid bond is further elongated to 1.472 Å (from 1.352 Å in **I-1**), thus becoming partly double. The length of that bond in final dioxolane **3** attains 1.547 Å, which corresponds to a classical $\text{C}_{sp^3}-\text{C}_{sp^3}$ bond.

The proposed mechanism provides a plausible explanation for the formation of 1,3-dioxolane **3** in the reaction of ethylene glycol (**2**) with acetylenic alcohol **1** via intramolecular cyclization of cyanoethylene intermediate. However, this reaction path is hardly feasible because of high energy barriers separating pre-reaction complex **PRC-1** and cyanoethylene intermediate **I-1** and in going from the latter to product **3** (Fig. 1). In fact, the reaction really occurs only in the presence of a catalytic amount of alkali [15].

Taking the above into account, we calculated the energy profile of analogous reaction where neutral ethylene glycol molecule was replaced by 2-hydroxyethoxide ion (**2a**) generated from the former under basic conditions (Scheme 3). Anion **2a** is characterized



by intramolecular hydrogen bond, as follows from the presence of the corresponding bond (+0.042 a.u.) and ring critical points (+0.032 a.u.) on the Bader diagram.

It could be presumed that the formation of alkoxide ion from alcohol **1** is possible under these conditions. However, participation of this anion in the reaction under study, which involves nucleophilic attack on the triple-bonded carbon atom, is hardly probable taking

into account reduced electrophilicity of ionized alcohol **1**. Furthermore, deprotonation of alcohol **1** should promote the reverse Favorskii reaction with formation of cyanoacetylene and formaldehyde, which is not observed experimentally [15].

Analysis of the computation data and energy profile of the reaction of 2-hydroxyethoxide ion (**2a**) with alcohol **1** (Fig. 1) led us to propose a mechanism shown

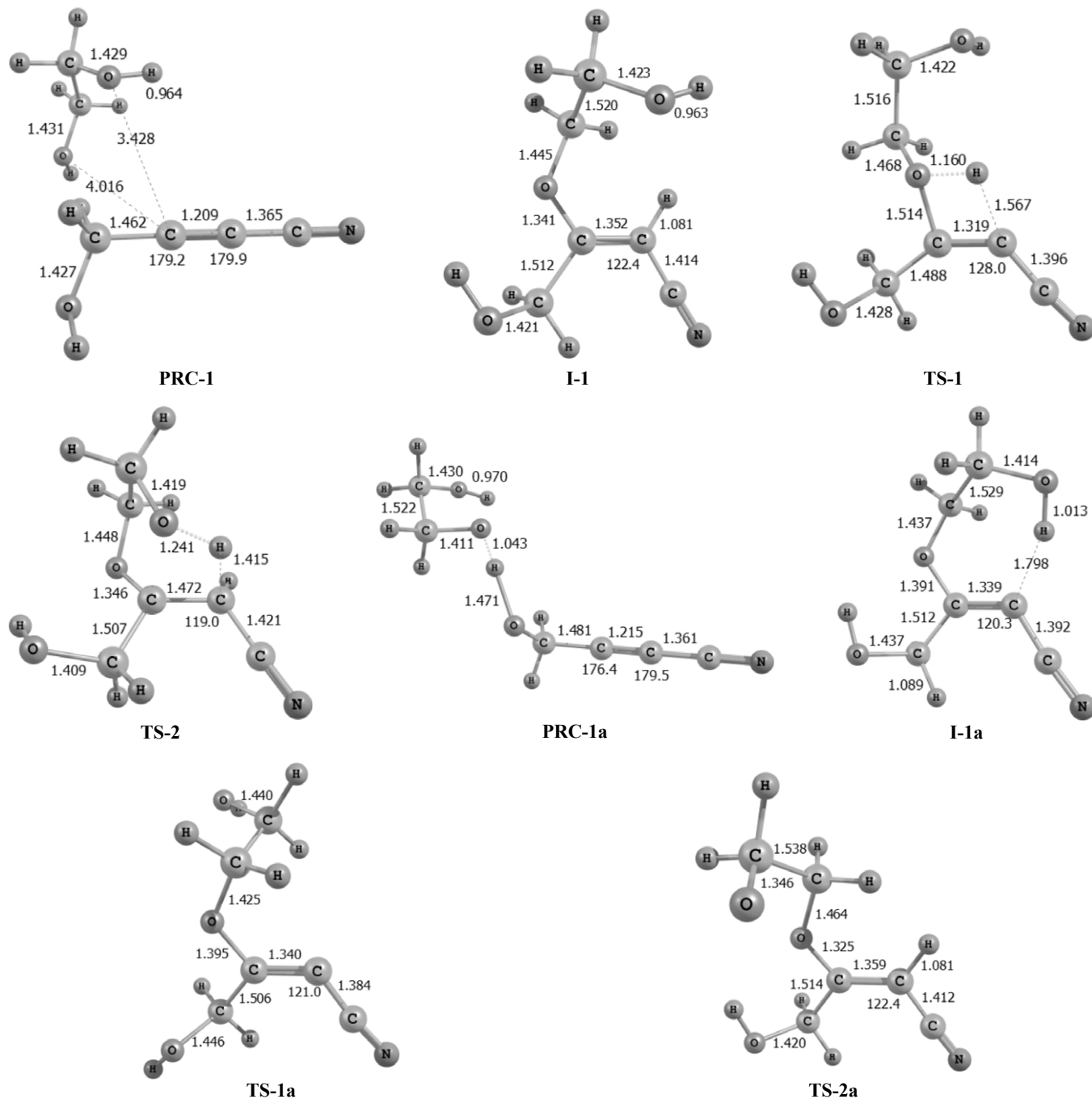
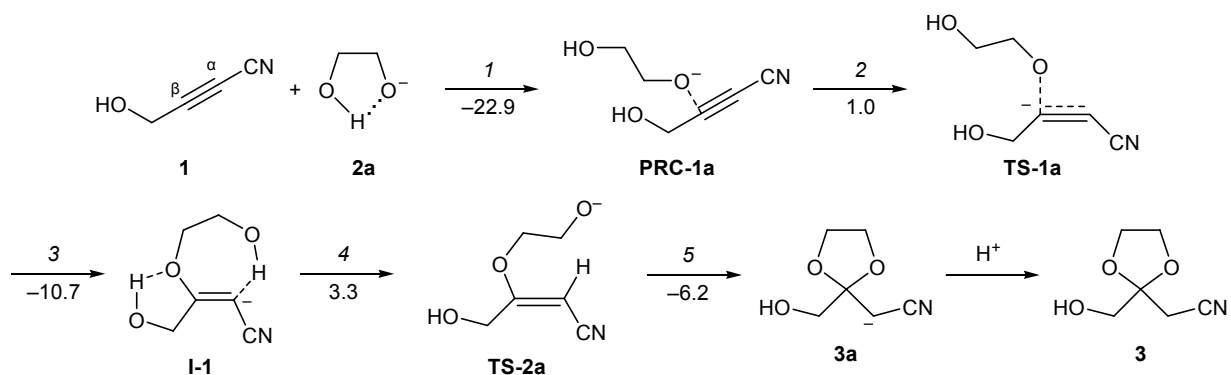


Fig. 2. Structures of prereaction complexes (**PRC-1**, **PRC-1a**), intermediates (**I-1**, **I-1a**), and transition states (**TS-1**, **TS-1a**, **TS-2**, **TS-2a**) according to B3LYP/6-311++G(*d,p*) calculations. Bond lengths (Å) and bond angles (deg) are given.

Scheme 4.



in Scheme 4 (the heat effects of each step are given in kcal/mol). Coordination of the negatively charged oxygen atom of anion **2a** to the β -carbon atom of alcohol **1** gives negatively charged prereaction complex **PRC-1a** (step 1) which is more stable than the initial reactant system. The gain in energy upon formation of **PRC-1a** is considerably higher than in the formation of **PRC-1** from neutral ethylene glycol molecule (22.9 against 2.4 kcal/mol). Complex **PRC-1a** undergoes low-barrier transformation (step 2) through transition state **TS-1a** into vinylic carbanion **I-1a** which represents the ground state of the system (its theoretical vibrational spectrum contains no imaginary frequencies) and is stabilized by 32.6 kcal/mol relative to the initial system. Carbanion **I-1a** overcomes a barrier of 3.3 kcal/mol to reach transition state **TS-2a** as a result of dissociation of O–H bond and formation of C–H bond in the olefinic fragment (step 4). The released oxygen atom of the ethylene glycol fragment acquires a negative charge and attacks the same β -carbon atom of the olefinic fragment, thus closing 1,3-dioxolane ring (step 5). The overall heat effect relative to the initial reactant system (**1** + **2a**) is -35.5 kcal/mol. Proton addition to 1,3-dioxolane carbanion **3a** yields final dioxolane **3**.

As follows from Fig. 2, the formation of anionic prereaction complex **PRC-1a** is accompanied by small changes of the geometric parameters of its components. For instance, the carbon–carbon triple bond elongates from 1.208 to 1.215 Å, the C–C \equiv C bond angle decreases from 179.7 to 176.4°, and the C–O⁻ bond length increases from 0.996 to 1.411 Å. Nevertheless, the cyanoacetylene moiety in **PRC-1a** remains essentially linear, i.e., the carbon atoms therein retain their sp -hybridization. However, the situation changes abruptly in going to transition state **TS-1a** on the reaction path from **PRC-1a** to vinylic carbanion **I-1a**. The acetylenic fragment in **TS-1a** is strongly bent due

to considerable steric strain [22, 23], and its configuration becomes typical of sp^2 -hybridized carbons. The C $^{\beta}$ C $^{\alpha}$ C bond angle decreases from 179.5° in **PRC-1a** to 121.0° in **TS-1a**, and the C $^{\alpha}$ –C $^{\beta}$ bond extends from 1.215 Å in **PRC-1a** to 1.340 Å in **TS-1a**, i.e., it becomes essentially double. Almost the same geometry corresponding to sp^2 -hybridization of the α - and β -carbon atoms is typical of intermediate carbanion **I-1a** and transition state **TS-2a**. Intramolecular cyclization of structure **TS-2a** yields 1,3-dioxolane carbanion **3a** where all carbon atoms have classical sp^3 -hybridization.

Vinyl carbanion **I-1a** is very stable (-32.6 kcal/mol) compared to the initial reactant system **1** + **2a** assumed to have a zero energy. Its stability is likely to be determined by intramolecular hydrogen bonding. The formation of seven-membered H-chelate ring in **I-1a** follows from the interatomic distance C $^{\alpha}\cdots$ H equal to 1.798 Å (Fig. 2) and the presence of the corresponding bond (+0.051 a.u.) and ring critical points (+0.012 a.u.) on the Bader diagram obtained by AIM analysis. On the other hand, analogous stabilization is provided by the second intramolecular hydrogen bond which closes a five-membered ring with participation of the oxygen atom in the ethylene glycol fragment: the O \cdots H distance is 2.165 Å (Fig. 2), and the Bader diagram contains bond (+0.018 a.u.) and ring critical points (+0.018 a.u.).

Turning back to the energy profile of the reaction of alkoxide ion **2a** with acetylenic alcohol **1** (Fig. 1), it is very important that the energy barriers corresponding to the transition from prereaction complex **PRC-1a** to vinyl carbanion **I-1a** (1.0 kcal/mol) and then to product **3a** (3.3 kcal/mol) are considerably lower than those in the addition of neutral ethylene glycol **2** to alcohol **1** (42.3 and 48.3 kcal/mol; Fig. 1). Thus, the real mechanism of the base-catalyzed addition of glycols to cyanoacetylenic alcohols involves deprotonation of the

former and intermediate formation of vinylic carbanion which undergoes intramolecular cyclization with closure of 1,3-dioxolane ring.

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 11-03-00022).

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