

The model of 1,3-dipolar cycloaddition reaction of 4,5-dihydro-1H-imidazole 3-oxide derivatives with alkynes

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Abstract

The influence of solvents and different structural factors on the rate of 1,3-dipolar cycloaddition reaction of the 4,5-dihydro-1H-imidazole 3-oxide derivatives with alkynes have been studied. Nitrones and alkynes have been ranged by their relative activity in this reaction. Using the DFT calculation with the triple zets basis set, the energy profile of the reaction has been plotted, and the structures and energy characteristics of the transition states have been determined. The mechanism of this reaction has been shown to be concerted and asynchronous. The validity of the used computational approach for the detailed investigation of 1,3-dipolar cycloaddition of nitrones has been demonstrated.

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1. Introduction

Well known 1,3-dipolar cycloaddition reactions of nitrones as 1,3-dipoles are used for a long time in the organic synthesis. Nevertheless, discussion about the mechanism of these reactions initiated in the early sixties of the past century [1,2] is still continuing. There are at least three substantially different variants of the 1,3-dipolar cycloaddition pathways: concerted (but asynchronous) mechanism [1,3] and two stepwise (biradical [2,4–6] and zwitterionic [7]) mechanisms. The number of stages and thereupon the structure of the transition state in the case of the concerted mechanism are fundamental questions concerning the reaction path.

Lately, the series of theoretical researches was focused on characterization of the structure and energy of the transition states in the 1,3-dipolar cycloaddition reactions [8–12]. The experimental data and *ab initio* calculations undoubtedly point out the predominant role of the orbital

interactions for the stereo- and regioselectivity in the foregoing reactions [13,14].

One of the insufficiently explored nitrone types is 4,5-dihydro-1H-imidazole 3-oxide derivatives [15]. The distinctive feature of these compounds is the presence of the heteroatomic substituent at the α -carbon atom of the nitrone group. This sp^3 -hybridized nitrogen atom is capable of efficient conjugation with π -system of the nitrone group, thereby determining the peculiarity of the latter.

There are numerous literature data concerning the rate constants of 1,3-dipolar cycloaddition reactions of nitrones to alkenes [16,17]. In particular, the slight decrease of the reaction rate with the enhance of the solvent polarity is noted [16,18], which is in accordance with the conception of the concerted mechanism of this process.

The reaction of 2-substituted 4,5-dihydro-1H-imidazole 3-oxide derivatives with activated alkynes, as we shown earlier, occurs with high regioselectivity [19]. The goal of our study is to ascertain the mechanism of 1,3-dipolar cycloaddition reactions of 4,5-dihydro-1H-imidazole 3-oxide derivatives with alkynes taking into consideration experimental data and the quantum-mechanical model of this process.

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2. Results and discussion

Investigation of the influence of solvents and substituents nature on the reaction rate and selectivity is very important when studying the reaction mechanism. We have reported [19] that variation of R_1 and R_2 substituents in the 4,5-dihydro-1*H*-imidazole 3-oxide derivatives **1** (Table 1) does not result in changing the regioselectivity of cycloaddition (Scheme 1).

The literature data [20] allows assumption that 1,3-dipolar cycloaddition is a reaction of first order on each reagent and fits the Eq. (1)

$$\text{rate} = k[\text{nitron}] [\text{alkyne}] \quad (1)$$

When the process is carried out under pseudo-first order conditions (the significant excess of one of the components), the solution of Eq. (1) is Eq. (2):

$$\ln [R_i] = -k_{\text{eff}} \times t + \text{Const} \quad (2)$$

where R_i is a minor component and k_{eff} is the effective rate constant.

As it follows from Eq. (2), for the reaction of first order on component R_i a linear dependence between $\ln [R_i]$ and reaction time t should be observed. The correlation between $\ln [\text{nitron}]$ and t in the reaction of derivative **1f** with 10-fold excess of alkyne **2e** in chloroform is outlined on Fig. 1. Similar correlations are obtained for some nitrones and alkynes in various solvents (Tables 2 and 3, respectively).

Thus, the reaction under consideration is described by kinetic Eq. (1) for different derivatives **1** and **2** irrespective of solvent nature that allows the values of rate constants k to be obtained.

Table 1
Nitrones **1** and alkynes **2** under investigation

Nitrones	R_1	R_2	Alkynes	R_3	R_4
1a	H	H	2a	H	H
1b	H	Me	2b	H	Ph
1c	H	Ph	2c	Me	Ph
1d	Me	Me	2d	Ph	Ph
1e	Me	Ph	2e	MeO	H
1f	Me	4-NO ₂ -C ₆ H ₄	2f	MeO	Ph
1g	Me	4-MeO-C ₆ H ₄	2g	MeO	CO ₂ Me
			2h	EtO	CF ₃

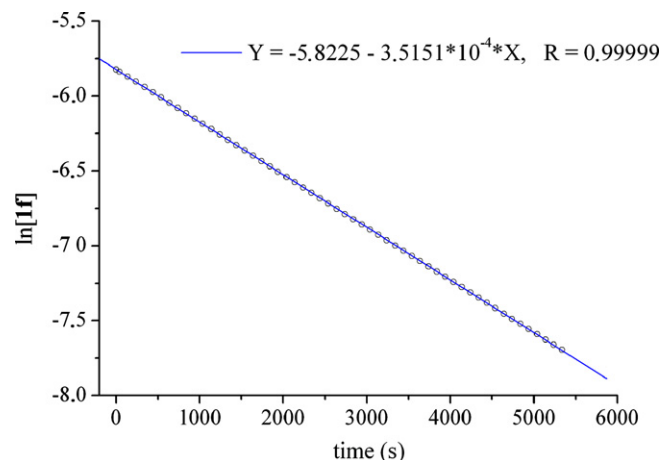


Fig. 1. First-order plot of the reaction of **1f** with 10-fold excess of **2e** in chloroform at 24 °C.

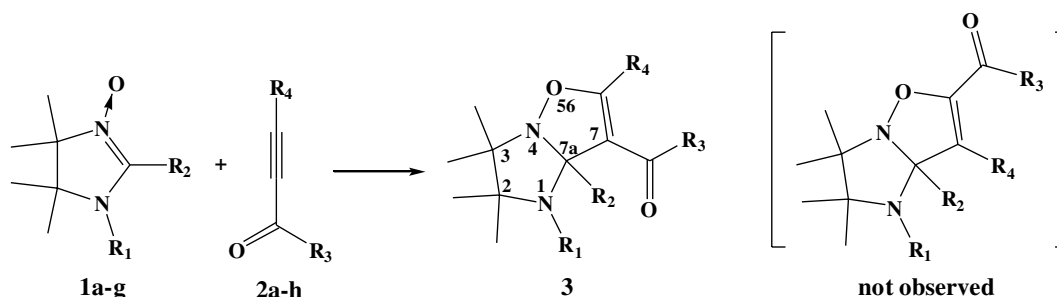
Only few data concerning the constant rate values for the reactions of nitrones with alkynes in some solvents were obtained [18,20] when acyclic *N*-alkyl-*C*-phenylnitrones **5** were studied (Scheme 2). The rate constants for the formation of cycloadducts **7a** and **7c** in some solvents are presented in Table 4 [18,20].

In the present work the rate constants for the cycloaddition of nitrones **1e** and **1f** with alkynes **2d–f** were determined using ¹H NMR and UV spectroscopy (Table 4). In order to compare the literature and experimental data, we also determined the rate constants for the formation of **7b** from **5b** and **2d** (Table 4).

It should be noted that cycloadduct **7b** formed from **5b** by the interaction with 1,3-diphenylpropynale **2d** is stable under the reaction conditions and does not rearrange to 2,3-dihydroisoxazole derivative **8b** even at 80 °C (Scheme 2), as it occurs in the case of similar 4*H*-isoxazole derivatives **7** [21]. The structure of **7b** was proved by X-ray analysis (Fig. 2).

2.1. Solvent effect

Data of Table 4 demonstrate that the rate of the reaction of nitrones **1** with disubstituted alkynes **2** noticeably increases with the enhancement of the medium polarity (Fig. 3).



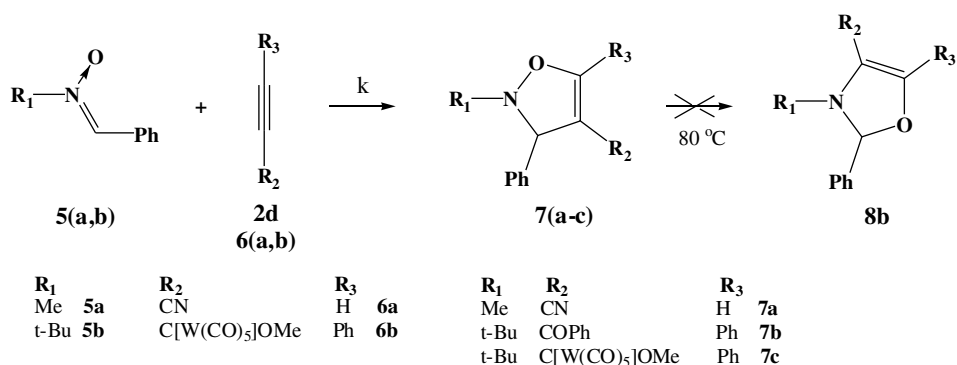
Scheme 1. Regioselectivity in the 1,3-cycloaddition reaction of the 4,5-dihydro-1*H*-imidazole 3-oxide derivatives **1** with alkynes.

Table 2
Pseudo-first order equations for the reactions of nitrones **1e** and **1f** with the excess of alkynes **2d–f** in different solvents

Nitrone	alkyne	Excess of alkyne	Solvent	Equation	R	Method
1e	2f	9.0	CCl ₄	$Y = -2.732 \times 10^{-4} \times X - 3.901$	0.9996	NMR
1f	2d	7.0	CCl ₄	$Y = -1.843 \times 10^{-4} \times X - 6.866$	0.99997	UV
		10.4	Acetone	$Y = -1.350 \times 10^{-3} \times X - 6.546$	0.99993	UV
		10.1	DMSO	$Y = -1.310 \times 10^{-3} \times X - 7.352$	0.99996	UV
	2e	10.0	CHCl ₃	$Y = -3.515 \times 10^{-4} \times X - 5.823$	0.99999	UV
		10.0	Acetone	$Y = -8.879 \times 10^{-5} \times X - 8.084$	0.9997	UV
		10.0	DMSO	$Y = -8.368 \times 10^{-4} \times X - 6.112$	0.99994	UV

Table 3
Pseudo-first order equations for the reactions of alkynes **2e** and **2f** with the excess of nitrone **1e**

Alkyne	Nitrone	Excess of nitrone	Solvent	Equation	R	Method
2e	1e	4.5	CHCl ₃	$Y = -0.0012 \times X - 4.713$	0.998	NMR
2f	1e	9.0	CCl ₄	$Y = -3.186 \times 10^{-4} \times X - 3.805$	0.9995	NMR



Scheme 2. Constant rates for the reactions of acyclic N-alkyl-C-phenylnitrones **5** with alkynes.

This effect is atypical for C-substituted nitrones **5** (cf. Table 4) and observed for nitrones **1** may testify the higher polarity of the transition states in comparison with the polarity of the reagents. At the same time, the relatively low influence of the solvent polarity on the reaction rate does not allow one to conclude that the zwitterionic intermediate is formed. Thus, the replacement of carbon tetrachloride by acetonitrile accelerates

[2+2] cycloaddition of the tetracyanoethylene to 3,4-dihydro-2H-pyran proceeding with the formation of the zwitterionic intermediate by a factor of 17,000 [22].

The absence of the mentioned tendency for the terminal alkynes is obviously the result of the formation of hydrogen bond C–H···O between the dipolarophile and the solvent or nitrone [23,24].

Table 4
The rate constants of cycloaddition reaction of nitrones **1e** and **1f** and **5** with alkynes **2d–f** and **6**

Nitrone	Alkyne	$k \times 10^{-4} \text{ (M}^{-1} \text{ s}^{-1}) \text{ at } 24^\circ\text{C}$							
		MeOH	CHCl ₃	C ₆ H ₆	CCl ₄	THF	Acetone	CH ₃ CN	DMSO
1e	2f ^a	<0.4	1.8	–	18	–	35	–	80
1f	2d ^b	–	61	–	274	620	950	1390	2110
	2e ^b	7.25	123	–	425	–	287	–	396
5a	6a ^c	34	–	190	–	–	140	–	150
5b	2d ^a	–	–	–	0.028	–	0.007	–	0.036
	6b ^c	–	–	–	–	2270	3510	3080	–

^a According to ¹H NMR.

^b According to UV spectroscopy.

^c At 25 °C.

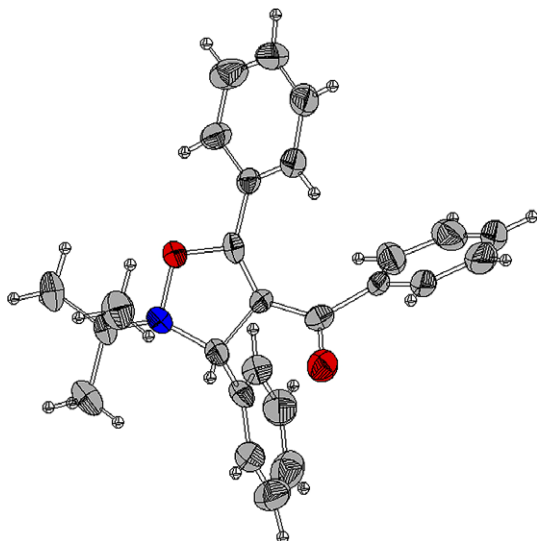


Fig. 2. Crystal structure of (2-*tert*-butyl-3,5-diphenyl-2,3-dihydroisoxazol-4-yl)phenyl-methanone **7b**, CCDC 293549.

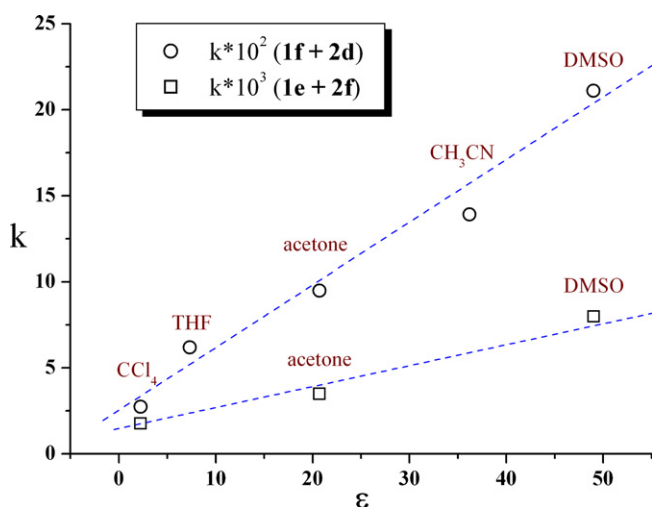


Fig. 3. Dependence of the rate constants k on solvent polarity (ϵ) in the reaction of nitrones **1f** and **1e** with alkynes **2d** and **2f**, respectively.

Solvents such as chloroform and, especially, methanol are capable of forming strong H bonds with the oxygen atom of nitrone [25,26] thereby hindering the reaction (Table 4).

2.2. Effect of substituents in alkyne

The nature of the substituent in alkyne is shown to be the important factor influencing the reaction rate. Using the method of competitive reactions and comparing the rate constants, the relative activities of alkynes **2** with respect to nitrones **1** were determined (Table 5).

The data of Table 5 demonstrate that the reaction rate increases, as a rule, with the enhance of the π -withdrawing effect of the substituent in alkyne; rate constants rises in

Table 5

Relative rate constants for the reactions of alkynes **2** with nitrones **1(d–g)** and **5a** in chloroform at 24 °C obtained from ^1H NMR and UV data

Alkynes	k_{rel}				
	1d	1e	1f	1g	5a^a
2f	–	5.2×10^{-3}	–	–	–
2c	–	1.26×10^{-1}	–	–	–
2d	–	3.94×10^{-1}	4.95×10^{-1}	–	–
2e	1	1	1	1	1
2b	16.5	18.7	13.7	18.1	–
2g	–	370	–	–	75
2a	–	810	–	–	–
2h	–	$>8 \times 10^4$	–	–	–

^a At 25 °C in CDCl_3 [27].

order: **2f** < **2c** < **2d** < **2b**. This tendency, however, has distinctive features. For example, the replacement of terminal alkynes **2a** and **2e** by their phenyl-substituted analogs **2d** and **2f**, respectively, leads to the diminution of the reaction rate by two orders of magnitude, on average (cf. Table 5). Taking into account regioselectivity of the reaction, this effect cannot be explained by steric hindrance. Another example is more than the 100-fold increase of the reaction rate of 4,4,4-trifluorobut-2-ynoate **2h** as compared to that of dimethylacetylenedicarboxylate (DMAD) **2g**, i.e. when the ester group is replaced by the trifluoromethyl residue, which has no π -withdrawing effect (Table 5). The ester group, however, remains to be the substituent determining the regioselectivity of the reaction.

Comparison of the relative reaction rates of nitrones **1** and “isolated” nitrone **5a** (Table 5) reveals significantly lower substrate selectivity of the latter in the reactions with alkynes; in other words, compounds **1** are more sensitive to the substituent nature in alkyne molecule than compound **5a**.

2.3. Effect of substituents in nitrone

In order to reveal the influence of substituents R_1 and R_2 in nitrones **1** on the reaction rate, a several experiments were carried out using the method of competitive reactions. Relative rate constants for the reactions of nitrones **1** with alkynes **2** are represented in Table 6.

The nature of R_2 directly bound to nitrone appreciably influences the reaction rate. Thus, the replacement of

Table 6

Relative rate constants for the reactions of nitrones **1** with alkynes **2** in chloroform at 24 °C obtained from ^1H NMR data

Nitrones	k_{rel}					σ_p^{+a}
	2a	2b	2e	2g	2h	
1b	–	–	2.2^b	–	–	–
1c	–	–	0.29	–	–	–
1f	1	1	1	1	1	0.79
1e	–	2.7	2.8	–	–	0
1g	2.9	6.2	6.1	4.7	6.9	–0.78
1d	–	18.9	17.1	–	–	–

^a Ref. [28].

^b At 21 °C.

methyl group (compounds **1b** and **1d**) by phenyl group (compounds **1c** and **1e**) leads to slow down the reaction by factors of 6–7 (Table 6), probably, due to increasing the steric hindrances. This assumption is in accordance with the fact that the (2,4-dimethyl)phenyl substituent considerably reduces the reactivity of the studied nitron, while 4,5-dihydro-1*H*-imidazole 3-oxide, bearing (2,4,6-trimethyl)phenyl substituent, is practically inactive with respect to dipolarophiles [19].

The *p*-nitrophenyl (**1f**), phenyl (**1e**) and *p*-methoxyphenyl (**1g**) substituents at position 2 of the imidazoline cycle have the same steric characteristics, while their π -withdrawing effects are noticeably different. The reactivity of nitrones is shown to increase with the enhancement of π -donor effect of the substituents (Table 6). This observation is consistent with the conclusion, based on Frontier Molecular Orbital Theory (FMO) [29]. Actually, the reactions are found to be controlled by the interaction of the HOMO of dipole with the LUMO of dipolarophile; [19] the nitron, therefore, plays a part of donor. Moreover, a good linear correlation between the reactivity ($\log(k_X/k_H)$) of *para*-aryl substituted nitrones **1(e–g)** and σ_p^+ constants is revealed (Table 6 and Fig. 4) that allows estimation of the sensitivity coefficient of the reaction (ρ).

The ρ value of the reaction of nitrones **1f** and **1g** with alkyne **2b** is -0.51 (for **2e** $\rho = -0.50$) and it is in compliance with the presence of insignificant positive charge on the carbon atom C-2 of imidazoline ring in the transition state. It is unlike the ρ value for solvolysis of (1-chloro-1-methylethyl)-benzene in 90% aqueous acetone is equal to -4.52 [28].

Attachment of the methyl group to the nitrogen atom of imidazoline ring (**R**₁) results in the increase of the reaction rate of nitron **1** by a factor of 7–10 (Table 6), that could be rationalized by enhance of the donor ability of the nitrogen atom bound to the nitron group. The influence of this nitrogen atom in itself on the nitron activity can be evaluated by comparison of the reaction rate constants for

N-*tert*-alkyl nitron **1e** and C-phenyl nitron **5b** (cf. Tables 4 and 6). These compounds differ from each other by the nitrogen atom attached to nitron group (**1e**). Nitron **1e** reacts with alkyne **2d** faster than **5b** by a factor of 2.7×10^4 in CCl₄ and of 4×10^5 in acetone [30]. Similar but not so significant activating effect of the α -heteroatomic substituent was demonstrated earlier for oxazoline-*N*-oxides **9** (Scheme 3 and Table 7) [31,32].

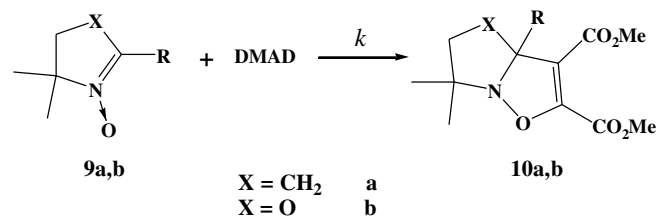
Thus, the influence of α -heteroatomic substituent on the nitron activity can be also evaluated by comparison of the relative rate constants k_{rel} for the reactions of nitrones **1e** and **9a** and **9b** with DMAD in chloroform as represented in Table 7.

2.4. Quantum-mechanical model of the reaction

In order to rationalize the peculiarities of the behavior of the 4,5-dihydro-1*H*-imidazole 3-oxide derivatives in the 1,3-dipolar cycloaddition reaction with alkynes and to consider its mechanism in detail, we constructed the quantum-mechanical model for the reaction of nitrones **1** with alkynes **2**.

As it was mentioned above, there are three possible variants of the cycloaddition mechanism: biradical stepwise, zwitterionic stepwise, and concerted pathways. The foregoing experimental data such as the increase of the rate constant with the enhance of the medium polarity (Table 4 and Fig. 3) and with the increase of the π -electron-donating effect of **R**₂ (Table 6 and Fig. 4) as well as the higher activity of **2b** as compared to **2c** and **2d** testify against the biradical mechanism. Thereupon, the calculation was performed with the conservation of the system multiplicity.

The energy surface for the cycloaddition reaction of **1a** with **2a** was plotted on coordinates of the lengths of the



Scheme 3. The influence of α -heteroatomic substituent on the nitron activity.

Table 7

Rate constants k and relative rate constants k_{rel} for the reactions of nitrones **1e** and **9a** and **9b** with DMAD in chloroform

Compound	R = Me k_{rel}	R = Ph	
		$k \times 10^{-4} \text{ (M}^{-1} \text{ s}^{-1}\text{)}$	k_{rel}
9a ^a	1	1.62	1
9b ^a	160	1.12×10^2	70
1e ^b	–	1.28×10^5	8×10^4

^a Ref. [32] for **9a** at 19 °C, for **9b** at 17 °C.

^b At 24 °C.

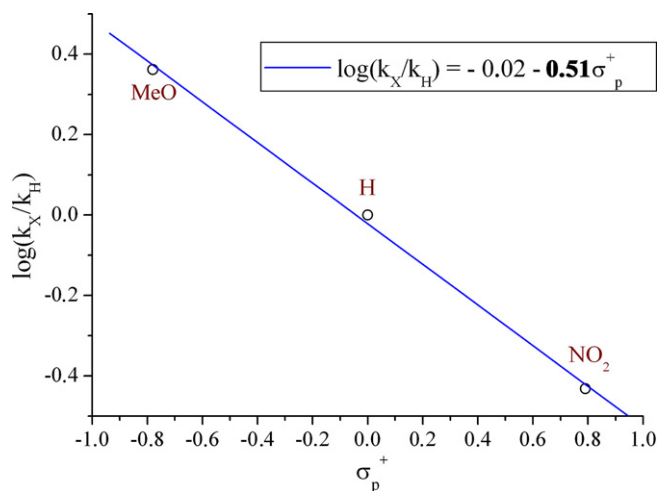


Fig. 4. Linear dependence of the reactivity ($\log(k_X/k_H)$) of *para*-aryl substituted nitrones **1 (e–g)** on σ_p^+ constants.

formed bonds C–C (r_1) and C–I (r_2) using DFT calculation with triple zets basis set (Fig. 5a). The lengths of C–C and C–O bonds in the product were taken as a datum.

The habitus of the plotted surface and, in particular, the absence of the local minimum (exclude the minimum of the reactants and products) demonstrates that the energy-optimal path is the concerted one. The “oblongness” of the forming C–C ($\Delta r_1^\#$) and C–O ($\Delta r_2^\#$) bonds is appreciably different ($\Delta r_1^\#$ noticeably more than $\Delta r_2^\#$), that implies substantial skewness of the transition state (Fig. 5a). Furthermore, the value of ρ obtained from the Hammett plot ($\rho = -0.51$, Fig. 4), which is quite different from those observed for typical ionic processes, [28] as well as not very significant influence of solvent polarity on the reaction rate (Fig. 3) testify against the zwitterionic mechanism but to the concerted one.

The structures of the series of the transition states for cycloaddition reaction of alkynes **2** with nitrones **1** and **5** were determined by the DFT computation method with triple zets basis set (for example, Fig. 5b). The values of activation (E_A) and formation (ΔE^f) energies and the alteration of dipole moments ($\Delta\mu^\#$) and bond lengths ($\Delta r_1^\#, \Delta r_2^\#$) of the transition states are presented in Table 8.

The comparison of the calculated values $-E_A$ and experimental values $\ln(k_{\text{exp}})$ for the reactions of **1e** with **2** demonstrates good agreement in the case of the internal alkynes (Fig. 6). The noticeable deviation of $-E_A$ observed for terminal alkynes **2a** and **2e** can be explained by the specific interaction between the dipolarophile and a dipole or a solvent, [23,24] (see above), which cannot be taking into account upon computation in the gas phase.

It should be noted, that the calculated values E_A are also in the agreement with the experimental data concerning the

influence of substituents R_1 and R_2 on the nitron reactivity. Thus, the sensitivity coefficient ρ , for the reaction of **1e–g** with **2e**, calculated from the data of Table 8 is -0.55 and it is consistent with the experimental value -0.50 . The E_A values for the reactions of N-unsubstituted nitron **1c** exceed those for N-methylated analogue **1e** that corresponds to the higher reactivity of the latter determined experimentally (Table 6).

According to the calculated data (Table 8), distinction between the energy barriers for the reactions of **1e** and **5b** with **2d** is 6.1 kcal/mol; this value corresponds to $k_{1e}/k_{5b} = 3 \times 10^4$ that coincides with the experimentally evaluated value (2.7×10^4) in CCl_4 solution. Good agreement between the DFT computation results and experimental data demonstrates the validity of the approach and allows its use for the interpretation of the studied process.

As it was mentioned above, the cycloaddition reaction proceeds non-synchronously, and the “oblongness” of the formed bonds $\Delta r_1^\#$ and $\Delta r_2^\#$ differs noticeably (Table 8). All transition states agree with asynchronous concerted processes where the shorter distance corresponds to that at the beta-conjugated position of propiolic derivatives ($\Delta r_2^\#$). Consequently, a substantial charge separation and a high polarity should be observed in the transition states of the studied nitrones. The positive charge is localized at C-7a atom (Fig. 5b), while the negative charge is localized at the interactive π -orbital of a dipolarophile. The polarity of such structure can be characterized by the difference between dipole moments ($\Delta\mu^\#$) of the transition state ($\mu^\#$) and the corresponding reaction product (μ_{product}) (Table 8).

The comparison of $\Delta r_1^\#, \Delta r_2^\#$, and $\Delta\mu^\#$ showed in Table 8 demonstrates the higher polarity of the transition states for nitrones **1** in comparison with that for nitrones **5**; in

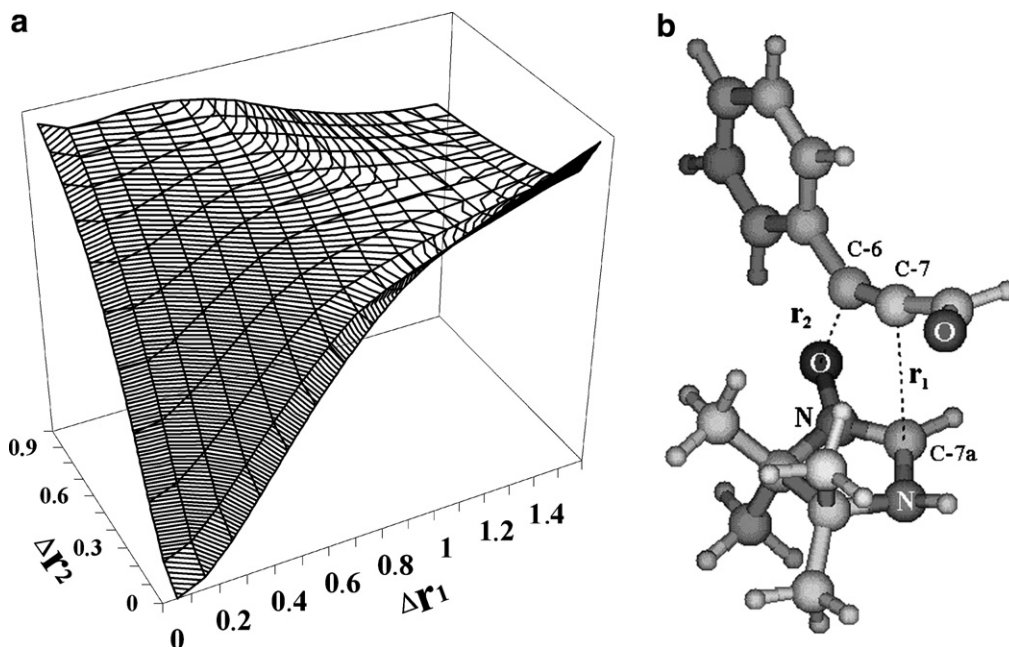


Fig. 5. The energy surface of the 1,3-dipolar cycloaddition reaction of **1a** with **2a**; coordinates are the lengths of the formed bonds C–C (r_1) and C–I (r_2) (a). The structure of the transition state for the reaction of **1a** with **2b**; atom numbering corresponds to that in the product (b).

Table 8

Activation energy ($E_A = E^\ddagger - E_{\text{reagents}}$), formation energy ($\Delta E_f = E_{\text{product}}^\ddagger - E_{\text{reagents}}^\ddagger$), alteration of the dipole moment ($\Delta\mu^\ddagger = \mu^\ddagger - \mu_{\text{product}}$), and interatomic distances ($\Delta r_i^\ddagger = r_i^\ddagger - r_{\text{product}}$) of the transition states for the reactions of nitrones **1** and **5** with alkynes **2**

Nitrone	Alkyne	E_A (kcal/mol)	ΔE_f (kcal/mol)	Δr_1^\ddagger (Å)	Δr_2^\ddagger (Å)	$\Delta\mu^\ddagger$ (D)
1a	2e	1.65	−46.06	1.09	0.462	2.03
	2a [33]	−2.83	−48.31	1.191	0.39	1.52
1b	2a [33]	−1.14	−43.12	1.248	0.318	2.85
1c	2c	11.95	−25.79	1.213	0.361	1.54
	2d	10.99	−25.05	1.264	0.341	2.20
	2b	9.62	−30.40	1.232	0.353	1.39
	2g	8.52	−30.31	1.228	0.416	3.88
1e	2a	3.53	−37.01	1.312	0.327	2.29
	2f	10.71	−27.82	1.288	0.458	2.11
	2c	9.44	−25.85	1.37	0.395	2.84
	2d	8.17	−24.13	1.421	0.361	3.32
	2e	5.83	−36.01	1.398	0.428	2.12
	2b	6.65	−32.20	1.378	0.384	2.88
	2g	5.82	−30.51	1.362	0.468	3.52
	2a	0.61	−38.73	1.47	0.364	3.39
	2h	0.53	−32.53	1.458	0.437	4.89
	2e	6.63	−36.35	1.365	0.442	0.73
1f	2g	6.98	−30.80	1.291	0.466	−0.64
	2e	4.64	−36.41	1.411	0.423	1.92
1g	2g	4.49	−30.93	1.392	0.463	3.47
5a	2f	13.74	−37.13	0.727	0.791	1.29
	2e	10.11	−44.28	0.932	0.537	0.60
	2g	9.30	−38.79	0.602	0.915	0.11
5b	2a	7.35	−46.67	1.046	0.45	1.38
	2d	14.27	−31.83	0.781	0.589	−0.86
	2a	8.31	−45.56	1.038	0.406	1.17

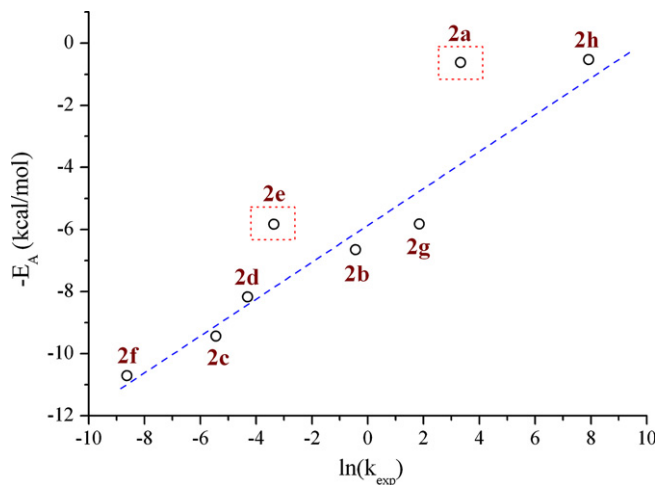


Fig. 6. Correlation plot of the DFT calculated values $-E_A$ and experimental values $\ln(k_{\text{exp}})$ for the reactions of nitrone **1e** with alkynes **2**.

other words, the process of the latter compounds proceeds more synchronously. This assertion is confirmed by the influence of solvents polarity on the reaction rate for **1** (Fig. 3) that is not observed for **5**. The reason of this fact is, probably, a high π -donor ability of nitrogen atom N-1. Its lone electron pair is capable of stabilizing the positive charge emergent on the C-7a atom in the course of the reaction. This effect becomes stronger with the increase of the electron-donating ability of the heteroatomic substituent, for example, upon attaching of the methyl group R_1

to N-1 atom (cf. Table 6). Besides, high sensitivity of **1** to the nature of the alkyne substituents can also be explained by the substantial charge separation in the transition state.

The common approach to the consideration of activity and regioselectivity in the concerted processes is the use of the FMO theory. In accordance with this approach, the more active alkynes should possess lower HOMO energy and, consequently, they should have substituents with more powerful π -withdrawing effect. This approach, however, is not always valid. Thus, the replacement of hydrogen atom in terminal alkynes **2a** and **2e** by phenyl group (alkynes **2d** and **2f**, respectively), as mentioned above, leads to the diminution of the reaction rate on average by two orders of magnitude (Table 5). Another example is more than the 100-fold increase of the reaction rate of 4,4,4-trifluorobut-2-ynoate **2h** as compared to that of DMAD **2g** (Table 5).

The consideration of the structures of the transition states allows one to solve the observed discrepancies taking into account their zwitterionic character. The structures of the reaction centers in the transition state essentially differ from those in the reactants: the s-character of C-6 atom is substantially reduced in comparison with the initial sp-hybridization, that prevents the conjugation of the substituent at the C-6 center with the interactive π -orbital of a dipolarophile. Besides, the dihedral angle between the π -system of the substituent on the C-6 carbon in the transition state and interactive π -orbital of dipolarophyl is near 90° . As a result, this substituent is capable of stabilizing the negative

charge only as σ -acceptor but not as π -acceptor. Moreover, the violation of the conjugation in the transition state additionally increases the activation barrier E_A , that causes the diminution of the reaction rate by two orders of magnitude in the case of **2d** and **2f**. At the same time, the substituent attached to C-7 atom being conjugated with interactive π -orbital is capable of efficient stabilizing its negative charge. Therefore, the reaction rate should increase heavily in the case of the location of the σ -acceptor function at the C-6 atom and the π -acceptor function, at the C-7 atom. The expressive example of such “combining” influence is a very high reactivity of ethyl 4,4,4-trifluorobut-2-ynoate **2h**, which is much more active than DMAD.

3. Conclusions

Thus, the influence of the solvents on the rate of the 1,3-dipolar cycloaddition reaction of 4,5-dihydro-1*H*-imidazole 3-oxide derivatives **1** with alkynes **2** has been studied. The series of relative activities of nitrones **1** and alkynes **2** in the reaction under investigation have been established. The structural factors influencing the rate constants have been revealed. Using the DFT calculation with the triple zets basis set, the energy profile of the reaction has been plotted and the structures and energy characteristics of the transition states have been determined. On the basis of calculated and experimental data, the mechanism of the reaction has been shown to be asymmetric but concerted one. Good correlation between the DFT computation results and experimental data demonstrates the validity of the approach and allows its use for the interpretation of the studied process.

4. Experimental

NMR ^1H and ^{13}C spectra were recorded on Bruker AC-200, AM-400 (^1H , ^{13}C) spectrometers; solvents were used as internal standards: DMSO (δ 2.54 ppm, δ 39.5 ppm), CHCl_3 (δ 7.24 ppm, δ 76.9 ppm), MeOH (δ 3.34 ppm, δ 49.86 ppm). UV spectra were measured with Specord M-40 spectrophotometer. An IR spectrum was recorded with a Bruker IFS 66 spectrometer for KBr pellet (concentration 0.25%, pellet thickness 1 mm). Thin layer chromatography monitoring was carried out on alumina plates (Fluka, Switzerland) with chloroform and chloroform/MeOH mixture (from 50:1 to 20:1) as eluents.

X-ray data were measured on Smart Apex diffractometer with graphite monochromated Mo-K α radiation. The structure was solved by statistical methods (BRUKER-SHELXS) and refined by the full-matrix least-squares method on F^2 (BRUKER-SHELXL). The positions of the hydrogen atoms were calculated geometrically and refined isotropically. Atomic coordinates, thermal parameters, bond lengths and bond angles have been deposited at the Cambridge Crystallographic Data Center; CCDCs contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at [www.ccdc.](http://www.ccdc.cam.ac.uk/conts/retrieving.html)

cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: (Internat.) + 44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk].

All calculations were carried out by DFT method using the original program PRIRODA developed by D.N. Laikov [34] The generalized gradient approximation (GGA) for the exchange-correlation functional by Perdew, Burke, and Ernzerhof [35] was employed. The orbital basis sets of contracted Gaussian-type functions of size (5s1p)/[3s1p] for H and (11s6p2d)/[6s3p2d] for C, N, O were used. Full geometry optimization of all the structures studied in this work was performed using analytical gradients and was followed by analytical calculations of the second derivatives of energy with respect to coordinates in order to characterize the nature of the resulting stationary points (minima or saddle points) on the potential energy surface (PES).

1,2-Disubstituted and 2-substituted 4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole 3-oxide derivatives **1a–1g** were synthesized according to Ref. [26] Spectral characteristics of the cycloadducts **2** are identical to that obtained earlier [19].

4.1. Determination of the rate constants of the reactions of **1f** and **2** by UV detection

The UV-spectra of the appropriate solvent (for compensation) and the solution of **1f** (1×10^{-3} – 3×10^{-3} M) in the same solvent were measured in order to determine the long-wave maximum of adsorption (the range was from 385 nm in MeOH to 468 nm in DMSO). Then, a solution (5 ml) containing the 5- to 20-fold excess of alkyne **2** was added to the solution of nitron **1f** (5 ml). UV-spectra of the reaction mixture were registered automatically every 100 s at 24 ± 1 °C. The depth of the reaction in most cases was more than 50%. The values of k_i were calculated in all points in the accordance with Eq. (1). Resultant value of k was obtained by k_i averaging.

4.2. Determination of the rate constants of the reactions of nitrones **1,5** and alkynes **2** by the ^1H NMR detection

A solution of alkyne **2** in 1 ml of appropriate deuterated solvent was added to a solution of nitron **1** or **5** in the same solvent. The ratio of reagents was varied from 10:1 to 1:10, while the concentration of minor component was approximately 1×10^{-2} M. ^1H NMR spectra of the reaction mixture were registered with the time domain from 1 min to 5 days at the 24 ± 1 °C. The depth of the reaction in most cases was more than 50%. The values of k_i were calculated in all points in the accordance with Eq. (1). The resultant value of k was obtained by k_i averaging.

4.3. Competitive reactions of nitrones **1**

A cooled solution of alkyne **2** (1×10^{-2} M) was added to a cooled solution of equimolar amount of two nitrones **1**

(1×10^{-2} M each). The nitron:alkyne ratio was from 1:0.5 to 1:0.9. The depth of the reaction was monitored by thin layer chromatography. After completion of the reaction the solvent was removed, and ^1H NMR spectra of the reaction mixture was registered. The ratio k_1/k_2 for the competitive reactions $\text{A} + \text{X} \rightarrow \text{N}$ (k_1), $\text{B} + \text{X} \rightarrow \text{M}$ (k_2) was calculated in accordance with the equation $k_1/k_2 = \ln(A/A_0)/\ln(B/B_0)$, where A_0 , B_0 and A , B are the initial and final concentrations of the corresponding nitrones.

4.4. Competitive reactions of alkynes 2

A cooled solution of nitron **1** (1×10^{-2} M) in CDCl_3 was added to a cooled solution of equimolar amount of two alkynes **2** (1×10^{-2} M each) in CDCl_3 . The alkyne:nitron ratio was varied from 1:0.5 to 1:0.9. The depth of the reaction was monitored by thin layer chromatography. After completion of the reaction ^1H NMR spectra of the reaction mixture was registered. The ratio k_1/k_2 for the competitive reactions $\text{A} + \text{X} \rightarrow \text{N}$ (k_1), $\text{B} + \text{X} \rightarrow \text{M}$ (k_2) was calculated in accordance with the equation $k_1/k_2 = \ln(A/A_0)/\ln(B/B_0)$, where A_0 , B_0 and A , B are the initial and final concentrations of the corresponding alkynes.

4.5. (2-*tert*-Butyl-3,5-diphenyl-2,3-dihydroisoxazol-4-yl)phenylmethanone (**7b**)

A solution of *N-tert*-butyl-*C*-phenylnitron **5b** (0.139 g, 0.78 mmol) and 1,3-diphenyl-propynone **2d** (0.27 ml, 0.94 mmol) in CCl_4 (3 ml) was refluxed for 9 h. The solvent was removed and the residue was treated with a small amount of hexane, the precipitate was filtered off and recrystallized from hexane–ethyl acetate mixture to give 0.181 g (60%) of **7b**.

^1H NMR (CDCl_3 , 200.13 MHz, δ , ppm): 1.83 (s, 9H, $-\text{C}(\text{CH}_3)_3$), 5.76 (s, 1H, 3-H), 6.90–7.50 (m, 15H, Ph). ^{13}C NMR (CDCl_3 , 50.32 MHz, δ , ppm): 25.0 (dm, $J = 127.0$ Hz, $\text{C}(\text{CH}_3)_3$), 61.4 (m, $\text{C}(\text{CH}_3)_3$), 70.3 (dt, $J = 140.3$ Hz, $J = 4.5$ Hz, C-3), 114.7 (d, $J = 5.9$ Hz, C-4), 127.2 (dt, $J = 160.3$ Hz, $J = 7.5$ Hz, 3-Ph, C-4'), 127.6 (m, 3-Ph, C-1'), 127.5, 127.6, 127.7, 128.2, 128.6, 129.1 (dt, $J = 160.5$ Hz, $J = 7.5$ Hz, 3,5-Ph, CO-Ph, C-2', C-3'), 130.1 (dt, $J = 160.5$ Hz, $J = 7.5$ Hz, 5-Ph, C-4'), 131.0 (dt, $J = 160.5$ Hz, $J = 7.5$ Hz, CO-Ph, C-4'), 138.7 (t, $J = 7.4$ Hz, CO-Ph, C-1'), 143.1 (t, $J = 7.4$ Hz, 5-Ph, C-1'), 161.9 (t, $J = 4.2$ Hz, C-5), 191.3 (t, $J = 3.9$ Hz, CO-Ph). λ_{max} (ethanol), nm (lg ϵ): 251 (4.11), 330 (3.84). IR (KBr): $\nu = 3055$, 2970, 1630, 1605, 1576, 1493, 1447, 1347, 1238, 1209, 1138, 1075, 887, 808, 772, 731, 701 cm^{-1} . M.p. 131–132 °C (from hexane–ethyl acetate). Found: C 81.40, H 6.61, N 3.67. Calculated for $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_3$: C 81.43, H 6.57, N 3.65.

Crystallographic data (CCDC 293549): $\text{C}_{26}\text{H}_{25}\text{NO}_2$, FW = 383.47, monoclinic, $P2_1/n$, $a = 5.9027(14)$, $b = 10.500(3)$, $c = 33.907(8)$ Å, $\beta = 90.816(5)^\circ$, $V = 2101.2(9)$ Å³, $Z = 4$, $D_c = 1.212$ g/cm³, $\mu = 0.076$ mm⁻¹, $2.03 < \theta < 20.81^\circ$, reflections collected/unique = 12,260/

2191, $R_{\text{int}} = 0.1435$, 363 parameters, Goof = 1.286, R indices ($I > 2\sigma_I$): $R_1 = 0.0816$, $wR_2 = 0.1926$, R indices (all data): $R_1 = 0.0947$, $wR_2 = 0.2008$.

References

- [1] R. Huisgen, Proc. Chem. Soc. (1961) 357.
- [2] R.A. Firestone, J. Org. Chem. 33 (1968) 2285.
- [3] R. Huisgen, J. Org. Chem. 33 (1968) 2291.
- [4] R.A. Firestone, J. Chem. Soc., (A) 9 (1970) 1570.
- [5] R.A. Firestone, J. Org. Chem. 37 (1972) 2181.
- [6] R.A. Firestone, J. Org. Chem. 41 (1976) 403.
- [7] L.R. Domingo, M.T. Picher, Tetrahedron 60 (2004) 5053.
- [8] D.V. Cristiana, F. Mauro, G. Remo, R. Augusto, J. Org. Chem. 65 (2000) 6112.
- [9] M.A. Silva, J.M. Goodman, Tetrahedron 58 (2002) 3667.
- [10] K. Marakchi, O.K. Kabbaj, N. Komiha, J. Fluorine Chem. 114 (2002) 81, CA 137:108952.
- [11] P. Merino, J. Revuelta, T. Tejero, U. Chiacchio, A. Rescifina, G. Romeo, Tetrahedron 59 (2002) 3581.
- [12] K. Kaliaperumal, V. Ponnambalam, J. Chem. Soc., Perkin Trans. 2 (12) (2002) 2130.
- [13] K. Fukui, Acc. Chem. Res. 4 (1971) 57.
- [14] I. Fleming, in: Frontier Molecular Orbitals and Organic Chemical Reactions, William Clowes and Sons, London, 1976, p. 258.
- [15] (a) R.C.F. Jones, J.N. Martin, P. Smith, T. Gelbrich, M.E. Light, M.B. Hursthouse, Chem. Commun. 19 (2000) 1949; (b) R.C.F. Jones, J.N. Martin, P. Smith, J. Heterocyclic Chem. 3 (2000) 481; (c) R.C.F. Jones, J.N. Martin, P. Smith, Synlett 7 (2000) 967.
- [16] R. Huisgen, H. Saidl, I. Bruning, Chem. Ber. 102 (1969) 1102.
- [17] (a) N.A. Akmanova, Yu.M. Shaul'skii, Ya.V. Svetkin, Org. Khim.; I.I. Lapkin (Ed.), Perm: Perm Gos. Univ. press. (1976) 88. Chem. Abstr., 88, 169274v; (b) Ya.D. Samuilov, S.E. Solov'eva, T.F. Girutskaia, A.I. Kononov, Zh. Org. Khim. 14 (1978) 1693, Chem. Abstr., 89, 214586g; (c) Ya.D. Samuilov, S.E. Solov'eva, A.I. Kononov, T.G. Mannafov, Zh. Org. Khim. 15 (1979) 279, Chem. Abstr., 90, 203132a; (d) Ya.D. Samuilov, S.E. Solov'eva, A.I. Kononov, Zh. Obshch. Khim. 49 (1979) 637, Chem. Abstr., 91, 38467z; (e) Ya.D. Samuilov, S.E. Solov'eva, A.I. Kononov, Dokl. Akad. Nauk SSSR 255 (1980) 606.
- [18] Y.-M. Chang, J. Sims, K.N. Houk, Tetrahedron Lett. 50 (1975) 4445.
- [19] S.A. Popov, N.V. Chukanov, G.V. Romanenko, T.V. Rybalova, Y.V. Gatilov, V.A. Reznikov, J. Heterocyclic Chem. 43 (2006) 277.
- [20] M.L. Yeung, W.-K. Li, H.-J. Liu, Y. Wang, K.S. Chan, J. Org. Chem. 63 (1998) 7670.
- [21] J.E. Baldwin, R.G. Pudussery, A.L. Qureshi, B. Sklarz, J. Am. Chem. Soc. 90 (1968) 5325.
- [22] (a) G. Steiner, R. Huisgen, J. Am. Chem. Soc. 95 (1973) 5056; (b) R. Huisgen, Acc. Chem. Res. 10 (1977) 117.
- [23] M.J. Copley, S.E. Holley, J. Am. Chem. Soc. 61 (1939) 1599.
- [24] S.S. Stanford, W. Gorby, J. Am. Chem. Soc. 63 (1941) 1094.
- [25] S.A. Popov, V.A. Reznikov, J. Heterocyclic Chem. 43 (2006) 293.
- [26] S.A. Popov, R.V. Andreev, G.V. Romanenko, V.I. Ovcharenko, V.A. Reznikov, J. Mol. Struct. 697 (2004) 49.
- [27] R. Huisgen, L. Fisera, H. Giera, R. Sustmann, J. Am. Chem. Soc. 117 (1995) 9671.
- [28] C.K. Ingold, in: Structures and Mechanisms in Organic Chemistry, Cornell University press, Ithaca and London, 1969, p. 1055.
- [29] J.J. Tufariello, in: A. Padwa (Ed.), 1,3-Dipolar Cycloaddition Chemistry, vols. 1 and 4, Wiley-Interscience, New York, 1984.
- [30] The rate constants for the reaction of nitron **1e** with alkyne **2d** in different solvents were estimated taking into consideration the data given in Tables 4 and 6. According to data from Table 6: k_{1e} : $k_{1f} \approx 2.7$, on average. Consequently, $k_{1e} + \mathbf{2d} \approx k_{1f} + \mathbf{2d} \times 2.7$ in various solvents, while the values of $k_{1f} + \mathbf{2d}$ are presented in Table 4.

- [31] S.P. Ashburn, R.M. Coates, J. Org. Chem. 49 (1984) 3127.
- [32] S.P. Ashburn, R.M. Coates, J. Org. Chem. 50 (1985) 3076.
- [33] The negative activation energy is the consequence of formal approach to the consideration of the activation barrier ($E_A = E^\ddagger - E_{\text{Reagents}}$). As is well known, in case of gas phase processes, the precoordination is preceding the reaction. In the course of this process the overall energy of system decreases (this energy decrease is $E_{\text{Precoordination}}$). If the value of true E_A less than absolute value of $E_{\text{Precoordination}}$, then formal E_A should be negative.
- [34] D.N. Laikov, Chem. Phys. Lett. 281 (1997) 151.
- [35] J.P. Perdew, K. Burke, M. Ernzerhof, Phys. Rev. Lett. 77 (1996) 3865.