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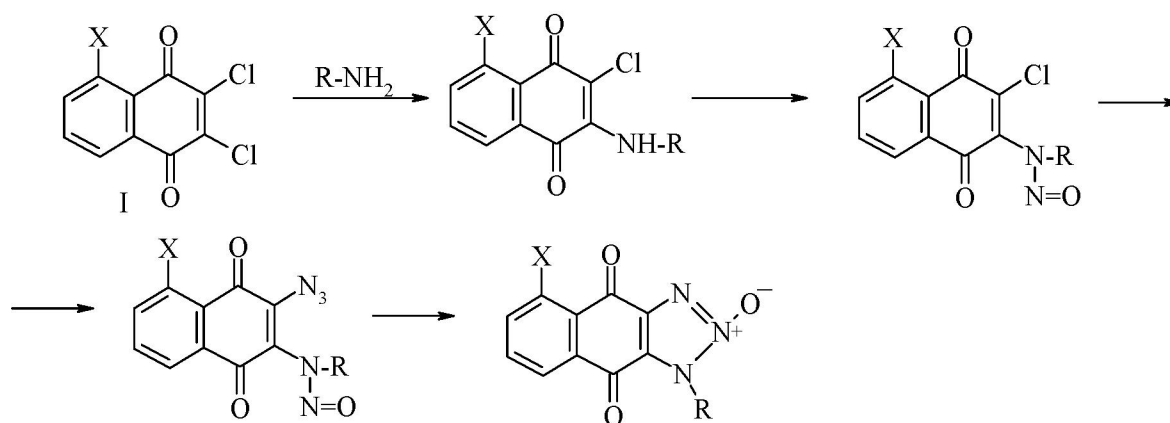
STUDY OF THE MECHANISM OF THE REACTION OF TRIAZOLIDE'S FORMATION OF USING THE DENSITY FUNCTIONAL THEORY

Abstract. We have analyzed the thermodynamic parameters of the reaction of the amination in the gas phase and in solution by calculation by density functional method using fully electronic basis set 6-31G(d). It was shown the dichlorojuglone aniline's thermodynamic and kinetic possibility of a reaction of condensation. It was estimated the transition states, activation energies and rate constants for the reaction of condensation.

Keywords: the theory of functional density; B3LYP/6-31G (d); naphthoquinones; the mechanism of the reaction.

Introduction

Works [1-2] have described an experimental approach to triazole oxides. The interest in compounds of this structure is due to the fact that some of them [3] have antitumor activity. Given this and lack of in-depth information about the properties of the condensed triazole oxides we will consider experimental and quantum-chemical peculiarities of their formation, as was shown earlier [2]. It is known that the simplest way to naftatriazole oxides is the following scheme:



X = H, OH

The aim of this work was to study the density functional method of the mechanism of the first reaction stage of condensation dichlorojuglone with aniline and the explanation of the observed experimental data. For all calculations there were used fully electronic basis set 6-31G (d) with density functional B3LYP. This calculation method is widely used for analysis of thermodynamic parameters of organic compounds.

Experimental part

All calculations were carried out using standard software package GAUSSIAN'03 [4]. For the theoretical study, we used quantum-chemical density functional method (DFT, density function theory methods). The calculations were performed using the hybrid density functional method B3LYP with a functional exchange Beck (B3) [5] and the correlation functional of Lee, Yang and steam (not LYP) [6]. For all atoms basis set 6 fully electronic-31G (d) was used. The geometries of all calculated molecules were fully optimized, the lack of imaginary frequencies confirmed their stationary. Optimization of transition States was carried out using the STQN method [7], transition states with only one imaginary frequency. The calculations in ethanol solution are carried out by the same methods, using a polarized continuum (PCM) [8]. The energy is calculated compounds adjusted to the zero vibration energy (ZPVE) and reduced to standard conditions (298.15 K, 1 ATM.) using thermal corrections to enthalpy and free energy.

Results and discussion

The accuracy of any quantum-chemical calculations is determined by the agreement of experimental and calculated from molecular geometry. The calculated bond lengths and the bond angles of the studied molecules together with the available experimental data are represented in tables 1-2.

Table 1 - The geometrical parameters of the juglone

Bond	R (exper.), Å	R (calc.), Å	the valence angle	ω (exper.), degree	ω (calc.), degree
C-C	1.35 ± 0.02	1.34	O-C-C	120 ± 1	119.4
C-C	1.51 ± 0.03	1.49	C-C-C	123 ± 2	121.8
C-C	1.44 ± 0.02	1.48	C-C-C	120 ± 2	122
C-O	1.2 ± 0.02	1.23	C-C-O	121 ± 2	120.3
O-H	1.51 ± 0.02	1.49	C-C-C	119 ± 1	117.5
C-C	1.37 ± 0.02	1.42	C-C-C	118 ± 1	120
C-C	1.51 ± 0.02	1.47	C-C-C	122 ± 1	120.7
C-O	1.33 ± 0.02	1.34	C-C-C	118 ± 1	118.2
C-C	1.44 ± 0.02	1.41	C-C-C	122 ± 1	120.1
C-C	1.38 ± 0.02	1.39	O-C-C	115 ± 2	118.2
C-C	1.42 ± 0.03	1.41	C-C-C	122 ± 1	119.4
C-C	1.36 ± 0.02	1.39	C-C-C	119 ± 2	120.2
C-C	1.4 ± 0.02	1.42	C-C-C	120 ± 2	121
			C-C-C	119 ± 2	119.5
			C-C-C	118 ± 1	120.6
			C-C-C	116 ± 1	119.3
			C-C-C	117 ± 1	119.4

Comparison of the calculated geometric parameters with experimental data shows that the calculated lengths of bonds mostly underestimated, and bond have been completed. However the analysis leads to good quality there was a problem with the correlation between the calculated and experimental bond lengths of and valence angles [9-12] for some of the studied molecules:

$$R^{\text{exp.}} = -0.04 + 1.03 R^{\text{calc.}} \quad (r = 0.996; s = 0.02; n = 22) \quad (1)$$

$$\omega^{\text{exp.}} = -17.9 + 1,14 \omega^{\text{calc.}} \quad (r = 0.982; s = 1.5; n = 32) \quad (2)$$

In these and the following correlation equations, r is the correlation coefficient, s is standard deviation and n is the number of compounds included in the correlation.

Table 2 - The geometrical parameters of the naphthazarine

Bond	R (exper.), Å	R (calc.), Å	the valence angle	ω (exper.), degree	ω (calc.), degree
C-C	1.431 ± 0.006	1.47612	C-C-H	120 ± 2	122.4
C-C	1.342 ± 0.007	1.34598	C-C-O	118.5 ± 0.4	119.8
C-C	1.413 ± 0.007	1.42717	C-C-H	120 ± 2	115.8
C-C	1.427 ± 0.005	1.4062	C-C-O	122.2 ± 0.4	122.4
C-C	1.436 ± 0.006	1.41946	C-O-H	104 ± 2	106.5
C-C	1.342 ± 0.007	1.37442	O-H-O	152 ± 4	147.3
C-O	1.301 ± 0.004	1.24774	H-O-C	99 ± 2	101.1
C-O	1.288 ± 0.004	1.33758	O-C-C	121.4 ± 0.4	122.4
C-H	0.96 ± 0.005	1.08626	C-C-C	119.7 ± 0.4	119.7
C-H	0.98 ± 0.005	1.08533	C-C-H	117 ± 3	117.9
O-H	1.06 ± 0.05	0.99638	C-C-H	122 ± 3	121.3
H-O	1.59 ± 0.05	1.7001	C-C-C	120.6 ± 0.4	121.8
			C-C-C	119.2 ± 0.3	117.8
			C-C-C	120 ± 0.4	120.3
			C-C-C	119.5 ± 0.4	119.9
			C-C-C	121.9 ± 0.4	120.8
			C-C-C	119 ± 0.4	119.3

The table 3 shows the calculated and experimental [13-15] values of wavelength UV spectra (λ), IR spectra (ω) spectra and the ^1H and ^{13}C NMR (δ) of some quinone molecules.

The correlation equations (3-5) show that our calculations allow to estimate the spectral parameters with a sufficient degree of accuracy.

$$\lambda^{\text{exp.}} = -16 + 1.06 \lambda^{\text{calc.}} \quad (r = 0.998; s = 7; n = 22) \quad (3)$$

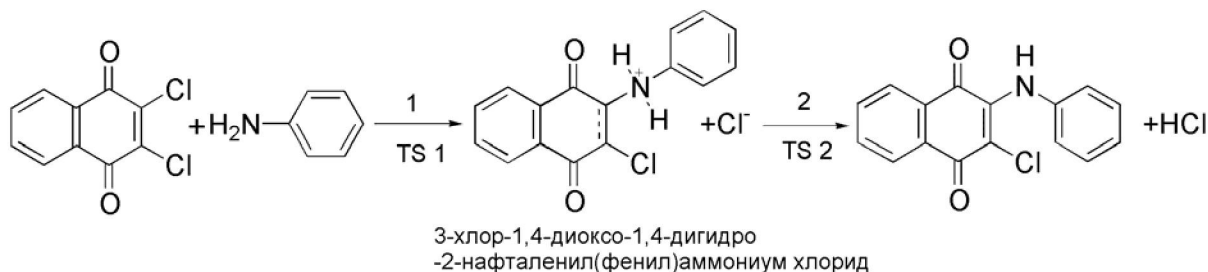
$$\delta^{\text{exp. } ^1\text{H}} = 1.23 + 0.83 \delta^{\text{calc. } ^1\text{H}} \quad (r = 0.995; s = 0.2; n = 19) \quad (4)$$

$$\delta^{\text{exp. } ^{13}\text{C}} = 4.7 + 0.92 \delta^{\text{calc. } ^{13}\text{C}} \quad (r = 0.996; s = 2.2; n = 8) \quad (5)$$

$$\omega^{\text{rcg/}} = 32 + 0.99 \omega^{\text{calc.}} \quad (r = 0.995; s = 30; n = 18) \quad (6)$$

We obtained a correlation ratio suggest that expected thermodynamic parameters are quite close to experimental values. In addition, in [16] it is shown that among the methods of the density functional (BLYP, B3LYP, PB86, B3P86, BPW91, B3PW91 and SVWN) B3LYP method most accurately predicts thermodynamic parameters with an absolute error of 13 kJ/mol.

On the basis of the experiment we can assume the mechanism for the first reaction stage of the formation of intermediate and transition states:



The table 4 shows the results of quantum-chemical calculations of the enthalpies (ΔH) and free Gibbs energies of the amination's reactions for some naphthoquinones with aromatic amines. From table 4 it is shown that all the reactions are thermodynamically favorable in the gas phase and in solvent. However, the solvent Gibbs energy is approximately two times larger value due to the salvation of the reagents in ethanol.

Table 3 - The calculated and experimental $^1\text{H-NMR}$ and UV spectra

Molecule	The chemical shift, ppm.		Wavelength, nm		Molecule	The chemical shift, ppm.		Wavelength, nm		
	exp.	calc.	exp.	calc.		exp.	calc.	exp.	calc.	
Naphthazarine	12.34	12.96	529	509	2 Anilino-3-harugon	7.18	7.05			
	7.14	7.35	319	333		7.32	7.28			
			279	278		7.34	7.33			
			226	227		7.36	7.41			
			216	222		7.78	7.69			
Dichlorotaurine	11.92	12.87	532	521		9.7	9.97			
	7.18	7.55	360	383		12.16	11.4			
			260	267		12.06	11.3			
			247	255		7.61	6.7			
Dichlormethane	7.81	8	341	340		7.38	6.68			
	8.2	8.6	333	333	7.09	6.4				
			282	278			332	328		
			252	253			258	252		
			231	228	1.4-Naphtine			246	242	
Juglone	11.9	12.7			214	227	1-Amino-9,10-anthraquinone		480	471.6
	7.54	7.85					2-Amino-9,10-anthraquinone		450	452
	7.27	7.5					1,6-Diamino-9,10-anthraquinone		490	476.7
	7.15	7.05					1,9-Diamino-9,10-anthraquinone		505	483
							1-Phenoxy-9,10-anthraquinone		364	336.6
Dichlorophen	11.38	12.4								
	7.77	8.11								
	7.64	7.75								
	7.39	7.47								

Table 4 - Thermodynamic characteristics of the reagents, products and transition states (kJ/mol)

Reagent	Arylamine	ΔH	ΔG		$\Delta\text{G}^\ddagger_{\text{EtOH}}$	E_a
			gas phase	EtOH		
2,3-Dichlor-1,4-naphthoquinone	Aniline	-46	-36	-45	80	94
	<i>p</i> -Toluidine	-46	-42	-47	78	91
	<i>m</i> -Toluidine	-45	-41	-45	74	94
	Anisidine	-60	-45	-59	64	76
	<i>p</i> -chloraniline	-44	-34	-40	89	100
2,3-Dichlorojuglone	Aniline	-51	-41	-47	75	86
	<i>p</i> -Toluidine	-51	-47	-43	73	85
	<i>m</i> -Toluidine	-49	-45	-41	77	87
	Anisidine	-65	-50	-55	98	68
	<i>m</i> -Toluidine	-45	-41	-45	74	94

To clarify the reaction mechanism it is important to know how adequately the chosen method can predict the activation energy of the reactions of amination. To this point of view, using B3LYP/6-31G(d) level of the theory, we have calculated transition states for several reactions (table. 4). For optimization of transition states, we used two methods: the traditional optimization of the transition state using the algorithm of berny(?) [17] and the method STQN (Synchronous Transit-Guided Quasi-Newton Methods) [7]. STQN method has proved to be most convenient to optimize transition structures. We have used the analyzed vibrations corresponding to the imaginary frequency, direction of changes in the structure along the reaction path (the IRC calculation [18, 19]) for verification of the transitional status.

Using both methods of calculation, we estimated transition states for several amination's reactions and using the resulting data we have calculated the energy of activation of these reactions in the gas phase according to the equation:

$$E_a = \Delta H^\ddagger + nRT, \quad (7)$$

where E_a is the activation energy, ΔH^\ddagger is the activation enthalpy, using the estimated enthalpies of reactant and transition state, n is the reaction order, R is the gas constant, T is the absolute temperature.

However, it is known that the reaction in reality take place in the solutions [2]. We have calculated the activation energy in the ethanol solution as the difference of free Gibbs energies in solution of the reagent and transition states (ΔG^\ddagger). In principle, the route of the reaction of the amination can pass sequentially through the first, the formation of the cat ion and then through the second transition state (Fig. 1a-b).

We calculated the cat ion and both the transition state. However, from the profile of the reaction of the amination (Fig. 2), built according to the energy change of the reactants, transition states, cat ion and the products of the reaction it was shown that the formation of the cat ion and the second transition state is thermodynamically not profitable. This is indicated by negative values of enthalpy and of the Gibbs free energy and activation energy calculated in relation to the second transition state. Apparently, this is due to the fact that the second transition state is a local maximum having a small value of negative-frequency vibrations ($\sim -45 \text{ cm}^{-1}$) and represents the vibration of the deformation of benzene ring in the amine (Fig. 1B). The visualization of the molecular orbitals confirms the findings.

From Fig. 3 a-g we can see that the maximum electron density of the HOMO orbital is located on naphthoquinone ring and under the rules of the Fukui nucleophilic reagent comes closer to the ring carbon atoms forming the first transition state. In the second transition state, the electron density in HOMO orbital is located mainly on the molecule of the amine. In the cat ion the maximum electron density in HOMO is located on the reverse side of the ring, which does not allow obtaining an effective interaction between the naphthoquinones and amine.

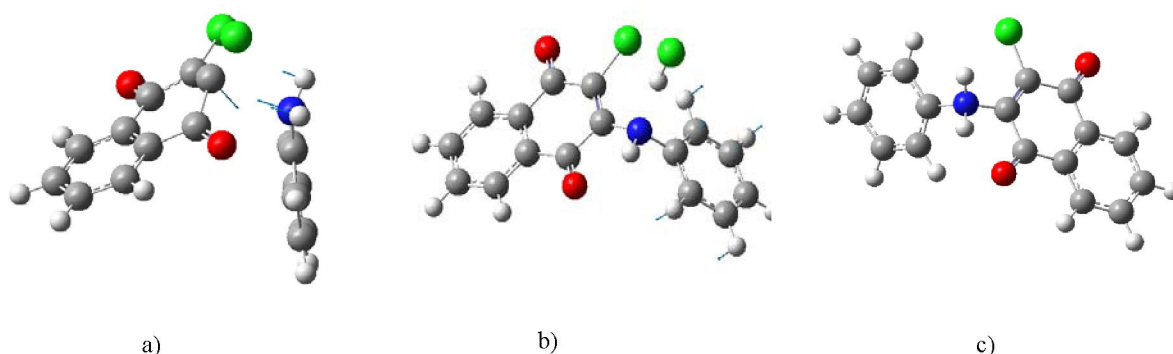


Fig. 1 - The optimized at the B3LYP/6-31G(d) structure of the first transition state (a), second transition state (b), cation (c)

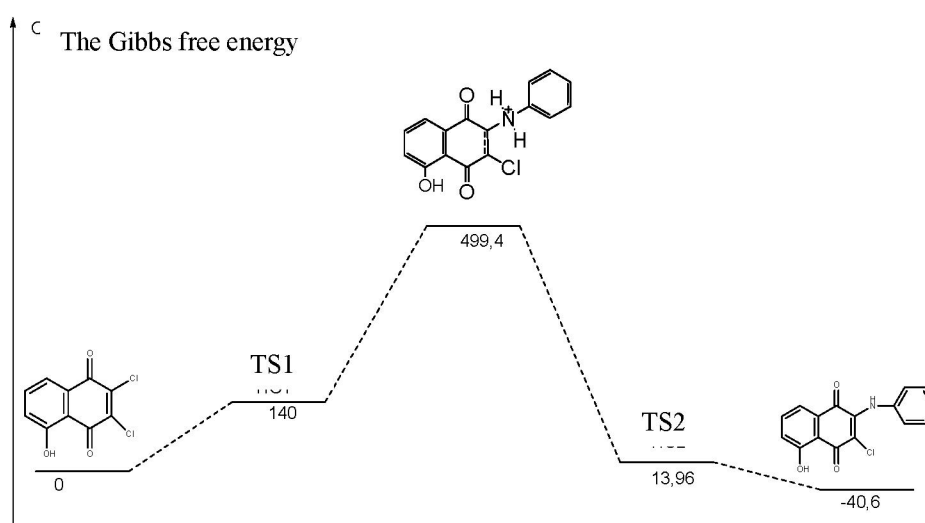


Fig. 2 - The full energy profile of the reaction amination juglone, (kJ/mol)

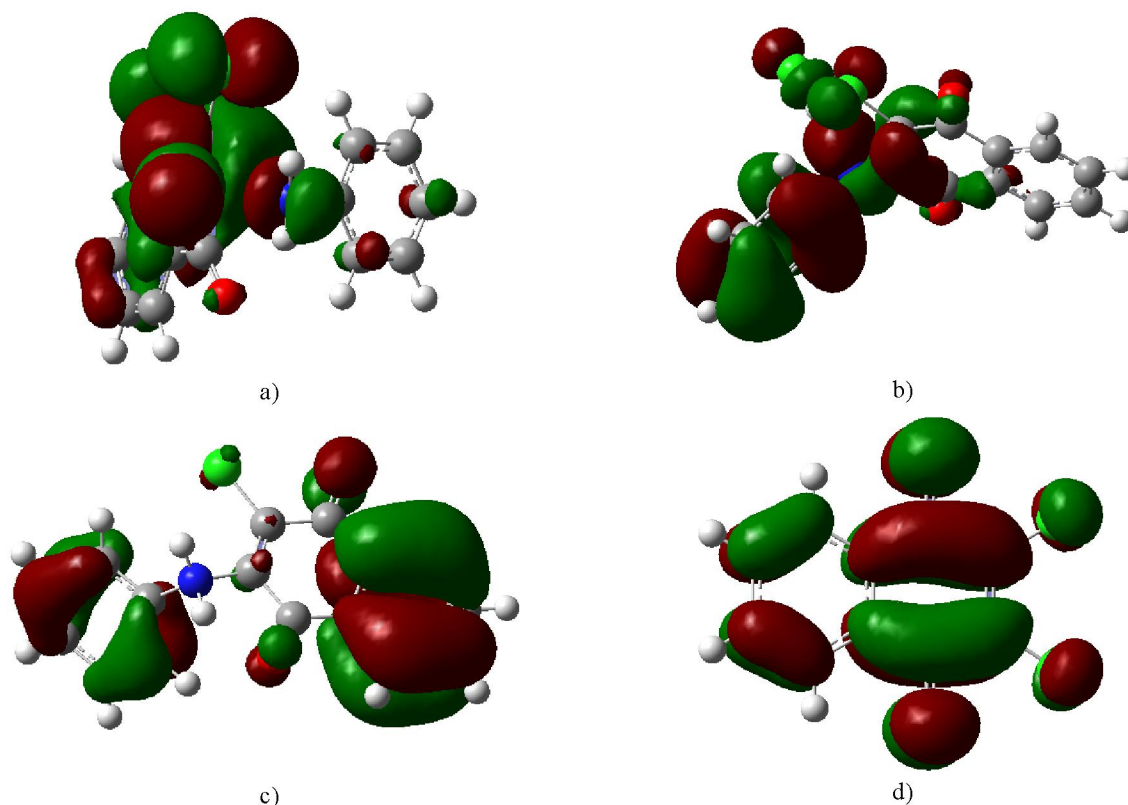


Fig. 3 - The highest occupied molecular orbitals of the first transition state (a), second transition state (b), cat ion (c), the lowest free molecular orbital of juglone (d)

The calculated by the first transition state values of the activation energy is less in the solution than in the gas phase and are close to known experimental values for S_NAr reactions [20]. The results of the calculation in all cases, the first transition states represent intermediates, in which the cleavage of the chlorine atom from the naphthoquinones and the formation of weak bonds between the carbon atoms of naphthoquinones and nitrogen of the amino group (1.8 Å) (Fig. 1A). This condition is really transitional because it has one negative vibrational frequency ($\sim -350 \text{ cm}^{-1}$), characteristic for the transition state and represents the valence vibration of the C-N bond. Considering all the above, we can assume that the reaction amination passes through the first transition state, which leads to significant activation energies.

The obtained values of the activation energy allowed to calculate on the base of the equations (8) and (9) the rate constant of the reactions in the gas phase [21] (tab. 5).

$$k = A e^{-\frac{E_a}{RT}}, \quad (8)$$

where k is the rate constant, A is the pre-exponential factor;

$$A = \left(\frac{k_B T}{h} \right)^{1/C_0} e^2 e^{\Delta S^\ddagger / R}, \quad (9)$$

where k_B is the Boltzmann's constant, h – Planck's constant, ΔS^\ddagger is the entropy of activation. For the calculation of the rate constant in the solution we have used the formula [22]:

$$k = \frac{k_B T}{h} e^{-\Delta G^\ddagger / RT}$$

Table 5 - The rate constants of the reactions amination (s⁻¹)

Reagents	Arylamine	K exp.	K calc. (gas)	K calc. (solution)
2,3-Dichlor-1,4-naphthoquinone	Aniline	0.5 · 10 ⁻³	1.64 · 10 ⁻¹¹	0.68
	<i>n</i> -Toluidine	0.4 · 10 ⁻²	1.89 · 10 ⁻¹⁰	1.65
	<i>n</i> -chloraniline	0.1 · 10 ⁻⁵	3.15 · 10 ⁻¹⁰	0.03
2,3-Dichlorojuuglone	Aniline	0.4 · 10 ⁻⁴	1.89 · 10 ⁻¹⁰	4.82
	<i>n</i> -Toluidine	0.1 · 10 ⁻³	5.87 · 10 ⁻⁹	10.32
	<i>m</i> -Toluidine	0.55 · 10 ⁻⁴	2.33 · 10 ⁻⁹	2.01
	<i>p</i> -chloraniline	0.7 · 10 ⁻⁵	2.09 · 10 ⁻¹¹	0.135

From the data of table 5 we can see that calculated in the gas phase rate constants is much less than experimental values, while in solution they are approaching the last. Of course, the absolute values of the calculated rate constants are quite far from the experimental values, but the order changes on a range of substituent in the amine is the similar.

Conclusion

1. It is shown that the density functional method to calculate the spatial and electronic structure of the reactants of the reactions amination of naphthoquinones gives adequate results in the prediction of geometrical parameters, ultraviolet and NMR spectra.

2. It was suggested the possible existence of the transition states in the reaction of amination of the naphthoquinones. We have calculated their electronic and spatial structure and shown that the reaction takes place only via the first transition state.

3. It was calculated the activation energies and rate constants for the reactions of amination of various other amines. It is shown that the lower activation energy in solution provide an acceptable rate constants compared to reactions in the gas phase.

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ТЫҒЫЗДЫҚТЫҢ ФУНКЦИОНАЛ ТЕОРИЯСЫН ҚОЛДАНЫП ТРИАЗОЛОКСИДТЕРДІҢ ТҮЗІЛУ РЕАКЦИЯСЫНЫҢ МЕХАНИЗМІН ЗЕРТТЕУ

Аннотация. Газды фазада және ерітіндіде аминдеу реакциясының термодинамикалық параметрлері толық электронды базисті жинақты 6-31G (d) қолданып тығыздық функционалы тәсілімен есептеу көмегімен талданды. Дихлорюглонның анилинмен конденсациялану реакциясының термодинамикалық және кинетикалық мүмкіндіктері көрсетілді. Конденсирлеу реакциясы үшін ауыспалы күйі, активтендіру энергиясы және жылдамдық константасы есептелді.

Түйін сөздер: тығыздықтың функционал теориясы; B3LYP/6-31G(d); нафтохинондар; реакция механизмі.

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ИССЛЕДОВАНИЕ МЕХАНИЗМА РЕАКЦИИ ОБРАЗОВАНИЯ ТРИАЗОЛОКСИДОВ С ИСПОЛЬЗОВАНИЕМ ТЕОРИИ ФУНКЦИОНАЛА ПЛОТНОСТИ

Аннотация. Проанализированы термодинамические параметры реакции аминирования в газовой фазе и в растворе с помощью расчетов методом функционала плотности с использованием полноэлектронного базисного набора 6-31G(d). Показана термодинамическая и кинетическая возможность реакции конденсирования дихлорюглона с анилином. Рассчитаны переходные состояния, энергии активации и константы скорости для реакции конденсирования.

Ключевые слова: теория функционала плотности; B3LYP/6-1G(d); нафтохиноны; механизм реакции.

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