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Quantum-chemical calculations of transitional states thermodynamic parameters of tautomers of initial *N,N'*-disubstituted thiourea derivative during the cyclization reaction in the conditions of different solvents application

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Aim. Theoretical substantiation of directions of the cyclization reaction in different solvents by means of quantum-chemical calculations of thermodynamic parameters of three tautomers of the initial N-ethyl-N'-[4-(6,7,8,9-tetrahydro-5H-[1,2,4]triazol[4,3-a]azepin-3-yl) phenyl]thiourea. **Methods.** Quantum-chemical calculations of relative energies, interconversion barriers, structural and thermodynamic parameters of tautomers of thiourea in dioxane, ethanol, dimethylformamide (DMFA) and tetrachlormethane were performed on the basis of the density functional theory applying the GAUSSIAN 09W software. The influence of the solvent was taken into account within the framework of the continuum polarized model. **Results.** In all the solvents under study, the cyclization reaction must proceed in one direction to form the N-ethyl-4-phenyl-N'-[4-(6,7,8,9-tetrahydro-5H-[1,2,4]triazol[4,3-a]azepin-3-yl) phenyl]-1,3-thiazole-2(3H)-imine. The smallest barrier of initial thiourea tautomers interconversion was observed in the presence of dioxane as a solvent; this fact indicated the advantage of synthesis conducting in this solvent precisely in comparison to ethanol, water, tetrachlormethane and DMFA. **Conclusions.** Dioxane is the most suitable solvent for cyclization.

Keywords: 5H-[1,2,4]triazol[4,3-a]azepines, cyclization, quantum-chemical calculations, activating energy, relative energy, saddle point (transitional state).

Introduction

Modern quantum-chemical methods gain widespread acceptance in the study of structure and reactivity of organic compounds [1-3]. One of the most important and interesting

directions of their application is related to the study of chemical reactions paths. The results of the theoretical research allow complementation and deepening of the interpretation of the experiment, and in some cases even its improvement by using in the synthesis more suitable solvent.

It was proved earlier that the molecule of *N*-ethyl-*N'*-[4-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazol[4,3-*a*]azepin-3-yl)phenyl]thiourea has a higher analgesic activity than ketorolac, the most common analogue with the same pharmacological action [4].

Investigation of the *N*-ethyl-*N'*-[4- (6,7,8,9-tetrahydro-5*H*-[1,2,4]triazol[4,3-*a*]azepin-3-yl)phenyl]thiourea isolated molecule in different media is also required for studying the environment influence on its structure, solving the problems of hydration, interaction with proteins, *etc.*; in particular, analgesic activity due to inhibition of cyclooxygenase activity (COX-1 and COX-2) and prostaglandins synthesis blockage.

Our earlier research on the regioselectivity of cyclization reaction of *N*-ethyl-*N'*-[4-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazol[4,3-*a*] azepin-3-yl)phenyl]thiourea with α-bromoketone in water and without solvent showed availability of application of quantum-chemical calculations of the electronic structure, geometry and thermodynamic parameters of initial thiourea tautomers, which was confirmed by the results of physical and chemical studies of the synthesized product of cyclization [5].

The next step of this research was theoretical substantiation of the direction of the cyclization reaction in conditions of synthesis in different solvents. The selection of the optimal solvent for synthesis was carried out by calculating the thermodynamic parameters of the initial tautomers in the medium of ethanol, DMFA, dioxane and tetrachlormethane using the licensed software product Gaussian W09, Revision A.02. This program provides an opportunity to calculate the physical and chemical parameters of the raw materials for synthesis both in gas phase and condensed state with high precision and reliability [6].

The most popular DFT functionals and PCM models nowadays allows the solution of such tasks as calculation and comparison of structural, electronic characteristics, relative energy of tautomers that theoretically may exist and energy barriers to their transformation; definition of the structure of intermediate products of the reaction.

It is known that during choosing a method of calculation the nature of a particular problem should be taken into account since various methods used in quantum-chemical calculations have specific disadvantages that limit their application.

The methods of the density functional theory of B3LYP and M06-2X were chosen as the main calculation methods for our purpose – the selection of solvent with the most favorable parameters for synthesis; the basis set 6-31 + G (d) and the continuum model PCM implemented in Gaussian W09, Revision A.02 were used. [7].These models are widely applied in the practice of solvation effects in heterocyclic compounds.

The popularity of the hybrid method Beck3-Lee-Yang-Parr (B3LYP) is due to the fact that its applying allows description of the processes that include a wide range of chemical transformations. However, a significant disad-

vantage of this method is that it does not take into account the dispersion interactions, which results in the underestimation of the activation energy value and inaccuracies in describing the processes where the essential role is played by the effects associated with Van der Waals interaction [1]. Thus, more accurate and at the same time accessible methods are necessary for describing complex chemical processes. For the calculations of thermochemical kinetics, weak intermolecular interaction and excited states, we proposed a complex of meta-hybrid functionals M06 [7], which is based on an improved generalized gradient approximation (GGA). The M06-2X method was specially designed for kinetic studies, it has 54 % of HF exchange function and is most effective in solving our problem.

The frequencies of harmonic oscillations were calculated for the determination of stationary points (minima with all positive frequencies; the transition state is corresponded to the presence of one imaginary frequency).

An analysis of the solvation effects, that we have carried out earlier for tautomers of *N*, *N'*-disubstituted thiourea in the frame of the PCM model with bases of medium size (B3LYP / 6-31 + G (d) and M06-2X / 6-31 + G (d)), found a fairly strong influence of the solvent on the position of tautomeric equilibrium in the studied compounds [5]. According to the research results, the additional optimization of tautomers geometry in solutions with the application of larger bases leads only to small changes in the activation energy and is not necessary. The estimated and experimental data are consistently identical, and this fact allows us to rely on the correctness of predictions of the influence of solvents on the thermodynamic characteristics of the compounds studied.

Materials and Methods

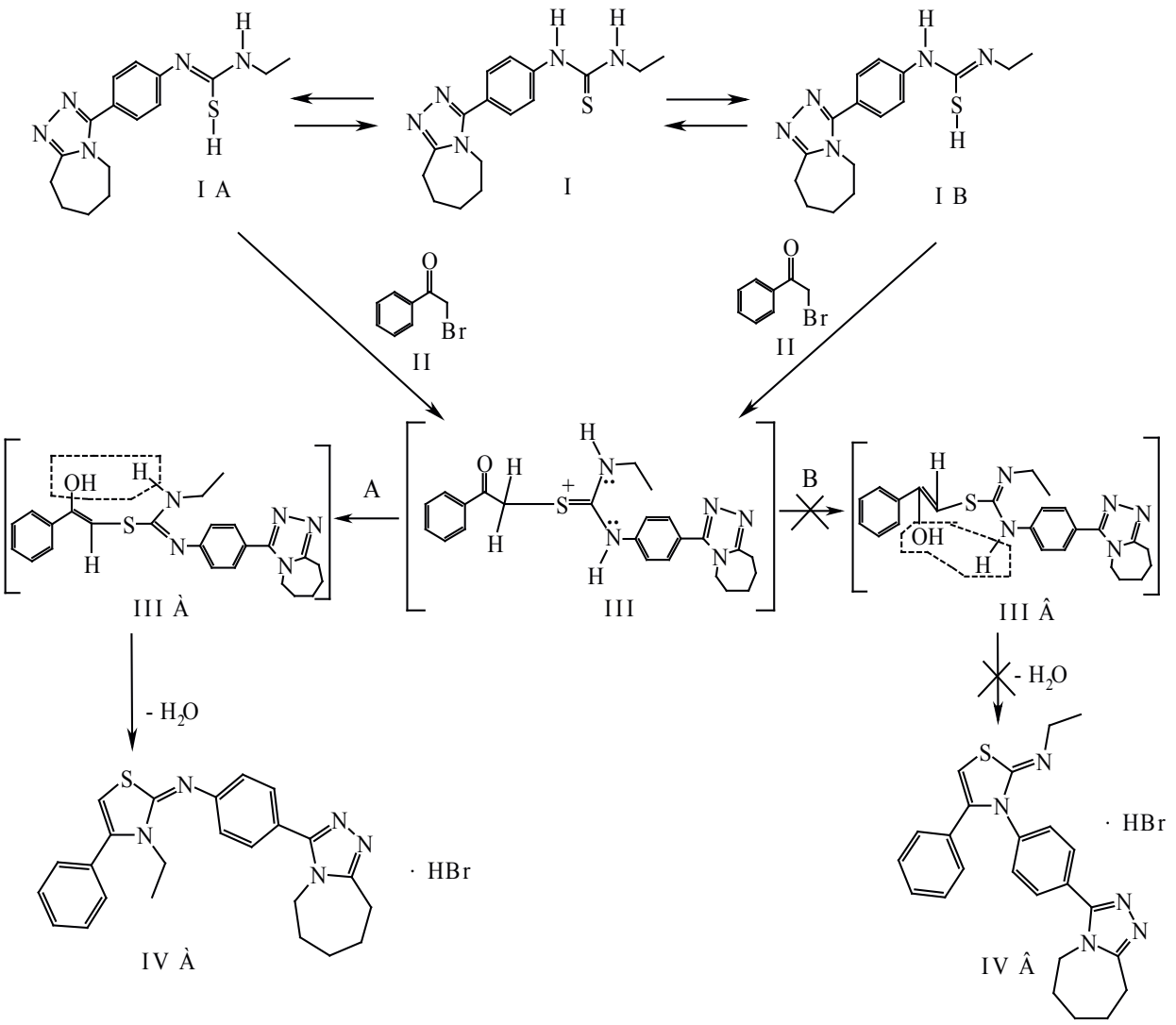
N-ethyl-*N'*-[4-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazol[4,3-*a*]azepin-3-yl)phenyl]thiourea ***I*** has two mobile hydrogen atoms in positions ***N*** and ***N'***, so the molecule can exist in different tautomeric forms ***I A*** and ***I B*** as it is shown in the Scheme 1.

During the interaction of *N*,*N'*-disubstituted thiourea ***I*** with 2-bromo-1-phenylethanone ***II*** [4, 8] by boiling in dioxane according to data of ^{1}H NMR spectroscopy, one product is formed. For this product two structures can be assumed: hydrobromide 3-ethyl-4-phenyl-*N*-[4-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazol[4,3-*a*]azepin-3-yl)phenyl]-1,3-thiazol-2(3*H*)-imine ***IV A*** and hydrobromide 3-[4-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazol[4,3-*a*]azepin-3-yl) phenyl]-4-phenyl-*N*-ethyl-1,3-thiazol-2(3*H*)-imine ***IV B***.

The formation of the 2-R-imino-1,3-thiazoline derivative ***IV A*** or ***IV B***, credibly occurs through the formation of acyclic intermediate ***III-III A*** or ***III-III B*** with 2-bromo-1-phenylethanone ***II*** followed by intramolecular cyclization, accompanied by loss of water molecule.

In order to establish the tautomer structure, the formation of which is most probable, we conducted quantum-chemical calculations using the software Gaussian W09.

Using the meta-hybrid method M06-2X applying a basis functions set 6-31 + G (d), the local minima and transition states (saddle points) of ***I***, ***IA*** and ***IB*** molecules in a medium of water, dioxane, ethanol, DMFA, tetrachlor-



Scheme 1

methane were investigated. For the spatial structures obtained, the thermodynamic parameters were calculated as well as the relative energies and activation energies of tautomeric transformations for the transition states ***I*** ↔ ***I A*** and ***I*** ↔ ***I B***. The calculations were carried out in the framework of the traditional B3LYP method.

Results and Discussion

The presence of only one set of Hydrogen protons signals in the ^{1}H NMR spectrum of the cyclized product synthesized testifies to the formation of one of the possible structures – ***IV A*** or ***IV B*** [5].

According to the results of quantum-chemical calculations obtained by two methods – B3LYP-

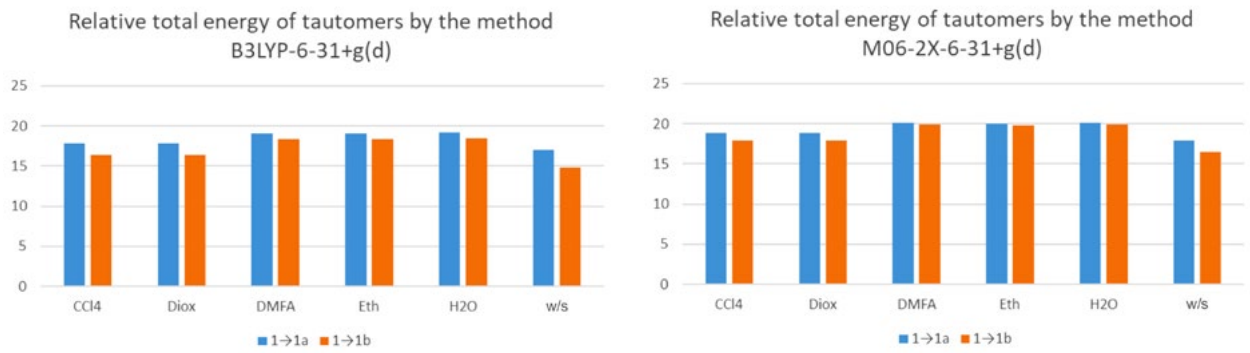


Fig. 1. Comparison of the relative energies of the corresponding tautomers in various solvents calculated by the methods B3LYP-6-31+g(d) and M06-2X-6-31+g(d)

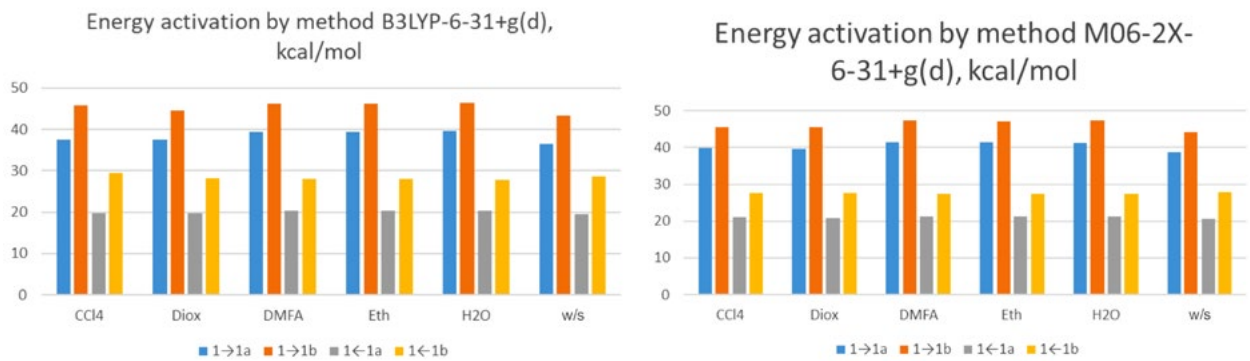


Fig. 2. Comparison of activation energies of corresponding tautomers in various solvents, calculated by methods B3LYP-6-31+g(d) and M06-2X-6-31+g(d)

6-31+g(d) and M06-2X-6-31+g(d) – in water and without solvent (w/s) [5], dioxane, ethanol, DMFA and tetrachlormethane (Fig. 1–2, tab. 1–4), ***I A*** is more stable isomer that is endothermically conducive to the ***IV A*** [formation]. The results of X-ray structure analysis finally confirmed the formation of the structure ***IV A*** [5].

The theoretical results of calculations of thermodynamic parameters of *N*-ethyl-*N'*-[4-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazol[4,3-*a*] azepin-3-yl)phenyl]thiourea ***I*** tautomers were obtained by the methods B3LYP and M06-2X after optimization of the molecules spatial structure in the medium of dioxane, ethanol, DMFA and tetrachlormethane. The calculated parameters – relative energy, activation energy, free energy of Gibbs and enthalpy – are given

Table 1. **Relative energy calculated by the methods B3LYP-6-31+g(d) and M06-2X-6-31+g(d), kcal/mol**

Method	B3LYP-6-31+g(d)		M06-2X-6-31+g(d)	
Transient states / Medium	***I→I A***	***I→I B***	***I→I A***	***I→I B***
CCl_4	17.857	16.363	18.829	17.988
Diox	17.849	16.349	18.821	17.975
DMFA	19.094	18.390	20.077	19.861
Eth	19.038	18.309	20.023	19.788
H_2O	19.154	18.476	20.136	19.940
w/s	17.017	14.806	17.959	16.505

Table 2. **The activation energy of tautomers *I A* and *I B*, calculated by the methods B3LYP-6-31+g(d) and M06-2X-6-31+g(d), kcal/mol**

Method	B3LYP-6-31+g(d)				M06-2X-6-31+g(d)			
Transient states / Medium	*I→I A*	*I→I B*	*I←I A*	*I←I B*	*I→I A*	*I→I B*	*I←I A*	*I←I B*
CCl_4	37.632	45.763	19.775	29.400	39.923	45.522	21.094	27.534
Diox	37.621	44.531	19.772	28.182	39.739	45.511	20.918	27.536
DMFA	39.350	46.284	20.256	27.894	41.456	47.288	21.379	27.426
Eth	39.435	46.210	20.396	27.901	41.388	47.213	21.365	27.425
H_2O	39.555	46.363	20.401	27.887	41.315	47.368	21.179	27.428
w/s	36.483	43.350	19.466	28.543	38.651	44.272	20.692	27.767

Table 3. **The value of enthalpy tautomers *I*, *I A* and *I B*, calculated by the methods B3LYP-6-31+g(d) and M06-2X-6-31+g(d), kcal/mol**

Method	B3LYP-6-31+g(d)		M06-2X-6-31+g(d)	
Transient states / Medium	I A	I B	I A	I B
CCl4	17.857	16.363	18.829	17.988
Diox	17.849	16.349	18.821	17.975
DMFA	19.094	18.390	20.077	19.861
Eth	19.038	18.309	20.023	19.788
H2O	19.154	18.476	20.136	19.940
w/s	17.017	14.806	17.959	16.505

Table 4. **The value of free energy of Gibbs tautomers *I*, *I A* and *I B*, calculated by the methods B3LYP-6-31+g(d) and M06-2X-6-31+g(d), kcal/mol**

Method	B3LYP-6-31+g(d)		M06-2X-6-31+g(d)	
Transient states / Medium	I A	I B	I A	I B
CCl4	15.194	13.823	16.340	15.539
Diox	15.187	13.809	16.336	15.527
DMFA	16.312	15.709	17.699	17.451
Eth	16.264	15.620	17.644	17.384
H2O	16.366	15.812	17.746	17.522
w/s	14.449	12.280	15.622	14.015

in tab. 1–4 and in fig. 1–2. All energy parameters are calculated in conditions *T*=298.15 K and *P*=1 ath.

As can be seen from the data in Tab. 1-4, in most cases for energy and energy barriers there is a reliable (1-2 kcal / mol) coincidence of the calculations results obtained by the methods M06-2X and B3LYP. The calculated data and the obtained data of the physical-chemical researches of the interaction product more accurately coincide with the application of the method M06-2X.

Thus, using the methods of B3LYP and M06-2X of the density functional theory, the main directions and transition states of the reaction that determine the formation of hydrobromide 3-ethyl-4-phenyl-N-[4-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazol[4,3-*a*]azepin-3-yl) phenyl]-1,3-thiazol-2(3*H*)-imine ***IV A*** were found regardless of the test solvents choice.

As can be seen from Table 1, a transition state ***I↔I A*** in dioxane has the lowest values of activation energy. The graphical representation of the 3D isomers of structure ***I*** and the activation energy of tautomeric transformations for the transition states ***IA↔I↔I B*** in dioxane for both methods is shown in Fig. 3

Despite the fact that the values of the thermodynamic potentials for transition states in dioxane and tetrachlormethane are the same, the activation energy and the relative energy

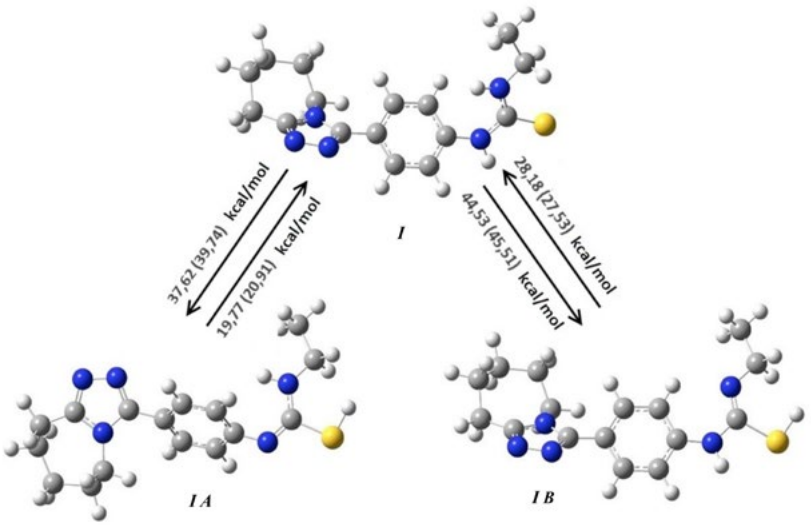


Fig. 3. Graphical view of the 3D isomers of structure ***I*** and activation energies of tautomeric transformations for the transition states ***IA*↔*I*↔*I B*** in dioxane by the methods B3LYP-6-31 + g (d) and M06-2X-6-31 + g (d) in brackets

of the transient state ***I*↔*I A*** in dioxane are the lowest. Compared with the values of these parameters of the transition states of compound ***I*** in dioxane, the corresponding parameters for transitional states ***I*↔*I A*** and ***I*↔*I B*** in the environment of other solvents (ethanol, DMFA and tetrachlormethane) have considerably higher values (Table 1–4), and hence, the synthesis in these solvents will be slower and will require additional conditions.

Taking into account these data, we can conclude that according to the two methods of quantum-chemical calculations, the reaction pathway by ***A***, which indicates the formation of hydrobromide 3-ethyl-4-phenyl-*N*-[4-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazol[4,3-*a*] azepin-3-yl)phenyl]-1,3-thiazol-2(3*H*)-imine ***IV A***, is the most probable, and the synthesis of the substance is the most energy-efficient in the environment of dioxane.

Conclusions

The obtained results of quantum-chemical calculations indicate that in all the solvents studied (dioxane, ethanol, DMFA, tetrachlormethane, water) the cyclization reaction theoretically should lead to the formation of hydrobromide 3-ethyl-4-phenyl-*N*-[4-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazol[4,3-*a*]azepin-3-yl)phenyl]-1,3-thiazol-2(3*H*)-imine. It was theoretically proved that the most appropriate solvent for the synthesis is dioxane. It is proposed to apply in the further research the method of quantum-chemical calculations M06-2X as more reliable.

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Квантово-хімічні розрахунки термодинамічних параметрів перехідних станів таутомерів вихідної *N,N'*-дизаміщеної тіосечовини у реакції циклізації при використанні різних розчинників

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Мета. Теоретичне обґрунтування напрямку проходження реакції циклізації в різних розчинниках за допомогою квантово-хімічних розрахунків термодинамічних параметрів двох таутомерів 1-етил-3-[4-(6,7,8,9-тетрагідро-5*H*-[1,2,4]тріазоло[4,3-*a*]азепін-3-іл)феніл]тіосечовини. **Методи.** Квантово-хімічні розрахунки відносних енергій, бар'єрів взаємоперетворення, структурних і термодинамічних параметрів таутомерів вихідної тіосечовини у середовищі діоксану, етанолу, ДМФА та тетрахлорметану були обчислені методами теорії функціонала густини з використанням програми GAUSSIAN 09W. Вплив розчинника враховували у рамках моделі континууму, що поляризується. **Результати.** Згідно одержаних результатів, в усіх досліджуваних розчинниках реакція циклізації має проходити в одному напрямку з утворенням гідроброміду 3-етил-4-феніл-N-[4-(6,7,8,9-тетрагідро-5*H*-[1,2,4]тріазоло[4,3-*a*]азепін-3-іл) феніл]-1,3-тіазол-2(3*H*)-іміну. Найменший бар'єр взаємоперетворення таутомерів вихідної тіосечовини повинен спостерігатися при використанні як розчинника діоксану, що свідчить про перевагу проведення синтезу саме у цьому розчиннику порівняно з етанолом, водою, тетрахлорметаном та ДМФА. **Висновки.** Теоретично обґрунтовано, що для проведення синтезу найбільш доцільним є використання як розчинника діоксану.

Квантово-химические расчеты термодинамических параметров переходных состояний таутомеров исходной *N,N'*-дизамещенной тиомочевины в реакции циклизации при использовании различных растворителей

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Цель. Теоретическое обоснование направления прохождения реакции циклизации в различных растворителях с помощью квантово-химических расчетов термодинамических параметров трех таутомеров N-этил-N'-[4-(6,7,8,9-тетрагидро-5Н-[1,2,4]триазоло[4,3-а]азепин-3-ил)фенил]тиомочевины. **Методы.** Кванто-вохимические расчеты относительных энергий, барьеров взаимопревращения, структурных и термодинамических параметров таутомеров исходной тиомочевины в среде диоксана, этанола, ДМФА и тетрахлорметана были вычислены методами теории функционала плотности с использованием программы GAUSSIAN 09W. Влияние растворителя учитывали в рамках модели поляризуемого континуума. **Результаты.** Согласно полученных результатов, во всех исследуемых растворителях реакция циклизации должна проходить в одном направлении с образованием гидробромида 3-этил-4-фенил-N-[4-(6,7,8,9-тетрагидро-5Н-[1,2,4]триазоло[4,3-а]азепин-3-ил)фенил]-1,3-тиазол-2(3Н)-имина. Наименьший барьер взаимопревращения таутомеров исходной тиомочевины должен наблюдаться при использовании в качестве растворителя диоксана, что свидетельствует о преимуществе проведения синтеза именно в этом растворителе по сравнению с этанолом, водой, тетрахлорметаном и ДМФА. **Выводы.** Теоретически обосновано, что наиболее подходящим растворителем для проведения циклизации является диоксан.

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