ОРГАНІЧНА ХІМІЯ / ORGANIC CHEMISTRY

UDC 547.233:544.362

Tetiana Yu. Sergeieva,[1,3] O. Yu. Voskoboynik,[2] Sergiy I. Okovytyy,[1,3,*]
S. I. Kovalenko,[2] Jerzy Leszczynski[3]

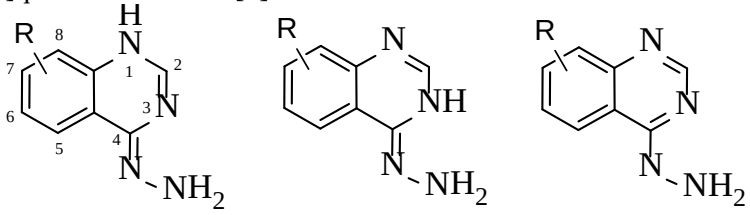
[1]*Oles Honchar Dnipropetrovsk National University, 72, Gagarina Ave., Dnipropetrovsk 49010, Ukraine*
[2]*Zaporozhia state medical university, Mayakovsky Ave., 26, Zaporozhia 69035, Ukraine*
[3]*Interdisciplinary center for Nanotoxicity, Jackson State University, 1400 Lynch str., Jackson, Mississippi 39217, USA*

TAUTOMERISM OF 4-HYDRAZINOQUINAZOLINES: VIBRATIONAL SPECTRA AND COMPUTATIONAL STUDY

The tautomerism of 4-hydrazinoquinazoline and its derivatives was investigated. Geometry and thermodynamic parameters were computed theoretically using Gaussian 03 software. All calculations were performed at the MP2 level of theory using the standard 6-31G(d) basis. Energetics and relative stabilities of tautomers were compared and analyzed in a gas phase. The effect of solvents (1,4-dioxane, acetic acid, ethanol and water) on the tautomeric equlibria was evaluated using PCM. It was determined that solvents induced slight changes in the relative stability. In all cases 4-hydrazinoquinazoline exists predominantly as the amino form. The variation of dipole moments was studied. The anharmonic vibrational wavenumbers for unsubstituted 4-hydrazinoquinazoline were calculated at MP2/6-31G(d) level and compared with experimental data. The modes of IR spectra were assigned. The calculated herein wavenumbers and intensities of amino form are in good agreement with those observed experimentally.

Keywords: tautomer; 4-hydrazinoquinazolines; ab initio; IR spectra; vibrational assignment.

Introduction. The most important route of organic chemistry is searching and synthesis of new compounds with promising properties for different areas. Various heterocyclic systems are suitable for this purpose due to structural diversity and possibility to functionalization. The presence of heteroatoms in aromatic rings induces fast migration of proton between them and, thus, existence of tautomers. Knowledge that can be obtained using experimental (NMR, vibrational spectroscopy) and theoretical approaches on predominant form and influence of substituents of different types on reactive centers are also important. This paper presents the results of quantum-chemical investigation of tautomeric properties in various substituted 4-hydrazinoquinazolines (1-5) which used as precursors for synthesis of biologically active 3-substituted 2*H*-1,2,4-triazino[2,3-c]quinazolin-2-ones [1].



a **b** **c**

R=H(**1**); 8-CH_3(**2**); 7-F(**3**); 6-Cl(**4**); 6-Br(**5**)

Scheme 1

* Correspoding author: Tel.: +380505919276; fax: +380563749841; e-mail address: sokovyty@icnanotox.org

Migration of a proton between the different nitrogen atoms in 4-hydrazinoquinazoline results in three tautomeric forms. Therefore, N-H vibrations in the IR spectra can not be *a priori* assigned to a certain tautomer. In this case it could be more informative to look at the vibrations associated with the deformation of pyrimidine ring, since the tautomeric forms are discriminated by the degree of conjugation between the pyrimidine and benzene fragments.

Computational details. The geometry optimization and harmonic frequency calculations of the three equilibrium structures for amine/imine tautomerization of 4-hydrazinoquinazolines (**1-5 (a-c**)) were performed employing 6-31G(d) [2] basis set at MP2 level [3] in a gas phase and taking into account solvent effects using PCM model. Since harmonic approximation overestimates vibrational frequencies we also calculated IR spectra of 4-hydrazinoquinazoline tautomers (**1 a-c**) in a gas phase using anharmonic approach. The assignment of calculated wavenumbers was aided by the animation option in GaussView 3.0 graphical interface for Gaussian programs, which gives a visual presentation of harmonic vibrational modes [4]. For visualization of anharmonic IR spectra calculated by Gaussian 09 Swizard program, revision 5.0 [5] was used.

Results and disscusion

Energies and relative stabilities. 4-Hydrazinoquinazoline is involved in amine-imine tautomeric equilibrium. Due to the proton transfer between the hydrazone nitrogen atom and the pyrimidine N_1, N_3 atoms one amino and two imino forms arise, which are labeled as a-c (Scheme 1). Earlier research on aminothiazoles, 3-amino-1,2,4-triazin-5-one and aminopyrimidine derivatives revealed that aromatic amino form prevalled in all aforementioned compounds [6-8]. This fact gives all reasons to hypothesize that amino form is predominant in our case as well.

The relative Gibbs free energy, populations of 4-hydrazinoquinazoline tautomers and their substituted derivatives are listed in Table 1. The numbering of atoms for 4-hydrazinoquinazoline is given in Scheme 1.

Calculations in the gas phase indicate that both imino forms (**a, b**) are less stable than the amino one (by 21.61 and 10.31 kJ/mol for 4-hydrazinoquinazoline (**1**) respectively). Since the properties of the medium may have a remarkable effect on the tautomeric equilibrium, we studied the population of 4-hydrazinoquinazoline tautomers in various solvents, including 1,4-dioxane, acetic acid, ethanol and water.

Analysis of tautomeric population shows, that polarity of the solvent does not change the order $P_c>P_b>P_a$ (Table 2). It should be mentioned that contribution of tautomer **a**, which is characterized by the highest dipole moment, increases simultaneously with the dielectric constant of the solvent.

The type and position of the substituent in the aromatic ring do not affect the trend mentioned above and still lead to the dominance of tautomer **c**.

Interestingly, calculations in the gas phase predict the increase abundance of imino form **b** in the series 8-CH_3<H<6-Br<6-Cl<7-F where substituent electron-withdrawing strength becomes more pronounced.

Vibrational assignments. The second step of the present investigation was to determine which of the three calculated IR spectra of the different tautomers matches the one obtained experimentally. Calculated at anharmonic level vibrational spectra of forms **1a-c** are shown in Figure 1B – D. Some vibration movements of 4-hydrazinoquinazoline form are presented in Figure 2.

Some overestimation of band frequencies is still observed after anharmonic corrections.

Table 1

Relative Gibbs free energies (ΔG_{rel}, kJ/mol) and tautomer populations (P,%) calculated at MP2/6-31G(d) level of theory at T = 298.15 K

	Gas phase		1,4-Dioxane		Acetic acid		Ethanol		Water	
Tautomer	ΔG_{rel}	P	ΔG_{rel}	P	ΔG_{rel}	P	ΔG_{rel}	P	ΔG_{rel}	P
	1									
a	21.61	0.02	16.53	0.13	12.70	0.60	11.10	1.13	10.96	1.19
b	10.31	1.57	7.81	4.16	12.03	0.79	9.96	1.78	10.16	1.64
c	0.00	98.42	0	95.71	0	98.61	0	97.10	0	97.20
	2									
a	27.87	0	22.91	0.01	17.40	0.09	15.77	0.18	15.37	0.21
b	11.88	0.84	9.21	2.42	12.53	0.65	12.38	0.69	12.31	0.71
c	0	99.16	0	97.57	0	99.26	0	99.14	0	99.09
	3									
a	22.10	0.01	15.88	0.16	12.03	0.77	11.38	1.01	11.01	1.16
b	8.34	3.39	6.81	6.09	9.13	2.47	10.97	1.19	8.99	2.61
c	0	96.59	0	93.75	0	96.76	0	97.79	0	96.24
	4									
a	20.61	0.02	14.44	0.26	10.37	1.47	8.38	3.27	8.24	3.37
b	8.56	3.11	4.63	13.46	7.92	3.93	9.70	1.93	7.68	4.23
c	0	96.86	0	86.28	0	94.61	0	94.80	0	92.39
	5									
a	21.54	0.02	16.07	0.14	11.75	0.85	9.51	2.07	8.98	2.55
b	9.20	2.43	4.54	13.87	8.19	3.56	8.10	3.64	8.10	3.62
c	0	97.56	0	85.99	0	95.58	0	94.29	0	93.83

Table 2

Dipole moments calculated at MP2/6-31G(d) level of theory

	DM, μ (gas phase)				
Tautomer	Gas phase	1,4-Dioxane	Acetic acid	Ethanol	Water
	1				
a	5.29	6.54	7.47	7.92	8.04
b	1.83	2.10	2.28	2.59	2.63
c	2.31	2.79	3.16	3.34	3.38
	2				
a	5.56	6.89	7.87	8.35	8.46
b	1.85	2.09	2.25	2.33	2.34
c	1.95	2.40	2.74	2.90	2.94
	3				
a	5.48	5.48	6.28	6.68	6.78
b	4.38	4.38	4.77	4.87	5.01
c	2.91	2.91	3.33	3.54	3.59
	4				
a	6.21	7.54	8.53	9.02	9.13
b	3.66	4.16	4.70	4.64	4.99
c	0.47	0.75	0.99	1.10	1.13
	5				
a	6.19	7.51	8.50	8.98	9.10
b	3.70	4.20	4.74	4.99	5.05
c	0.50	0.79	1.02	1.14	1.17

The region above 1500 cm^{-1} corresponds to the stretching vibrations of CH, CH_2, CH_3, N-H, C-N, C=O groups; the bands below 1500 cm^{-1} are related to twisting, rocking and deformation vibrational modes of different groups as well as skeletal vibrations.

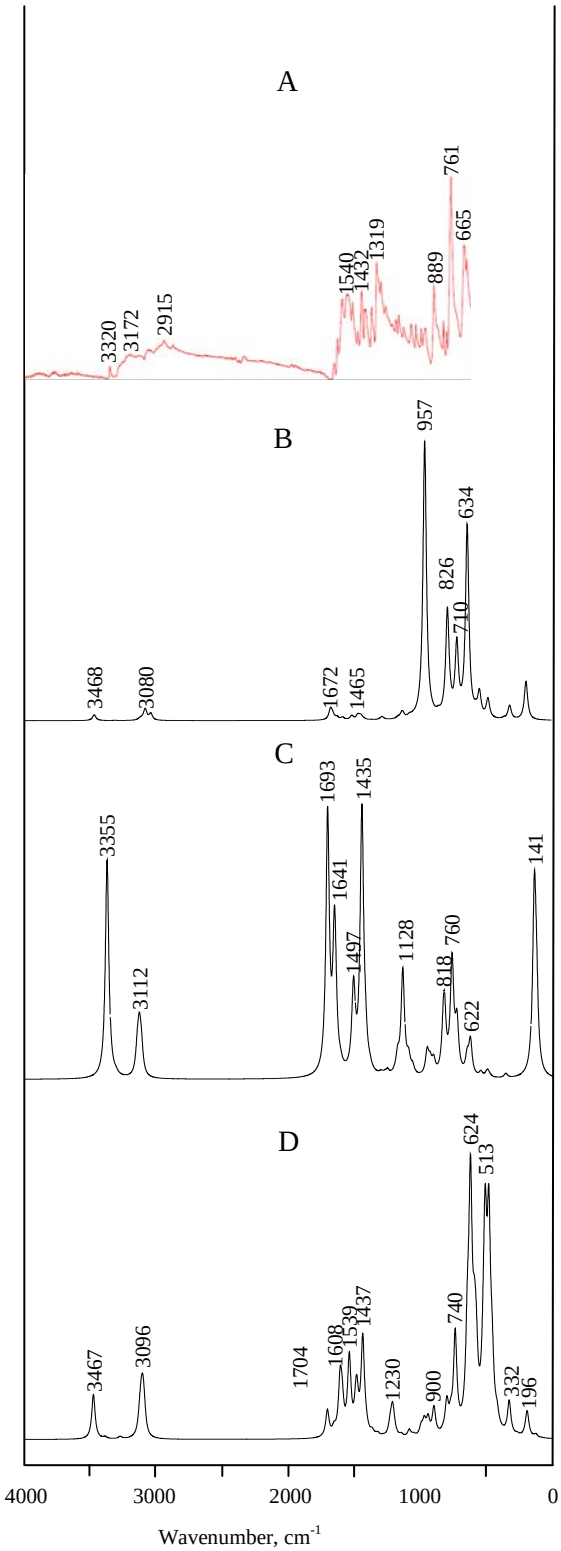


Fig. 1. The experimental (a) and predicted (b-d) at MP2/6-31G(d) level of theory IR spectra of 4-hydrazinoquinazoline

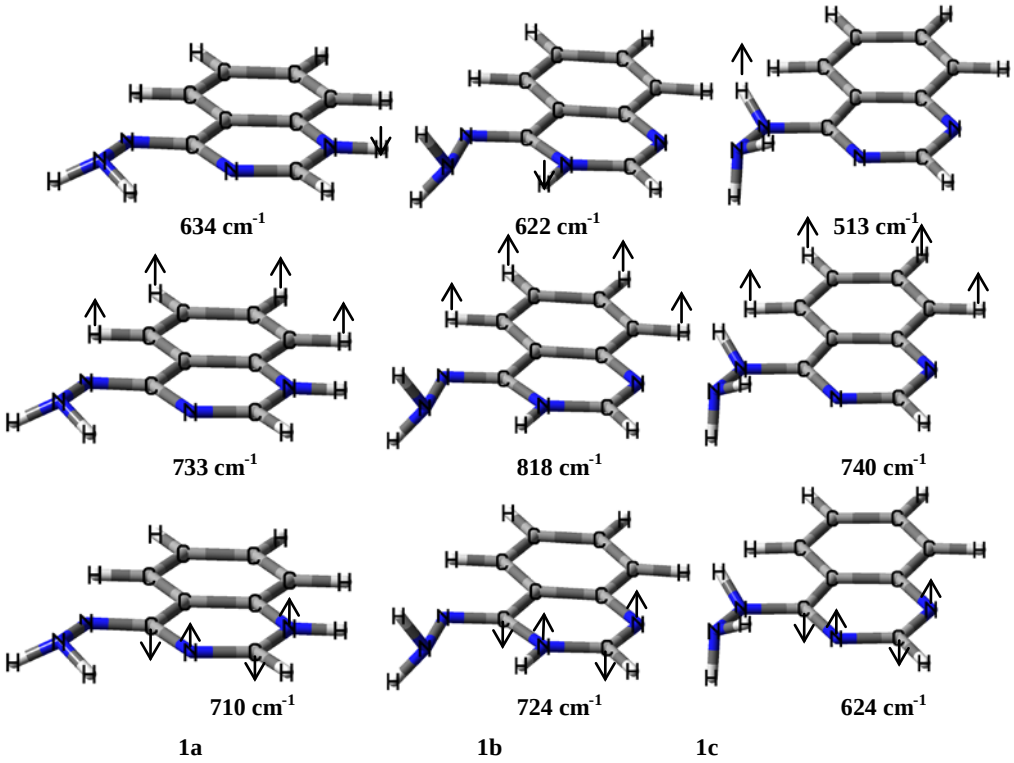


Fig. 2. Some vibration movements of 4-hydrazinoquinazoline form (1a-c)

N-H vibrations:

N-H stretching frequencies in pyrimidine ring (imino forms (**1a/b**)) and hydrazine fragment (amino form (**1c**)) were detected theoretically at 3468/3355/3467 cm^{-1} for tautomers **1a/1b/1c**. The calculated wavenumbers do not contradict experimentally obtained value 3320 cm^{-1}. These modes are expected as reported N-H vibrations at 3483/3482 cm^{-1} in 2-quinazoline/4-quinazoline systems [9] and 3477 cm^{-1} in the case of tegafur (six membered ring with two Nitrogen atoms) [10].

The bands located at 634/622/513 cm^{-1} for tautomers **1a-c** arise from N-H wagging movement. The values of modes match experimentally predicted frequency (661 cm^{-1}) and data collected in [9]. The intensity of this vibration for tautomers **1a**, **1b** is much lower compare to form **1c**.

NH_2 vibrations:

The frequencies 1693 and 1704 cm^{-1} for tautomers **1b** and **1c** respectively found from the theoretical assignment belong to NH_2 scissoring vibration, which is supported by obtained value 1718 cm^{-1} for creatininium benzoate [11] and 1647 cm^{-1} in the case of 3-amino-2-phenyl quinazolin-4(3H)-one [12]. In contrast to **1b** and **1c**, NH_2 scissoring mode for tautomer **1a** (1655 cm^{-1}) is negligibly low intense.

Bands at 1162, 1128 and 1230 cm^{-1} for **1a**, **1b, 1c** tautomers were attributed to the NH_2 wagging vibration.

C-H vibrations:

The existence of one or more aromatic rings can be determined from C-H vibrations, which are typically exhibited around 3000 cm^{-1} [13] as multiple weak bands compared to aliphatic C-H stretching. In our case the computed wavenumbers of modes corresponding to C-H vibrations are 3080, 3112, 3096 cm^{-1} for **1a**, **1b**, **1c** respectively.

Usually, systems similar to those presented in this paper have a group of bands in the region 1000 cm^{-1}, which correspond to in-plane and out-of-plane C-H deformations of the benzene ring [14]. As follows from the theoretical predictions, in our case C-H out-of-plane vibrations occur at 818 and 740 cm^{-1} for tautomers b,c respectively. For tautomer a this mode assigned at 732 cm^{-1}. It is worth mentioning that again the weakest band observes in the spectrum of the form 1a.

C-C, C-N, C=N vibrations:

The in-plane deformation of benzene and pyrimidine rings resulted from stretching of C-N, C=N, C-C bonds was identified as a series of bands in the range 1400-1600 cm^{-1}.

The strongest band (761 cm^{-1}) in experimental IR spectrum in our opinion arises from pyrimidine ring torsion vibration (out-of-plane movement). The latter is considered similar to the results determined from *ab initio* study at 710/724/624 cm^{-1} (forms **1a-c**). As could be seen form Fig.1, **1c** is the only tautomer characterized by highly intensive band.

The comparison of theoretically calculated IR spectra for each tautomer with experiment ((Fig.1, (1)) shows that the spectrum of form **1c** (Fig.1, (4)) is the most reproducible.

The modes located at 600-900 cm^{-1} due to out-of-plane C-H, N-H vibrations of pyrimidine ring, appear in the experimental spectrum as strongest, which are supported also by analysis of calculated spectra. Again, the relation between theoretically predicted localization and intensity of bands in the tautomer **1c** is in a good agreement with experimental spectrum.

A series of signals calculated in the region of 1400-1600 cm^{-1} is attributed to stretching deformations of aromatic quinazoline system. The IR spectra of tautomers **1a**, **1b** are characterized by weak intensity of the same vibration modes which is resulted from protonation of one of pyrimidine Nitrogen atoms followed by partial violation of the conjugation between benzene and pyrimidine rings as a consequence.

Conclusions. The molecular geometry, energetical properties of 4-hydrazinoquinazoline and its derivatives were calculated using MP2/6-31G(d) level of theory. The IR spectra of three possible unsubstituted tautomers of 4-hydrazinoquinazoline were simulated using the same approach.

The computational studies based on thermodynamical properties favor the amino tautomer over its imino forms in four solvents with different polarity. Moreover, the theoretical IR spectrum of form **1c** is in a good agreement with experimental. The present quantum chemical investigation may further play an important role in understanding of dynamics of these molecules.

Acknowledgments. This work has been supported by Interdisciplinary Center for Nanotoxicity, Grant # HRD-0833178. Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by National Science Foundation grant number OCI-1053575. S. O. and T. S. also acknowledge the Ministry of Education and Science, Youth and Sport of Ukraine for financing of Internship in Jackson State University (Mississippi, USA).

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Татьяна Ю. Сергеева,[1,3] А. Ю. Воскобойник,[2] Сергей И. Оковитый,[1,3]
С. И. Коваленко,[2] Ежи Лещинский[3]

[1]Днепропет ровский национальный университ ет имени Олеся Гончара, пр. Гагарина, 72, Днепропет ровск 49010, Украина

[2]Запорож ский государст венный медицинский университ ет , пр. Маяковского, 26, Запорож ье 69035, Украина

[3]Меж дисциплинарный цент р исследования нанот оксичност и, Дж ексонский государст венный университ ет , Дж ексон, Миссисипи 39217, США

ТАУТОМЕРИЯ 4-ГИДРАЗИНОХИНАЗОЛИНОВ, КОЛЕБАТЕЛЬНЫЕ СПЕКТРЫ И КОМПЬЮТЕРНОЕ МОДЕЛИРОВАНИЕ

Исследована таутомерия 4-гидразинохиназолина и его производных. Проведен теоретический расчет геометрии и термодинамических параметров с использованием

программы Gaussian 03, метода MP2 и стандартного базисного набора 6-31G(d). Проанализирована и сопоставлена энергия и относительная устойчивость таутомеров в газовой фазе. Оценено влияние растворителей (1,4-диоксан, уксусная кислота, этанол и вода) на таутомерное равновесие с использованием PCM. Установлено, что растворители вносят незначительный эффект в изменение относительной стабильности.

Во всех случаях 4-гидразинохиназолин существует преимущественно в виде амино формы. Изучено изменение дипольных моментов. Рассчитаны ангармонические колебания для незамещенного 4-гидразинохиназолина. Полученные данные сопоставлены с экспериментом. Проведено соотнесение полос для ИК-спектров. Рассчитанные длины волн и их интенсивности для амино формы хорошо согласуются с экспериментальными.

Ключевые слова: таутомер; 4-гидразинохиназолин; ab initio; ИК-спектры; ангармоническое приближение.

Тетяна Ю. Сергеєва,[1,3] О. Ю. Воскобойник,[2] Сергій І. Оковитий,[1,3]
С. І. Коваленко,[2] Єжи Лещинський[3]

[1]Дніпропетровський національний університет імені Олеся Гончара, пр. Гагаріна, 72, Дніпропетровськ 49010, Україна
[2]Запорізький державний медичний університет, пр. Маяковського, 26, Запоріжжя 69035, Україна
[3]Міждисциплінарний центр дослідження нанотоксичності, Джексонський державний університет, Джексон, Міссісіпі 39217, США

ТАУТОМЕРІЯ 4-ГІДРАЗИНОХІНАЗОЛІНІВ, КОЛИВАЛЬНІ СПЕКТРИ ТА КОМП'ЮТЕРНЕ МОДЕЛЮВАННЯ

Досліджено таутомерію 4- гідразинохіназоліну та його похідних. Проведено теоретичний розрахунок геометрії і термодинамічних параметрів з використанням програми Gaussian 03, методу MP2 і стандартного базисного набору 6-31G (d). Проаналізовано і співставлено енергію та відносну стійкість таутомерів у газовій фазі. Оцінено вплив розчинників (1,4-діоксан, оцтова кислота, етанол і вода) на таутомерну рівновагу з використанням PCM. Встановлено , що розчинники вносять незначний ефект у зміну відносної стабільності.

У всіх випадках 4-гідразинохіназолін існує переважно у вигляді аміно форми. Вивчено зміну дипольних моментів. Розраховані ангармонічні коливання для незаміщеного 4-гідразинохіназоліну. Отримані дані співставлені з експериментом. Проведено віднесення смуг для ІЧ-спектрів. Розраховані довжини хвиль та їх інтенсивності для аміно форми добре узгоджуються з експериментом.

Ключові слова: таутомер; 4-гідразинохіназолін; ab initio; ІЧ-спектри; ангармонічне наближення.

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Надійшла до редколегії 03.04.13