ОРГАНІЧНА ХІМІЯ / ORGANIC CHEMISTRY

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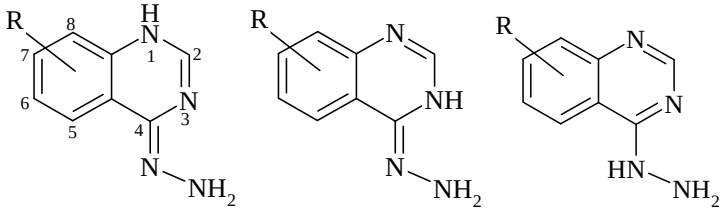
TAUTOMERISM OF 4-HYDRAZINOQUINAZOLINES: VIBRATIONAL SPECTRA AND COMPUTATIONAL STUDY

The tautomerizm of 4-hydrazinoquinazoline molecule and its derivatives was investigated. Geometry and thermodynamic parameters were computed theoretically using Gaussian 03 software. All calculations were performed at the ab-initio (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) using PCM on the tautomeric equlibria was evaluated. 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 using the same approach as geometry optimization and compared with experimental data. The assignments of IR spectra modes were done. 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 rout of organic chemistry is searching and synthesis of new compounds with promising properties for wide range of branches. Various heterocyclic systems are suitable for this purpose due to structural diversity and ability to functionalization. Presence of heteroatoms in aromatic rings causes fast migration of proton between them and, thus, existence of tautomers. Knowledge that can be obtained using experimental (NMR, vibrational spectroscopy) and theoretical approaches about predominant form and influence of substituents of different types on reactive centers is 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 previously described 3-substituted 2H-1,2,4-triazino[2,3-c]quinazolin-2-ones [1]. Additionally, upon replacement of hydrazino group with triazine ring, compounds show high biological activity.



a **b** **c**

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

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

Computational details. The geometry optimization and harmonic frequency calculations of three equilibrium structures for 4-hydrazinoquinazolines (**1-5 (a-c**)) amino/imino tautomerization were performed employing 6-31G(d) [2] basis set with the MP2 method [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 (1) tautomers using anharmonic approach in a gas phase. 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 shape [4]. For visualization of anharmonic IR spectra based on frequencies and intensities calculated by Gaussian 09 Swizard program, revision 5.0 [5] was used.

Results and disscusion

Energies and relative stabilities. 4-Hydrazinoquinazoline is involved in amino-imino tautomeric equilibrium. Due to proton transfer between hydrazone Nitrogen atom and pyrimidine N_1, N_3 atoms one amino and two imino forms arise which are distinguished as **a-c**. Earlier research involving aminothiazoles, 3-amino-1,2,4-triazin-5-one and aminopyrimidine derivatives reveals that aromatic amino form is prevalence for all aforementioned compounds [6-8]. This fact gives all reasons to presume amino form of being predominant in our case as well.

The Relative Gibbs Free Energy, Population of 4-hydrazinoquinazoline tautomers and its substituted derivatives are listed in Table 1. Numbering of atoms for 4-hydrazinoquinazoline is given above.

Calculations in a gas phase indicate that both imino forms (**a, b**) are less stable than amino (on 21.61 and 10.31 kJ/mol for 4-hydrazinoquinazoline (**1**) respectively). Since 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 show, that polarity of a solvent does not change the order Pc>Pb>Pa. It should be mentioned that contribution of tautomer **a**, which is characterized by the highest dipole moment (Table 2), increases simultaneously with dielectric constant of a solvent.

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

Interestingly, calculations in a gas phase predict increased abundance of imino form **b** as substituent varies in a series 8-CH_3<H<6-Br<6-Cl<7-F where substituent electron-withdrawing strength is becoming more pronounced.

Vibrational assignments. The second step of the present investigation was to determine which of three possible IR spectra that correspond to different tautomers calculated theoretically relates to the one obtained experimentally. The vibration spectra of forms **1a-c** based on *ab initio* quantum-chemical calculations at anharmonic level (**2-4**) are shown in **Figure 1**. Some vibration movements of 4-hydrazinoquinazoline form are presented in **Figure 2**.

In spite of using anharmonic corrections explicitly, overestimation of band frequencies is still observed.

Table 1

Values of Relative Gibbs Free Energy (ΔG_{rel}, kJ/mol) and Tautomers Population (P,%) calculated at MP2/6-31G(d) level of theory at T = 298.15 K

	Gas		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

Values of Relative Gibbs Free Energy (ΔG_{rel}, kJ/mol) and Tautomers Population (P,%) calculated at MP2/6-31G(d) level of theory at T = 298.15 K

	DM, μ(gas)				
Tautomer	Gas	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 main characteristic bands belong to aromatic compounds depicted on IR spectra locate between 4000-500 cm^{-1}. The region above 1500 cm^{-1} corresponds to stretching vibrations of CH, CH_2, CH_3, N-H, C-N, C=O groups other bands below 1500 cm^{-1} are related to twisting, rocking and deformation vibrational modes of different groups including skeletal vibrations.

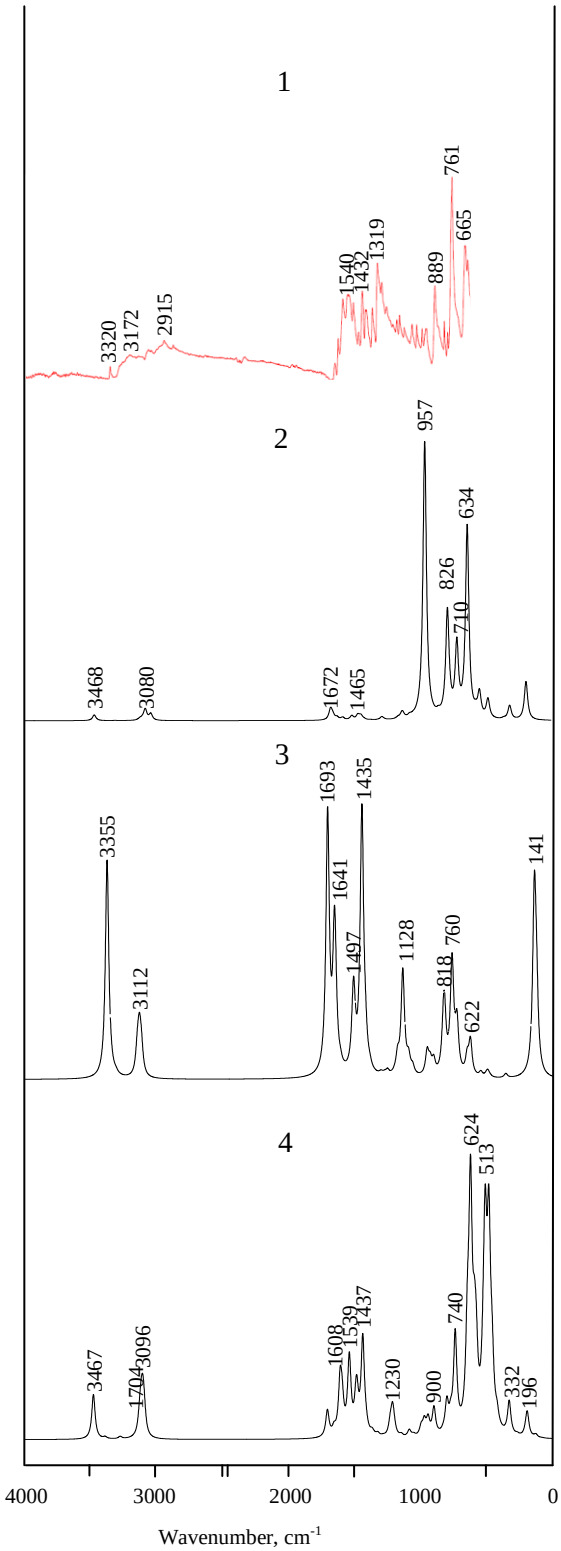

Fig. 1. The experimental (1) and predicted (2-4) at MP2/6-31G(d) level of theory IR spectra of 4-hydrazinoquinazoline

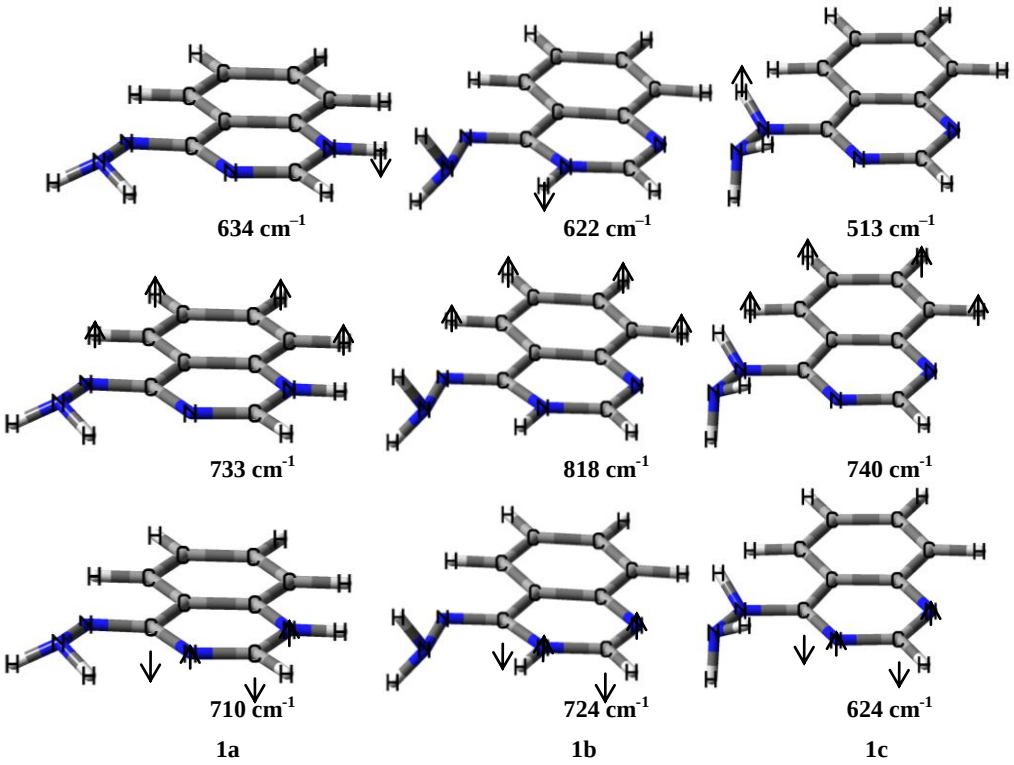

Fig. 2. Some vibration movements of 4-hydrazinoquinazoline form (1a-c)

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.

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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, *ab-initio* (MP2) метода и стандартного 6-31G(d) базисного набора. 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.

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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, *ab-initio* (MP2) методу і стандартного 6-31G (d) базисного набору. 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 РСМ. 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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REACTIONS OF 2,3-DIHYDRO-1,5-BENZODIAZEPINONES-2 DERIVATIVES QUATERNIZATION

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РЕАКЦІЯ КВАТЕРНІЗАЦІЇ ПОХІДНИХ 2,3-ДИГІДРО-1,5-БЕНЗОДІАЗЕПІНОНІВ-2

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РЕАКЦИЯ КВАТЕРНИЗАЦИИ ПРОИЗВОДНЫХ 2,3-ДИГИДРО-1,5-БЕНЗОДИАЗЕПИНОНОВ-2

Показано, что алкилирование 1-алкил-4-метил-2,3-дигидро-1,5-бензодиазепинонов-2 алкилгалогенидами приводит к образованию четвертичных солей. Установлено, что в отличие от алкилирования незамещенных в положении 1 1,5-бензодиазепинонов-2, для протекания реакции кватернизации необходим большой избыток алкилгалогенида и длительное (18-46 ч) кипячение в бензоле. Четвертичные соли выделены с выходом 45-77% в виде кристаллических осадков или масел. На выход четвертичных солей существенное влияние оказывает природа алкилгалогенида и заместителя в положении 4. Не удалось получить четвертичные соли, используя в качестве субстратов 1-алкил-4-фенил-2.3-дигидро-1,5-бензодиазепиноны-2, даже при кипячении с иодистым метилом в бензоле в течение 80 ч. Структура синтезированных соединений подтверждена с помощью данных ИК-спектров и спектров ЯМР ^{1}H.

Ключевые слова: 1,5-дигидробензодиазепиноны-2, алкилирование, кватернизация.

Введение. Среди используемых в настоящее время в медицине психотропных средств особое место занимают транквилизаторы – производные 1,4-бензодиазепинов. Спектр их фармакологического действия характеризуется

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