Imine-enamine tautomerism in bicyclic systems in gas phase and solution: a computational study

H. Moghanian[1], A. Mohamadi*[2]

[1] *Young Researchers and Elite Club, Dezful Branch, Islamic Azad University, Dezful, Iran*
[2]*Department of Chemistry, Farahan Branch, Islamic Azad University, Farahan, Iran*

DFT calculations have been carried out on the bicyclic imines to investigate the influence of ring size on the imine-enamine tautomerisms. Molecular geometries and energetic of imines and enamines in gaseous phase have been obtained using B_3LYP levels of theory, implementing 6-311^{++}G(d,p) basis set. Then, important molecular parameters, IR frequencies, NBO and energetic results in the gas phase were extracted. The energetic results show that relative stability of enamine tautomer (versus imine tautomer) increases with the increase of ring size and calculated frequencies show that by decreasing *N*-containing ring size from 6-membered to 4-membered ring, the frequency of C=N in imine tautomer decreases. In addition variation of NBO charges on atoms in the gas phase are studied.

Key words: DFT study, Tautomerism, Bicyclic, Imine, Enamine, NBO analysis.

INTRODUCTION

Tautomerism is one of the fundamental processes in (bio) organic chemistry that underlies most of the important condensation reactions. It has been extensively studied experimentally and theoretically. For example, tautomerisms in keto-enol [1-5], imine-enamine [6-8], purines [9], pirimidines [10] and many other systems [11-13] have been studied during past two decades. Thereupon, compounds containing different tautomers can be the subject of interest by theoretical chemists.

Imines formations are a particularly important chemical reaction in some biological processes [14, 15] for example, the covalent binding of carbonyl-containing compounds to an enzyme usually involves the formation of an imine. The imine moiety is formed by condensation of carbonyl groups of ketone or aldehyde with a primary or secondary amine. Equilibrium between imine and enamine may be established when at least one hydrogen atom on the imine nitrogen. The relative equilibrium of these species depends on the symmetry of the parent ketone and the substituents on the amine [16].

In this study we focused our research on imine-enamine tautomerism in bicyclic systems. These *N*-containing heterocycles have three tautomeric forms, one is imine form (I) and others are enamine forms (E_a and E_b). The physicochemical characteristics of some of the heterocycles were experimentally determined. For example, spectrophotometric data for hexahydroindole that previously expressed as the enamine form (E_b) showed no band in the NH-stretching region in accordance with the imine structure [17]. In the absence of experimental data, it is of special interst to characterize theoretically the imine-enamine tautomeric equilibria to obtain information about the thermodynamic and kinetic aspects.

In this research, molecular parameters, relative energies, NBO analysis and vibrational frequencies of imines and enamines in deferent ring have been calculated using B_3LYP/6-311^{++}G** level of theory. Details of computations and the results obtained in this work are presented below.

COMPUTATIONAL METHODS

The ground-state properties of the all tautomers have been calculated by using B_3LYP method at 6-311^{++}G(d,p) basis set level. All computations have been performed on a personal computer using the Gaussian 03 program package [18] and Gauss view molecular visualization program [19]. The B_3LYP method has been validated to give results similar to that of the more computationally expensive MP_2 theory for molecular geometry and frequency calculations [20, 21]. Moreover, several papers have been published on study of tautomerism in similar systems by B_3LYP method [22-28].

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* To whom all correspondence should be sent:
E-mail: azin.mohamadi@gmail.com
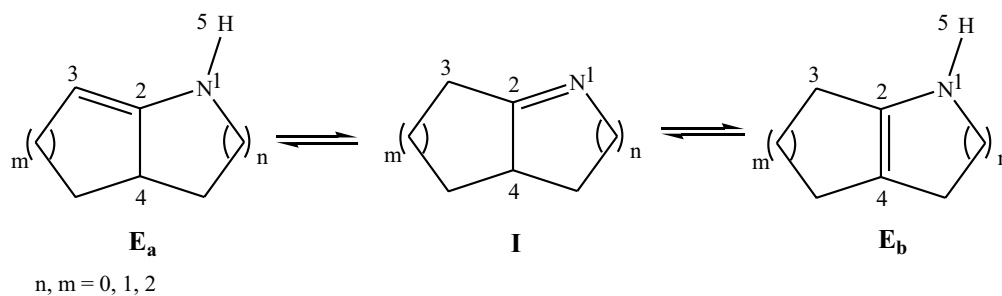
Fig. 1. General structures for possible tautomers

RESULTS AND DISCUSSION

Optimized parameters

The general structures and numbering of possible tautomers are presented in Figure 1. The selected molecules can be presented by three tautomers, imine (I), enamine (E_a) and enamine (E_b).

Because of cyclic structure of these molecules, geometric isomers (cis or trans for double bond) have not been considered in this study (trans endocyclic double bond cannot exist in 4-6-membered rings). Moreover, the most stable conformer was found and used in the calculations. In other word, only the most stable conformer of each structure has been considered in this study. The tautomerism in the selected structures is similar to 1,3-sigmatropic rearrangement. This subject has been attracted considerable attention of scientists especially in cyclic system [30-32]. The optimized structures of tautomers are presented in Figure 2.

Important aspects of molecular structure can be observed in Table 1.The N_1-C_2 bond length, reported in the first column of table, lies in the range of 1.262-1.293 Å in I tautomers, 1.381-1.416 Å in E_a tautomers and 1.386-1.439 Å in E_b tautomers. In I the tautomers, the N_1-C_2 bond length decreases with the increase of *N*-containing ring size, because of decreasing in ring strain. The C_2-C_3 bond length lies in the range of 1.486-1.523 Å in I tautomers, 1.331-1.351 Å in E_a tautomers and
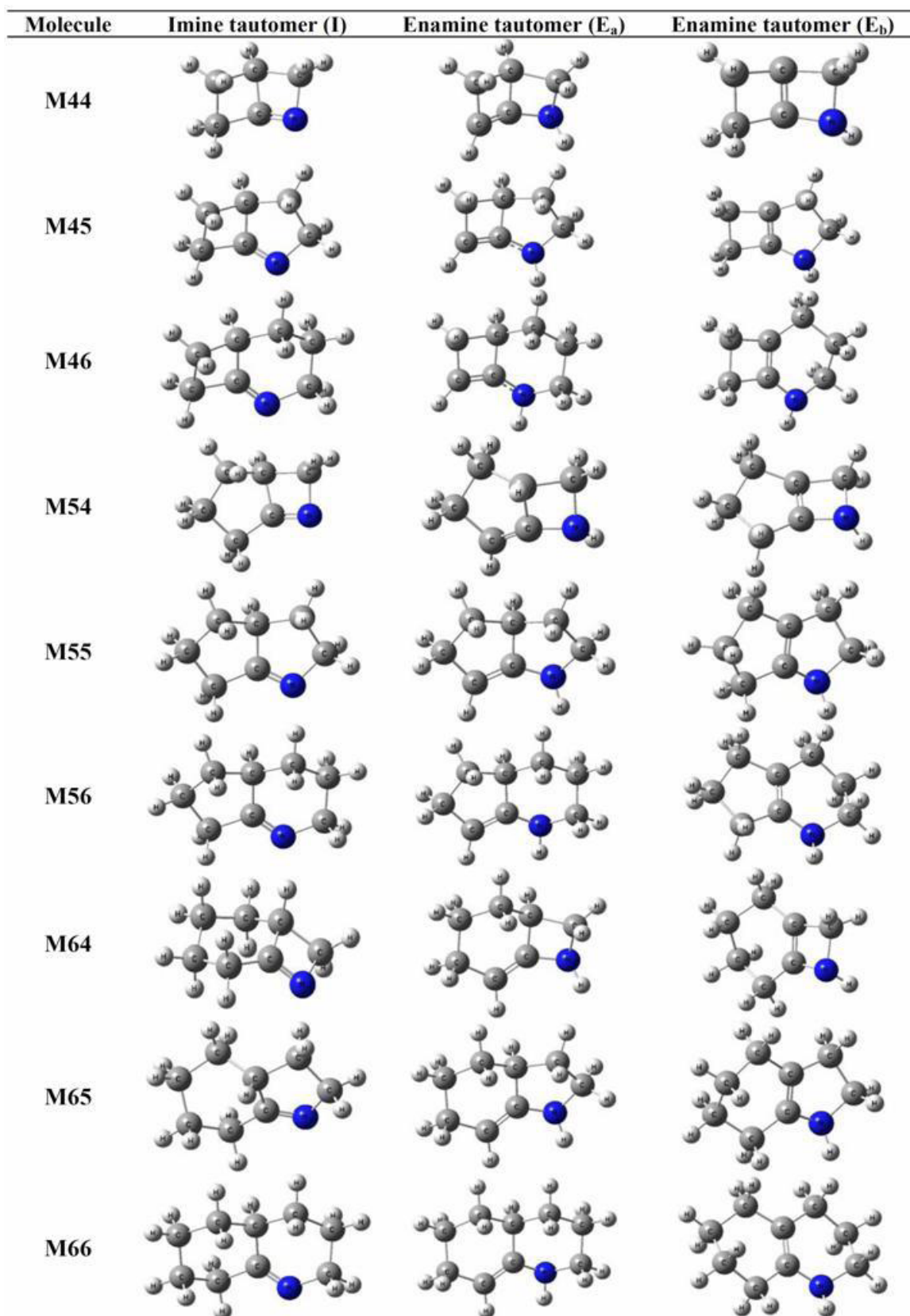
1.487-1.531 Å in E_b tautomers. The C_2-C_4 bond length lies in the range of 1.496-1. 1.530 Å in I tautomers, 1.484-1.520 Å in E_a tautomers and 1.330-1.348 Å in E_b tautomers. Also, The N_1-H_5 bond length lies in the range of 1.008-1.017 Å in E_a tautomers and 1.011-1.019 Å in E_b tautomers.

According to Table 2, N_1-C_2-C_3 angles are in the range of 118.4-137.8 in I tautomers, 122.7-147.8 in E_a tautomers and 114.1-145.7 in E_b tautomers. The N_1-C_2-C_4 angles are in the range of 100.3-130.6 in I tautomers, 92.7-122.5 in E_a tautomers and 97.2-127.3 in E_b tautomers. In all tautomers, the N_1-C_2-C_4 angles increases with the increase of *N*-containing ring size, because of decreasing in ring strain.

Moreover, the C_2-N_1-H_5 angles, reported in the last column of Table 2, lies in the range of 111.9-119.3 in E_a and E_b tautomers that their amounts are about hybridational angles of central nitrogen.

Energies

Gibbs free energies and other important thermodynamic and kinetic parameters of all structures at 298.15 K and one atmosphere were illustrated in Table 2. The Gibbs free energy difference (ΔG) between I and E_a tautomers at B₃LYP/6-311^{++}G(d,p) level of theory lies between -2.43 and -11.36 kcal/mol and ΔG between I and E_b tautomers lies between -1.23 and -18.82 kcal/mol. These data show that by increasing the *N*-containing ring size, the relative stability of E_b enamine versus imine I tautomer increase. When the ring size decreases, the ring strain increase and all double bond strengths affect more than single bonds. It is clear that the C=C double bond affect more than C=N double bond by ring strain and its energy decreases more than C=N energy. Therefore, the relative stability of imine tautomer

Molecule	Imine tautomer (I)	Enamine tautomer (E_a)	Enamine tautomer (E_b)
M44			
M45			
M46			
M54			
M55			
M56			
M64			
M65			
M66			

Fig. 2. Optimized structures of the most stable conformer of tautomers.

Table1. Important molecular parameters of optimized structures at $B_3LYP/6-311^{++}G(d,p)$ level of theory.

Molecule	Distance (Å)				Angle (deg)		
	N_1-C_2	N_1-H_5	C_2-C_3	C_2-C_4	$N_1-C_2-C_3$	$N_1-C_2-C_4$	$C_2-N_1-H_5$
M44I	1.293	-	1.504	1.496	134.3	101.9	-
M44E$_a$	1.416	1.017	1.351	1.484	146.1	97.6	116.8
M44E$_b$	1.435	1.017	1.531	1.336	144.4	98.7	118.8
M45I	1.266	-	1.511	1.506	137.8	118.9	-
M45E$_a$	1.381	1.010	1.350	1.492	147.8	112.5	117.4
M45E$_b$	1.398	1.013	1.518	1.330	145.7	115.5	117.3
M46I	1.262	-	1.516	1.522	132.8	130.6	-
M46E$_a$	1.382	1.013	1.348	1.505	141.9	122.5	114.3
M46E$_b$	1.386	1.012	1.511	1.341	137.0	127.3	115.8
M54I	1.288	-	1.498	1.496	137.0	101.4	-
M54E$_a$	1.409	1.014	1.335	1.498	146.7	94.2	119.2
M54E$_b$	1.439	1.018	1.496	1.331	143.1	97.9	116.5
M55I	1.269	-	1.508	1.518	131.1	117.2	-
M55E$_a$	1.383	1.008	1.340	1.509	137.9	108.9	118.9
M55E$_b$	1.403	1.013	1.498	1.337	131.3	113.9	115.9
M56I	1.267	-	1.523	1.528	123.3	127.6	-
M56E$_a$	1.392	1.012	1.343	1.518	130.1	117.8	113.5
M56E$_b$	1.395	1.011	1.506	1.344	122.5	124.6	114.5
M64I	1.289	-	1.486	1.503	133.4	100.3	-
M64E$_a$	1.415	1.014	1.331	1.509	138.2	92.7	119.3
M64E$_b$	1.439	1.019	1.487	1.339	134.6	97.2	115.7
M65I	1.273	-	1.506	1.523	125.5	116.1	-
M65E$_a$	1.396	1.008	1.340	1.515	128.8	107.0	118.1
M65E$_b$	1.414	1.013	1.498	1.341	121.8	112.7	114.8
M66I	1.274	-	1.515	1.530	118.4	126.5	-
M66E$_a$	1.408	1.013	1.344	1.520	122.7	114.4	111.9
M66E$_b$	1.407	1.011	1.512	1.348	114.1	122.7	113.0

Table 2. Relative Energies (ΔE), Relative Zero-Point Energies (ΔE_0), Relative Gibbs Free Energies (ΔG), and equilibrium constant (K_{eq}) for all tautomers.[a,b]

Molecule	E$_a$				E$_b$			
	$\Delta E_{(I-E)}$	$\Delta E_{0(I-E)}$	$\Delta G_{(I-E)}$	$K_{eq(I-E)}$	$\Delta E_{(I-E)}$	$\Delta E_{0(I-E)}$	$\Delta G_{(I-E)}$	$K_{eq(I-E)}$
M44	-11.37	-11.36	-11.35	2.09E+8	-19.24	-19.05	-18.82	6.26E+13
M45	-11.42	-11.36	-11.36	2.13E+8	-13.33	-13.14	-12.92	2.96E+9
M46	-8.45	-8.46	-8.53	1.79E+6	-6.00	-5.85	-5.70	1.51E+4
M54	-3.72	-3.80	-3.98	8.27E+2	-9.94	-9.82	-9.70	1.29E+7
M55	-6.15	-6.06	-6.09	2.91E+4	-7.03	-6.90	-6.84	1.03E+5
M56	-3.31	-3.36	-3.53	3.87E+2	-1.57	-1.40	-1.23	7.97E+0
M64	-4.29	-4.29	-4.30	1.42E+3	-8.50	-8.38	-8.20	1.03E+6
M65	-2.10	-2.11	-2.43	6.04E+1	-1.21	-1.25	-1.57	1.42E+1
M66	-3.78	-3.77	-3.84	6.53E+2	-1.79	-1.40	-1.41	1.08E+1

[a] $\Delta E_{(I-E)} = E_I - E_E$, $\Delta E_{0(I-E)} = E_{0I} - E_{0E}$, $\Delta G_{(I-E)} = G_I - G_E$, $K_{eq(I-E)} = [I]/[E]$.
[b] All energetic data have been reported in kcal/mol.

Table 3. Most important calculated NBO charge and frequencies of tautomers.

Molecule	NBO					Frequency (cm^{-1})		
	N_1	C_2	C_3	C_4	H_5	C=N	C=C	N-H
M44I	-0.486	0.288	-0.412	-0.301	-	1623	-	-
M44E$_a$	-0.652	0.215	-0.307	-0.260	0.354	-	1630	3503
M44E$_b$	-0.654	0.159	-0.400	-0.118	0.359	-	1644	3484
M45I	-0.462	0.295	-0.417	-0.285	-	1739	-	-
M45E$_a$	-0.646	0.198	-0.300	-0.240	0.373	-	1690	3587
M45E$_b$	-0.648	0.157	-0.379	-0.114	0.366	-	1727	3539
M46I	-0.464	0.297	-0.418	-0.277	-	1775	-	-
M46E$_a$	-0.645	0.186	-0.282	-0.232	0.364	-	1697	3548
M46E$_b$	-0.644	0.160	-0.380	-0.113	0.368	-	1748	3568
M54I	-0.456	0.299	-0.447	-0.301	-	1672	-	-
M54E$_a$	-0.645	0.200	-0.308	-0.255	0.362	-	1716	3538
M54E$_b$	-0.646	0.164	-0.418	-0.112	0.351	-	1725	3472
M55I	-0.459	0.305	-0.440	-0.288	-	1735	-	-
M55E$_a$	-0.643	0.196	-0.310	-0.247	0.377	-	1717	3621
M55E$_b$	-0.646	0.171	-0.405	-0.109	0.361	-	1719	3542
M56I	-0.472	0.313	-0.435	-0.284	-	1748	-	-
M56E$_a$	-0.643	0.186	-0.283	-0.245	0.363	-	1697	3564
M56E$_b$	-0.644	0.177	-0.402	-0.114	0.365	-	1730	3578
M64I	-0.455	0.291	-0.439	-0.287	-	1685	-	-
M64E$_a$	-0.647	0.195	-0.297	-0.249	0.359	-	1758	3536
M64E$_b$	-0.649	0.172	-0.423	-0.107	0.345	-	1748	3458
M65I	-0.465	0.308	-0.436	-0.282	-	1714	-	-
M65E$_a$	-0.647	0.191	-0.390	-0.245	0.373	-	1730	3618
M65E$_b$	-0.650	0.177	-0.411	-0.103	0.358	-	1730	3539
M66I	-0.474	0.310	-0.423	-0.277	-	1719	-	-
M66E$_a$	-0.651	0.188	-0.268	-0.246	0.358	-	1706	3551
M66E$_b$	-0.647	0.176	-0.402	-0.111	0.360	-	1723	3573

versus enamine tautomer increases by decreasing the ring size.

In addition, from Table 2 it is easily seen that relative stability of compounds with more ring strain such as M$_{44}$, M$_{45}$, M$_{54}$, M$_{55}$ and M$_{64}$, the enamine tautomer E$_a$ (exocyclic form) will be more stable than enamine tautomer E$_b$ (endocyclic form). Equilibrium constants of tautomeric interconversions were calculated from Gibbs free energies using $\Delta G = -RT \ln K_{eq}$. The equilibrium constant for conversion of tautomer E$_a$ to I and at B$_3$LYP/6-311^{++}G(d,p) level of theory lies between 6.04×10^1 and 2.13×10^8, and for conversion of tautomer E$_b$ to I lies between 7.97 and 6.26×10^{13}. In accordance with ΔG between tautomers, in compounds with more ring strain, enamine tautomer E$_a$ is major than enamine tautomer E$_b$ (Table 2).

Frequencies

Three important vibrational frequencies of all structures are listed in Table 3. These presented frequencies include imine C=N double bond, enamine C=C double bond and NH bond. In the last column, N_1-H_5 frequency (this frequency only exists in tautomers E$_a$ and E$_b$) is reported. In tautomers E$_b$ the magnitude of this frequency increases with the increase of N-containing ring size. Also, the C=N frequencies in imine tautomers increases with the increase of *N*-containing ring size and the C=C frequencies that exists in enamine tautomers lie between 1630 and 1758 cm^{-1}. The C=C frequencies in M$_{44}$ shows lower magnitude and it correspond to low present of S orbital in these tautomers. The variation of frequencies versus ring size is important because they shows meaningful relation between empirical parameters

(frequency) and simple theories, such as bond angle, ring's strain and hybridation.

NBO analysis

The calculated values NBO charges using the Natural Population Analysis (NPA) of optimized structures of imine-enamine tautomers in the gas phase are listed in Table 3. Nitrogen atom in the all of the tautomers carries the largest negative charge, and among in carbon atoms C_3 carries the largest negative charge. The N_1 and C_3 atoms in all imine-enamine tautomers will most effectively interact with electrophiles.

CONCLUSIONS

In this work, DFT calculation has been applied to study of tautomerism in bicyclic imines and enamines with deferent rings in the gas phase. The following points emerge from the present study:

1.   In the title compound imine form was more stable than the other tautomers in the gas phase.

2.   The energy data shows that the relative stability of enamine tautomer versus imine tautomer increases with the increase of ring size.

3.   Calculated frequencies show that by decreasing *N*-containing ring size, the frequency of C=N in imine tautomer decreases.

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ИМИНО-ЕНАМИННА ТАВТОМЕРИЯ ПРИ БИ-ЦИКЛИЧНИ СИСТЕМИ В ГАЗОВА ФАЗА: ИЗЧИСЛИТЕЛНО ИЗСЛЕДВАНЕ

Х. Моганиан[1], А. Мохамади*[2]

[1]Клуб за млади изследователи, Клон Дезфул, Ислямски университет Азад, Дезфул, Иран

[2] [a]Департамент по химия, Клон Фарахан, Ислямски университет Азад, Фарахан, Иран

(Резюме)

Извършени са DFT-изчисления относно би-цикличните имини за да се изследва влиянието на размера на пръстена върху имин-енамин-тавтомерията. Определени са геометрията на молекулите и енергетиката на имините и енамините в газова фаза при използването на B$_3$LYP-нива на теорията, прилагайки 6-311^{++}G(d,p) базисна мрежа. По този начин са определени важни параметри на молекулите, като ИЧ-честотите, NBO и резултати за енергетиката им в газова фаза. Резултатите за енергетиката показват, че относителната стабилност на енаминната тавтомерна форма (спрямо иминната) нараства с размера на ръстена. Изчислените честоти показват, че намаляването на размера от 6- на 4-атомен пръстен юестотата на C=N връзката в иминния тавтомер намалява.Освен това са изследвани и измененията на NBO-товарите на атомите в газова фаза.