A quantum-chemical study on bi(1,2,3-triazole) molecule

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The conformational analysis of 4,4'-bi(1H-1,2,3-triazole) A, 5,5'-bi(1H-1,2,3-triazole) B and 5,5'-bi(2H-1,2,3-triazole) C tautomers of flexible bi(1,2,3-triazole) molecule containing various reaction centres has been performed by semiempirical methods AM1 and PM3. Furthermore, electronic properties of the tautomers and the effect of conformational changing on their electronic properties have also been investigated. In order to determine the orientation sites of proton attacks at the bitriazole system, molecular electrostatic potentials of the tautomers have been calculated. Conformations and electronic properties of the monoprotonated species of the tautomers have also been studied. Proton affinity of the tautomers has been calculated for different nitrogens, and possible protonation centres determined. Moreover, the complex formation ability of the tautomers with metal cations has been evaluated and discussed.

In our previous studies, the electronic properties and the conformations of 3,3'-bi(1H,1,2,3-triazole) and 3,4'-bi(4H-1,2,4-triazole) molecules have been reported1,2. In continuation of our interest in the quantum-chemical study of bitriazole systems, we wish to report here the results obtained from the investigation of the tautomers of bi(1,2,3-triazole) system. In fact, the stability and related properties of the tautomers of the selected molecule are important from some chemical aspects such as alkylation, substitution, cyclcondensation and complex formation. They are also important from the biochemical point of view such as nucleoside formation, and from the point of pharmacological investigations such as planning for the synthesis of new triazole derivatives having potential biological activity. Indeed, quite a number of articles have been recently devoted to the synthesis and pharmacological investigation of certain 1,2,3-triazoles as well as 1,2,4-triazole derivatives, many of which have a wide range of biological activities.

It is known that 1H- and 2H-forms of 1,2,3-triazole molecule exist in a tautomeric equilibrium in gaseous or liquid medium3. Hence, various tautomeric forms for bi(1,2,3-triazole) molecule containing two 1,2,3-triazole rings are possible. The relative stabilities of 1H-1,2,3-triazole and 2H-1,2,3-triazole tautomers have not been precisely determined as yet. But, 1H-tautomer of 1,2,3-triazole molecule has been found to be more stable than 2H-tautomer according to the calculations by MNDO, AM1 and PM3 semiempirical methods4,5. For this reason, it appears interesting to investigate the relative stabilities of 4,4'-bi(1H,1,2,3-triazole) A, 5,5'-bi(1H,1,2,3-triazole) B and 5,5'-bi(2H,1,2,3-triazole) C tautomers of flexible bi(1,2,3-triazole) molecule (Scheme I). To determine the relative stabilities of tautomers A, B and C, their quantum-chemical investigation and the determination of their stable conformations appear to be important. On the other hand, metal complexes of the triazole and its derivatives have been known6,7. The complex formation ability of a ligand essentially depends upon its ionization potential and proton affinity8. At the same time, a change in conformation affects the complex formation ability of the ligands. The conformation assumed upon complexation for a flexible molecule often does not correspond to the equilibrium conformation of the free ligand9. However, experimental determination of the protonation centers of the molecules having heteroatoms differing from each other in position is generally difficult10,11. In fact, experimental investigation of the conformational behavior of such a molecule may give some important evidence about the stable conformations. Hence, theoretical conformational analysis of the tautomers of flexible bi(1,2,3-triazole)
molecule containing competitive protonation centres and theoretical calculations of the protonation parameters have also been considered to be important. Theoretical investigation of this type reveals that conformational and tautomeric changing in the bitriazole molecule affects its proton affinity and other properties. On the other hand, selectivity of the complex formation ability of bi(1,2,3-triazole) molecule involving competitive coordination centres may be evaluated and the stability of metal complexes may be predicted according to the results obtained. In addition, theoretical investigation of the metal complexes formed by a flexible ligand such as bi(1,2,3-triazole) molecule appears to be important from the point of their formation mechanism.

Literature reveals that ab initio methods as well as modern semiempirical methods are used for the conformational analyses and calculations of proton parameters of heterocycles and biheterocycles. However, AM1 and PM3 routes are used for the calculation of proton affinities of various heterocyclic compounds. Also, ZINDO/I method has been used for the investigation of electronic properties of complex compounds. In the present study, the electronic properties and the conformational forms of tautomers A, B and C of bi(1,2,3-triazole) molecule have been investigated using semiempirical methods AM1 and PM3. Furthermore, the proton affinity values of the bitriazole molecule for different nitrogen atoms have been calculated by AM1 and PM3 routes. The electronic properties and stabilities of the complexes formed by the tautomers of bi(1,2,3-triazole) molecule have been investigated using ZINDO/I method. All the calculations related to the study were performed using HYPERCHEM 3.0 program on an IBM PC Pentium-133 computer.

Results and Discussion

The tautomers of bi(1,2,3-triazole) molecule (Scheme 1) may exist in various conformational forms due to their flexibility. In order to determine the stable conformations of the tautomers, their conformational analyses were performed with full geometry optimization by AM1 and PM3 routes. According to the results obtained by these two methods, the conformations of tautomers A and C corresponding to the global minimum are the planar trans-conformations (\( \phi = 180^\circ \)) with maximum conjugated 1,2,3-triazole rings (Scheme 1, A2 and C2). In accordance with AM1 and PM3 methods, the conformations of tautomer B corresponded to \( \phi = 176.479^\circ \) and \( \phi = 177.766^\circ \) respectively and were found to be the most stable conformations. These conformations may be assumed as nearly as trans-forms. The conformations corresponding to \( \phi = 68.889^\circ \) and \( \phi = 64.640^\circ \) are the most unstable conformations of tautomer A with maximum energy, according to AM1 and PM3 routes, respectively. The results obtained from the two methods reveal that tautomer C involves two 1,2,3-triazole rings which are almost perpendicular to each other. The conformation of tautomer B with maximum energy is found to correspond to \( \phi = 92.066^\circ \) (AM1) and \( \phi = 7.712^\circ \) (PM3) values. The calculated total energies \( (E_{\text{tot}}) \) for stable (trans) conformations of tautomers A, B and C, the internal rotation barriers \( (\Delta E) \) and the internal rotation angles corresponding to minimum and maximum \( (\phi_{\text{min}} \text{ and } \phi_{\text{max}}) \) are given in Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
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The results obtained for internal rotation angles of the conformations of tautomers A and C corresponding to minimum and maximum are in agreement with each other according to AM1 and PM3 routes. The stable conformation of the tautomer B is essentially oriented by the NH...HN repulsive interactions of the molecule and the internal rotation angles of each tautomer are calculated by AM1 and PM3 methods.

\[ \phi = 0^\circ \quad \phi = 180^\circ \]

**Scheme 1**
Table 1 — Total energies (in kcal/mol), internal rotation barriers (in kcal/mol) and internal rotation angles (in degree) for tautomers A, B and C of bi(1,2,3-triazole) molecule.

<table>
<thead>
<tr>
<th>Tautomer</th>
<th>$E_{tot}$</th>
<th>$\Delta E$</th>
<th>$\Phi_{min}$</th>
<th>$\Phi_{max}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AM1</td>
<td>PM3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>-41598.839</td>
<td>-41598.840</td>
<td>4.401</td>
<td>180</td>
</tr>
<tr>
<td>B</td>
<td>-41595.832</td>
<td>-41595.832</td>
<td>0.951</td>
<td>176.479</td>
</tr>
<tr>
<td>C</td>
<td>-41583.980</td>
<td>-41583.980</td>
<td>2.283</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>-34710.580</td>
<td>-34710.580</td>
<td>4.097</td>
<td>179.130</td>
</tr>
<tr>
<td>B</td>
<td>-34709.318</td>
<td>-34709.318</td>
<td>2.563</td>
<td>177.766</td>
</tr>
<tr>
<td>C</td>
<td>-34702.840</td>
<td>-34702.840</td>
<td>2.429</td>
<td>180</td>
</tr>
</tbody>
</table>

other. But, a similar conformity is not observed for the results corresponding to $\Phi_{max}$ values. The results related to the conformational forms of the tautomers of bi(1,2,3-triazole) molecule were obtained by AM1 and PM3 routes in the study and are in agreement with those obtained for the conformations of some conjugated biheterocyclic molecules by semiempirical and ab initio methods.

As seen from Table 1, in contrast to others, the $\Delta E$ values of tautomer B obtained by AM1 and PM3 methods are relatively different from each other.

According to AM1 and PM3 methods, the tautomerisation energies (in kcal/mol) related to bi(1,2,3-triazole) molecule were respectively found as $-3.007$ and $-1.262$ (A-B), $-14.859$ and $-7.740$ (A-C), and $-1.852$ and $-5.478$ (B-C). These results reveal that the relative stability of the tautomers of bi(1,2,3-triazole) molecule is A>B>C. The most stable tautomer is A and the most unstable tautomer is C.

Since 1H- and 2H-forms of 1,2,3-triazole establish a tautomeric equilibrium in gaseous and liquid phases, it is possible to consider that bi(1,2,3-triazole) molecule may also be found in a tautomeric equilibrium involving tautomers A, B and C in the same media.

In order to investigate the basicity and to find out the possible coordination centres, the determination of orientation sites of electrophilic proton attacks at the bitriazole system containing different proton-acceptor centres is important. Moreover, search of the effect of tautomeric and conformational changing onto proton affinity and other properties of bi(1,2,3-triazole) molecule is also important. For this reason the electronic properties of cis ($\Phi=0^\circ$) and trans ($\Phi=180^\circ$) conformations (Scheme 1) of the tautomers A, B and C were studied using AM1 and PM3 routes. Their heats of formation ($\Delta H_{f}^\circ$ in kcal/mol), energies of frontier molecular orbitals ($E_{HOMO}$ and $E_{LUMO}$ in eV) and dipole moments ($\mu$, in Debye) were calculated. For example, according to AM1 method, the calculated values of A1 (cis) and A2 (trans) structures were respectively found as 177.117 and 173.277 ($\Delta H_{f}^\circ$), $-9.194$ and $-9.099$ ($E_{HOMO}$), $-0.238$ and $-0.092$ ($E_{LUMO}$), and $7.761$ and $0.051$ ($\mu$). The results obtained indicate that the trans-conformation of each tautomer is relatively more stable than cis-form according to the two methods used in the study.

In fact, the stability of biheterocyclic systems depends upon conjugation between hetero rings and the interactions between atoms or groups attached to rings. In our bitriazole system, the conjugation between the two 1,2,3-triazole rings is almost the same for both cis- and trans-conformations of the tautomers. But, steric and electronic interactions between ortho-groups of the triazole rings play an important role on the stabilities of the conformations. Hence, the trans-conformations are more stable than cis-forms of the bitriazole system. Thus, tautomers A and C involve repulsive interactions between N···N and CH...HC ortho groups in cis-conformation and attractive interactions between CH...N ortho groups in trans-conformation (Scheme 1). In other words, lone pair-lone pair and hydrogen-hydrogen interactions in cis-conformation and lone pair-hydrogen interaction in trans-conformation must be taken into consideration. However, the total energy difference between cis- and trans-forms of tautomer B is low (0.542 kcal/mol, AM1) and the two conformations involve hydrogen-hydrogen interaction between ortho groups.

The results obtained by the two semiempirical methods indicate that tautomer A has the lowest ionization potential (IP) (IP= $-E_{HOMO}$) and tautomer B has the highest ionization potential among the tautomers of bi(1,2,3-triazole) molecule. For example, the IP values (in eV) of A2, B2 and C2 structures were respectively found to be 9.099, 9.819 and 9.484 according to AM1, and 9.228, 10.058 and 9.372 according to PM3. So, tautomers A and B must have the highest and the lowest electron-donor character, respectively.

In order to find out the possible protonation centres of bi(1,2,3-triazole) molecule, the molecular electrostatic potentials (MEP) (in kcal/mol) of the tautomers were also calculated for cis- and trans-
conformations using AM1 and PM3 methods. The electrostatic contour maps indicate that the electrophilic attack of proton predominantly occurs on N-3 and N-3' atoms at cis- and trans-conformations of tautomers A and B. However, proton attacks are essentially easier onto N-1 and N-1' atoms for the two conformations of tautomer C.

In order to determine the exact protonation sites of the tautomers of bi(1,2,3-triazole) molecule, the proton affinity (PA) of each nitrogen atom being potential protonation centre was examined using AM1 and PM3 routes. Thus, the stable conformations and the heats of formation (ΔH°, in kcal/mol) for the cations formed from the protonation of each nitrogen atom of the tautomers were determined with full geometry optimization by AM1 and PM3 methods. For example, ΔH° values of the protonated forms of A1 and A2 were respectively found as 364.957 and 361.960 for N-1, 358.235 and 354.250 for N-2, and 334.354 and 337.070 for N-3, using AM1 method.

Conformational analysis of the monoprotonated species reveals that the stable conformations of monocations have nearly planar structures. Although trans-conformations of tautomers A and C are relatively more stable than cis-forms, cis-conformations of monocations formed by N-3 protonation of tautomer A and N-1 protonation of tautomer C are more stable than the corresponding trans forms, according to the semiempirical methods used.

The proton affinity values (in kcal/mol) for different nitrogens of A, B, and C tautomers of the bitriazole molecule were calculated by the equation given below:

\[ PA = 367.2 + ΔH°(M) - ΔH°(MH⁺) \]

Where, PA is proton affinity, ΔH°(M) is the heat of formation for the molecule, ΔH°(MH⁺) is the heat of formation for the cation and 367.2 is the heat of formation for the proton (kcal/mol)\(^6\).

The results indicate that the proton affinity values obtained by AM1 and PM3 routes may be considered to be in conformity with each other. The molecule possesses the highest proton affinity for N-3 atom of tautomer A. The proton affinity value calculated for N-3 atom of tautomer A in cis-form is higher than that of trans-conformation (878.485 and 851.055, respectively; AM1). On the other hand, tautomers B and C possess higher proton affinity for N-3 (824.072 for B1 and 820.759 for B2; AM1) and N-1 (819.516 for C1 and 807.449 for C2; AM1) atoms, respectively. But, the proton affinity value of tautomer C calculated for N-1 is lower than that of tautomer B calculated for N-3. Tautomer A has the highest proton affinity and tautomer C possesses the lowest proton affinity among the tautomers of the bitriazole molecule. In cis- and trans-forms of tautomer B, the difference between the proton affinities calculated for N-3 is very low. However, the proton affinity values of tautomers A and C calculated for N-3 and N-1 atoms in cis-forms respectively are higher than those of in trans-conformation. As a result of the interactions between the lone pair electron orbitals of N-3 and N-3' atoms for tautomer A and of N-1 and N-1' atoms for tautomer C through space during the conversion of the molecule from trans-conformation to cis-form, the individual protonation centres join in a common system. Hence, the MEP gradient and proton affinity of tautomers A and C increase during the conversion of trans-form to cis-conformation. This behaviour indicates that the reactivity and the basicity of tautomers A and C increase in cis-conformation.

In compliance with the proton affinity values of the tautomers of bi(1,2,3-triazole) molecule containing several nitrogen atoms differing from each other in position, the protonation of the molecule in two conformations is predicted to occur at N-3 (N-3'), N-3 (N-3') and N-1 (N-1') atoms for tautomers A, B, and C, respectively. This means that the electrophilic attack of metal ions to the molecule may be easier at these nitrogen atoms. According to the proton affinity values, tautomer A in cis-conformation possesses the highest complexing ability among the tautomers of the bitriazole molecule. Also, a metal complex formed by tautomer A is the most stable one among the same type complexes formed by other tautomers of bi(1,2,3-triazole) molecule.

In order to confirm the results, the electronic properties and stabilities of the predicted Fe\(^{2+}\) complexes of tautomers A and C were investigated with full geometry optimization using ZINDO/1 method. Formation of Fe(4,4'-Bi 1HTr)\(^3\) (IA) and Fe(5,5'-Bi 2HTr)\(^3\) (IC) type complexes of bi(1,2,3-triazole) molecule has been considered. Obviously, these types of complexes involve the attachment of Fe\(^{2+}\) ion to N-3/N-3' and N-1/N-1' atoms in tautomers A and C, respectively.

The total energies (E\(_{tot}\), in kcal/mol), heats of formation (ΔH° in kcal/mol) and positive charge densities of iron (Q\(_{Fe}\)) for complexes IA and IC were found as -72045.188 and -72005.210, -2731.058 and
-2691.79, and 0.899 and 0.893, respectively. The Fe-N (Fe-N₁') bond length for 1C and the Fe-N₁ (Fe-N₁') bond length for 1A were respectively calculated as 1.996 Å and 1.994 Å.

These results reveal that complexes 1A and 1C are approximately planar. Complex 1A is 39.978 kcal/mol more stable than complex 1C. The length of Fe–N bond in complex 1A is shorter than that in complex 1C. The positive charge of Fe²⁺ ion is partially delocalized on the ligand in both the complexes.

Therefore, theoretical investigation of the tautomers of bi(1,2,3-triazole) molecule and of their metal complexes reveals that tautomer A is the most stable one among other tautomers of the bitriazole molecule and that the conformation of A corresponding to global minimum is planar trans, according to AM1 and PM3 semiempirical methods. Tautomer A has the highest proton affinity and the highest complex forming ability among the tautomers of the bitriazole molecule. Tautomer A forms relatively stable Fe²⁺ complexes than tautomer C. So, the metal complexes of bit(1,2,3-triazole) molecule are essentially formed via tautomer A.

References