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On tautomerism of 1,2,4-triazol-3-ones

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ABSTRACT

The 1,2,4-triazol-3-ones and their 3-methoxy-1,2,4-triazole analogs 5-substituted by F, BeH, NO_2, BH_2, and $N(CH_3)_2$ groups, exhibiting extreme electron donor–acceptor properties on both σ- and π-type of valence orbitals, were studied at the B3LYP/aug-cc-pVTZ level. The 5-substituted 2,4-dihydro 1,2,4-triazol-3-one keto tautomer is predicted to be the only form present in the gas phase and water solution. In contrast, protonation favors complex equilibria between one keto and two hydroxy tautomers. Transformation of keto tautomers to hydroxy ones changes the ring σ-electrons population by more than 0.3 *e* and that of the π-electrons by *ca.* −0.3 *e*. Protonation shifts the σ- and π-electron populations by similar values but in opposite directions. The analogous changes in 3-methoxy-1,2,4-triazole tautomers are smaller (a matter of 0.02–0.04 *e*). The HOMA geometrical aromaticity index of the keto tautomers is always lower than the indices of the hydroxy forms. The BH_2 and NO_2 π-electron withdrawing substituents increase aromaticity of the studied systems while the $N(CH_3)_2$ or BeH π- or σ-electron donating substituents, decrease aromaticity of the systems.

1. Introduction

Triazolone system is placed at the 56th position of the top 100 most frequently used rings in small molecule drugs listed in the FDA Orange Book [1]. It is present in *Trazodone* and *Nefazodone*: antidepressants [2,3], *Aprepitant* and *Fosaprepitant*: antiemetics [4,5], and *Itraconazole* and *Posaconazole*: antifungal agents [6]. The triazolone core constitutes a multitude of natural and synthetic heterocyclic systems of potential use in *human and veterinary* medicine [7–10]. The triazolone system may undergo quite complex tautomerism.

Tautomerism is a phenomenon of coexistence of constitutional isomers (*i.e.*, isomers of different connectivity) resulting from a relocation of a moiety from one site of a molecule into another with simultaneous redistribution of the π-electron charge of the unsaturated bonds. The reversible interconversion of tautomers can occur in every state of matter, can be either intra- or intermolecular, solvent assisted or not, and the repositioned moiety, usually H atom, can be charged or neutral, can occur in the ground or excited electronic state [11–13]. The tautomeric sites can be within a (heterocyclic) ring or within a chain, or both [11–16]. The definition suggest a relatively simple phenomenon, however, it includes a variety of interconnected molecular properties/processes such as mesomerism, aromaticity, protonation state, stereochemistry, conformation, polymerization, photostability, hydrolysis, and metabolism [17].

Tautomerism is widespread in biomolecules and is important for many biological and biochemical processes. It is considered as an essential factor in modifying properties of neutral or protonated bases in nucleic acids which, in consequence, leads to mispairing of the bases [18–20]. Also, it manifests itself by a wide variety of carbohydrate forms in biosystems [21]. A lot of pharmaceutically active molecules, for example those containing 4-, 5- or 6-membered heterocyclic rings, are capable of existing as two or more tautomeric (prototropic) structures [22,23]. Yet, *Warfarin*, the anticoagulant drug, can potentially exist in 40 distinct tautomeric forms of the two enantiomers [24]. The most importantly, adopting a certain tautomeric form influences bioactivity of a drug [25–27]. This is why tautomerism is worth to study, understand, and predict possible tautomeric equilibria of important building blocks for potential new drugs.

We have been computationally studying tautomerism and substituent effect in 5-membered heterocycles: histamines [28–32], simple diazoles [33,34], simple triazoles [35,36], guanazole [37], oxadiazolones and their mono- and disulfur analogs [38], and fosfoles [39,40], 6-membered diazinone rings [41], fused 5- and 6-membered rings in deazapurine heterocycle [42,43], and indenes [44,45], fused two 6-membered rings in quinolizine [46] and

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quinolines [47,48], and fused 6- and 7-membered rings in benzodiazepinones [49]. Tautomerism of triazolones has been primarily studied because of great importance of 3-nitro-1,2,4-triazole-5-one (NTO), first synthesized in 1905 [50], yet, developed in mid 1980s at Los Alamos National Laboratory [51] as a potential high-performance insensitive energetic material [52,53]. X-ray structure of NTO unequivocally indicates presence of carbonyl group in C5 position and location of two H atoms in positions N1 and N4 [54,55]. Early computational studies [56,57] were in perfect agreement with the crystallographic data. Solvatochromic studies of 3-nitro-1,2,4-triazol-5-one anion showed that in highly polar organic solvents NTO anion mainly exists in the form of the 1H tautomer [58]. This is in agreement with the X-ray structures observed in NTO salts [59]. On the other hand, the ESR spectra of NTO radical demonstrated presence of two tautomers with H-atoms localized at N1 and N2 or N1 and N4 and electron localized at N4 and N2, respectively [60]. Quite recent computational studies on substituted triazolones have also been focused mainly on explosive mechanism context and have considered either group tautomerism rather than prototropism [61] or tautomers of 1-nitroso-1,2,4-triazol-5-one-2-oxide [62].

The aim of this paper is to make a deeper insight into tautomerism of 5-substituted 1,2,4-triazol-5-ones in both neutral and protonated forms. We demonstrate that although the neutral compounds are quite insensitive to substituents, be they electron donating or electron withdrawing ones, the tautomerism in protonated forms is clearly substituent dependent. We show also that protection of the carbonyl group against participation in tautomeric equilibria by transforming it into methoxy group (in 5-substituted 3-methoxy-1,2,4-triazoles) does not lead to a reduction in complexity of tautomeric equilibria. We argue that considering the triazolone drug actions one should consider not only neutral forms but also protonated ones and derivatives able to exist in some physiological environments.

2. Calculations

Structure optimization was carried out using the DFT B3LYP functional [63,64] combined with the aug-cc-pVTZ basis set [65,66]. Reliability of results obtained using B3LYP functional and Dunning type of basis sets in calculations of the ground state geometries has been widely assessed [67]. For all studied system it was checked that all harmonic frequencies were real indicating that the local minima structures were found. The relative abundance of structures was estimated by the Gibbs free energy ΔG referred to the most stable form. All the calculations were performed by using the Gaussian 09 suite of programs [68]. The aromaticity analysis was based on HOMA aromaticity indices [69–72] and on the B3LYP/aug-cc-pVTZ optimized geometries. The influence of the substituent effect by means of sEDA and pEDA descriptors within NBO approach [73] according to expressions presented in [74–76] and orbital populations were read off from Gaussian outputs using EDA-Reader program [77].

3. Results and discussion

It is known that a substituent can change the tautomer equilibria in five-membered heterocycles [33,34]. Here, we deal with 5-substituted derivatives of neutral and protonated 1,2,4-triazole: 1,2,4-triazol-3-ones and 3-methoxy-1,2,3-triazoles. They may exhibit complex tautomeric equilibria in neutral and protonated states (Schemes 1 and 2) which may influence the drug activity in environment favoring one of the forms of the triazolone medicine.

3.1. Notation

The tautomers of 5-substituted 1,2,4-triazol-3-one are presented in the left side of Scheme 1, while their protonated forms are depicted at the right side. First, let us accept the labeling which, however, disagrees with the IUPAC recommendations allows for a consequent notation of the tautomers. The labeling of the five-membered rings is constant and identical to that of 1,2-dihydro-[1,2,4]triazol-3-one. The basic structure is denoted as **12** because the H atoms are attached to the N-atoms labeled as 1st and the 2nd. The analogous structures with H-atoms attached to the 1st and 4th or 2nd and 4th N-atoms are respectively denoted as **14** and **24**. As the O atom is also a center of the H-atom residence, the OH-type tautomers are identified by single Figs. 1, 2 and or 4 denoting place of residence of the second H-atom. Since the H-atom of OH group, practically coplanar with the ring, can additionally be directed either toward one or the other side of the C-O bond, these two positions are labeled by an extra letter **a** or **b**. The notation distinguishes two types of tautomers: these with the C=O group are denoted by the two-figure code and those with the OH group are denoted by the one-figure code supplemented by letter **a** or **b**. The last but not least, the half-ring insight the ring of the tautomer **14** is symbolizing the ring non-Kekuléanity, *i.e.*, an absence of a formula in which each bond is represented by either a single or a double bond [48]. The half-ring notation replaces a series of resonance structures necessary to express complexity of the charge distribution in non-Kekuléan structures. However, we are aware that use of such a notation is criticized by computational chemists strictly respecting classical organic chemistry rules [13].

The convention for the protonated 5-substituted 1,2,4-triazol-3-ones and their protonated forms is analogous (Scheme 2). However, this time the C=O tautomer received three-figure code, **124**, while the OH-type of tautomers have two-figure codes with the additional letter **a** or **b**. Also, the same convention with the additional letter **m** preceding the code guarantees the unambiguousness of the notation for the 5-substituted 3-methoxy 1,2,4-triazoles.

3.2. Tautomerism

The importance of the substituent effect has been continuously increased in drug and material discovery. The effect can be analyzed using several descriptors including, first and foremost, Hammett constants constructed based separately on *para*- and *meta*-substituted benzoic acids [80,81]. In 2009 new substituent effect descriptors denoted as sEDA and pEDA were introduced [74]. The construction was grounded on series of over 30 benzene monoderivatives and NBO analysis of population of valence electrons [82,83]. The sEDA and pEDA descriptors express electron shift between the core molecule and a substituent within separated σ- and π-electron systems, respectively. The sEDA descriptor expresses in fact the functional group electronegativity. On the other hand, the pEDA descriptor expresses substituent action on the ring π-valence orbitals and reveals the resonance effect [74–77].

To demonstrate influence of the substituent on the tautomeric equilibria five substituent exhibiting extreme electron donor–acceptor properties on both σ- and π-type of valence orbitals were selected according to their sEDA and pEDA substituent effect descriptors [74,77]. Indeed, the F substituent is the strongest σ-electron acceptor (sEDA = −0.621 *e*) and a weak π-electron donor (pEDA = 0.078 *e*); BeH is one of the strongest σ-electron donors (sEDA = 0.396 *e*) and a weak π-electron acceptor (pEDA = −0.056 *e*); BH_2 is the strongest π-electron acceptor (pEDA = −0.142 *e*) and quite a significant σ-electron donor (sEDA = 0.173 *e*); $N(CH_3)_2$ is the strongest π-electron donor (pEDA = 0.174 *e*) and quite a strong σ-electron acceptor (sEDA = 0.173 *e*); and NO_2 is a