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A theoretical study of π-stacking interactions in *C*-substituted tetrazoles

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ABSTRACT

The π-stacking effects of benzene ring (Ben) with 1H- and 2H-tetrazole derivatives (1H-TZ-X and 2H-TZ-X) substituted at C5 (where X is Cl, COH, NO, NO_2, CN, NH_2, OH, OCH_3, SH and H) has been investigated by the quantum mechanical calculations at the M06-2X/6-311++G** level. The results indicate the 1H-TZ-X||Ben complexes (|| donates π-stacking interaction) are more stable than 2H-TZ-X||Ben while in unstacked forms, 1H-TZ-X is less stable than 2H-TZ-X. All substituents enhance the π-stacking interaction relative to the unsubstituted ones and enhancement is higher for the electron-withdrawing substituents (EWSs). Also, investigation of the local and direct effect of substituents in stacking interaction showed that all substituents regardless of whether are electron donating or electron withdrawing have an additive effect in π-stacking interaction. Excellent correlations were found between the binding energies of the complexes and combination of substituent constant terms. The results showed that the electrostatic interaction alone is not responsible for stacking stabilization but charge penetration is important. Furthermore, analysis of aromaticity, AIM, ESP and NPA were investigated to obtain aromaticity index, non-bonding interactions, chemical reactivity and polarity (dipole moment), respectively.

1. Introduction

Bioisosterism is useful strategies for design of new drugs in medicinal chemistry [1]. Bioisosters are functional groups that are used as a replacement for another groups and exhibit the same biological activities [2]. The carboxylic acid plays a main role in the biochemistry corresponding to living systems and in drug design [3]. Since, acidity of tetrazole (CN_4H_2) and its derivatives is similar to carboxylic acid group (—CO_2H), they can be used as isosteric replacement of carboxylic acids in biological activities, medicine, drug design, agriculture, etc. [4–9].

Recently, renewed interest has been grown in the chemistry of nitrogen-rich heterocycles and their derivatives, particularly tetrazole [9–11]. The X-ray diffraction data show that tetrazole exits as its 1H-tautomer in the solid state [12]. On the other hand, both the 1H and 2H-tautomers coexist in the gas phase. However, photoelectron and mass spectroscopy studies indicate that the 2H-tautomer is slightly more preferable than the 1H- tautomer and it dominates in the gas phase [10,13]. In solution, 1H- and 2H-tautomers coexist but it is important to note that in polar solvents the tautomeric equilibrium shift to the more polar 1H-tautomer [14].

The quantum mechanical calculations at various reliable levels can be used to accurate prediction of tautomeric equilibria of tetrazole and other similar compounds. Several theoretical studies on the tetrazole system have been carried out in the past few decades [15–17].

Chen and coworkers investigated 49 tetrazole derivatives and the results showed the 2H-tetrazoles are more stable than the 1H-tetrazoles [18], whereas for tetrazole anions the 1-substituted tetrazole are more stable than 2-substituted one. Furthermore, the study of substituent effect indicated that the order of stability of tetrazole tautomers is C-substituted tetrazolate ions > N1-substituted ones > N2-substituted tetrazolate anions. Elsewhere, Sosnowska calculated the energy of 10 tetrazoles substituted at C5 by the DFT method at the B3LYP/6-311++G** level for two tautomeric forms (1H- and 2H-tetrazoles) [19]. The results showed that 2H-tetrazoles are more stable than 1H-tetrazoles and aromaticity indices of 1H-tetrazoles are lower than for 2H-tetrazoles. On the other hand, stability of 1H- and 2H-tautomers have been investigated at various high levels of theory [14,20], as well. It was confirmed that 2H-tetrazoles are more stable than the 1H-tetrazoles thermodynamically, and the formation enthalpy of

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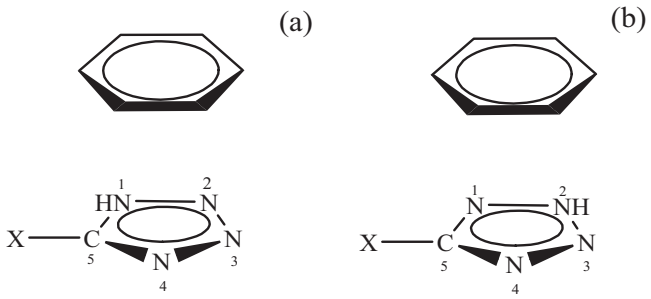
2H-tetrazole was predicted to be lower than the 1H-tetrazole. The influence of the solvent on the stability of tetrazole tautomers was also studied using the PCM model. The results indicated that the 1H-tautomer (more polar one) is more stable than the 2H-tautomer in solutions with ε (dielectric constant) ≥ 7 [14,20].

Noncovalent interactions between aromatic rings such as π-stacking are ubiquitous in natural and synthetic systems [21,22] and have been found to play a central role in the protein folding [23], stabilization of DNA [24], supermolecular chemistry [25], crystal packing [26] carbon nanotube structures [27] and drug-protein interactions [23]. For that reason, investigation of π-stacking interactions were and still are, an interesting subject for numerous researchers [28–34]. The π-stacking interaction in the benzene dimer has extensively been studied as the simplest π-π stacked system [35–38]. The strength and geometry of the π-stacking interactions can be tuned by substituent effects, leading to a powerful avenue for everything of drug design in order to development of novel drugs [39–42]. Hunter and sunders posit that the substituents can inductively add or withdraw the π electron cloud of the substituted benzene and thus lead to less or more favorable electrostatic interactions in comparison with substituted benzene [43]. In this case, substituents act as nonlocal and indirect, and affect second benzene via π system corresponding to substituted benzene. During a computational work, Wheeler and Houk showed that there is a good correlation between the binding energies of the monosubstituted aromatics and the Hammett σ_{meta} values [44]. Thus, similar to the Hunter and Sanders model, they suggested that the binding in arene–arene is guided by electrostatic interactions [45]. On the other hand, Wheeler and Houk described local and direct interaction of substituents by the HX···C6H6 model (where X is substituent) and posited that the direct interaction between substituent and π could of unsubstituted benzene guide the binding in benzene-substituted benzene dimers [39,40]. This study indicated that the binding energies of monosubstituted benzene–benzene dimer can be predicted from the HX···C6H6 binding energies [34]. Recently, such simple models have investigated by Sherrill and coworkers, Grimme et al. and Wheeler and Houk [43]. They indicated all substituents regardless of their EW or ED character enhance the π-stacking interactions in benzene dimer in comparison with unsubstituted case, thus, electrostatic interactions alone is not responsible for the stacking.

In addition hydrogen bond, π-stacking interaction is considered one of the most important noncovalent interactions in binding drug to the active site of protein. Almost all drugs are aromatic and can bind to active site via π-stacking interaction with aromatic amino acid. Since, the properties of many drugs and the strength of drug-protein interactions can be controlled by π-stacking, therefore, investigation of these interactions can also be helpful in the structure-based drug design [46,47].

Since, tetrazole fragment as an aromatic heterocyclic is widely used in biological systems, and its properties and applications change during tautomerism. Thus, it was interesting to us to study the π-stacking effect on stability of the tetrazole tautomers substituted at C5 [11]. In the present work, the influence of the π-stacking interaction of benzene ring with tetrazole tuatomers substituted at C5 (where X is Cl, COH, NO, NO_2, CN, NH_2, OH, OCH_3, SH and H) have been investigated at the M06-2X/6-311++G** level (Scheme 1). The ESP values around the nitrogen hetero-atoms of the TZ tautomers are used as a measure of their hydrogen bonding capacity. The simple models such as 1H-TZ-X||Ben and 2H-TZ-X||Ben complexes can be useful for the novel drug design because they provide a good insight about the intrinsic strength of π-stacking interactions. In principle, the results of this study can be used for the improvement of π-stacking interactions of drug in active site and show that stability of TZ tautomers may alter in the presence of such interactions. To the best of our knowledge any similar investigation has not been previously reported on π-stacking between tetrazoles and benzenes.



Scheme 1. 1H- and 2H-tetrazole π-stacking with benzene (where X is Cl, COH, NO, NO_2, CN, NH_2, OH, OCH_3, SH and H) with atomic numbering.

2. Computational

The geometry of the 1H- and 2H-TZ-X derivatives and 1H-TZ-X||Ben and 2H-TZ-X||Ben complexes were optimized using the hybrid meta exchange-correlation functional M06-2X [48] method in conjunction with the 6-311++G** basis set. The most stable complexes are in parallel-displaced geometry. To examine the local and direct effect of substituents in the benzene dimer binding energies, a simple model was considered by replacing the nitrogen, carbon and hydrogen atoms of TZ tuatomers substituted at C5 with a hydrogen atom (HX···Ben). The hydrogen atom was placed along the C5-X bond and then the single point calculations was performed for the HX···Ben complexes obtained from 1H-TZ-X||Ben and 2H-TZ-X||Ben at the M06-2X/6-311++G** level. In addition, single point interaction energies were calculated by the B3LYP-D3 [49,50] dispersion corrected functional as suggested by Grimme for noncovalent contacts [51,52]. Topological properties of the electron charge density were calculated by AIM method using the AIM2000 program [53] at the M06-2X/6-311++G** level. Moreover, the electrostatic potential values around the nitrogen hetero-atoms in 1H-TZ-X||Ben and 2H-TZ-X||Ben complexes and in 1H- and 2H-TZ-X derivatives were calculated by Multiwfn 3.2 package [54] as a measure of their hydrogen bonding capacity. To evaluate the total dipole moment, the NPA [55] analysis was carried out at the M06-2X/6-311++G** level by the NBO3.1 [56] program. The charge transfer was calculated as the sum of atomic CHELPG charges on TZ in the 1H-TZ-X||Ben and 2H-TZ-X||Ben complexes. The computations have been performed using the Gaussian 09 [57] suite of programs.

3. Results and discussion

The optimized 1H-TZ-X||Ben and 2H-TZ-X||Ben complexes are shown in Figs. 1 and 2. The binding energies (E_b) of 1H-TZ-X||Ben and 2H-TZ-X||Ben complexes ($E_b = E_{1H\text{-}TZ\text{-}X||Ben/2HX||Ben} - E_{1H\text{-}TZ\text{-}X/2H\text{-}TZ\text{-}X} - E_{Ben}$) calculated at the M06-2X/6-311++G** level, are summarized in Table 1 (the energies of the 1H- and 2H-TZ-X derivatives ($E_{1H\text{-}TZ\text{-}X}$, $E_{2H\text{-}TZ\text{-}X_{2X}}$) have been inserted in Tables S1 and S2 in Supporting Information).

As can be seen in Tables S1 and S2, the 2H-TZ-X derivatives are more stable than 1H-TZ-X. Both the electron donating and withdrawing substituents (EDSs and EWSs) increase the magnitudes of the energies relative to the unsubstituted ones and the trend of stability is Cl > SH > NO_2 > NO > OCH_3 > COH > CN > OH > NH_2 > H. This order of stability is similar to results reported by Sosnowska [19] for two tautomeric forms (1H- and 2H-tetrazoles) substituted at C5 that were optimized at the B3LYP/6-311++G** level.