

Tautomerism of protonated imidazoles: A perspective from ab initio valence bond theory[☆]

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ABSTRACT

The tautomerism of protonated imidazoles concerns one aromatic (1H-Imi⁺) and one nonaromatic (4H-Imi⁺) tautomers. Both experiments and computations have shown that substituents to the imidazole ring can change the relative stability of tautomers. A detailed theoretical study of the inherent mechanism would benefit the rational design of experimental syntheses related to imidazoles. In this work, we used the block-localized wavefunction (BLW) method to explore the factors governing the tautomerism between 1H-Imi⁺ and 4H-Imi⁺. While π resonance always favors the aromatic tautomer 1H-Imi⁺, the aromaticity noticeably reduces with electron donating groups (EDGs) as substituents due to the increased π - π repulsion, leading to the stability of 4H-Imi⁺ over 1H-Imi⁺ with EDGs such as NH₂ and OH. For electron withdrawing groups (EWGs), the reduced π - π repulsion promotes the aromatic stability and favors 1H-Imi⁺. DFT computations were also performed to study the tautomerism mechanisms. Results show that tautomerism can hardly occur in gaseous phase, but in aqueous solution, water molecules can build hydrogen bonding network with 1H-Imi⁺ and facilitate the hydrogen transfers.

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1. Introduction

Tautomerism of heterocyclic compounds, as exemplified in Fig. 1, is ubiquitous and plays an essential role in the understanding of organic and biological processes, notably in the early establishment of the DNA structure [1–4]. Generally, aromaticity plays a primary role in rationalizing and understanding tautomeric preferences for simple heterocyclic molecules [5–7], and the correlation between aromaticity and tautomerism has been extensively explored [6,8,9]. For complex systems, however, electronic effects from functional groups and their intramolecular interactions with the remaining part of the molecule dictate the tautomeric preference. [9–11] Cyranski et al. even showed that there was no simple relationship between the π -electron delocalization and the stability of tautomers in nucleobases [12]. Some nonaromatic 2H-imidazole I-oxides have been reported by Simmonds et al. and Elguero

et al. [13–15]. Interestingly, recent experimental and theoretical studies by Draghici et al. and Lederer et al. [16–18] revealed that in spite of the preference of aromatic arrangement in unsubstituted imidazolium (un-Imi⁺), the addition of methylamino substituents to the 2 and 5 positions reverses this preference and stabilizes the nonaromatic tautomer instead (see Fig. 1).

Compared with NH (1H-Imi⁺) tautomers, CH (4H-Imi⁺) tautomers of imidazole and its derivatives have been paid little attention due to their absence of aromaticity. Obviously, the substituent effect dominates the tautomeric preference of CH tautomers. For the different preferences with different substituents as shown in Fig. 1, Draghici et al. have pointed out that “This trend may be partly explained by the decreasing aromatic stabilization of imidazole upon addition of electron-donating substituents to the 2 and 5 positions” and “In the 4H-imidazole tautomer, on the other hand, electron-donating amines can contribute extensively to resonance stabilization.” [16]. In fact, tautomerism can be affected by a number of factors notably including π electron delocalization, intramolecular hydrogen bonding, substituent effect, polarity of the solvent, and temperature. The substituent effects on the electron delocalization have been extensively reviewed by Krygowski and Stepien [19]. Krygowski et al. also suggested that a nonaromatic π -

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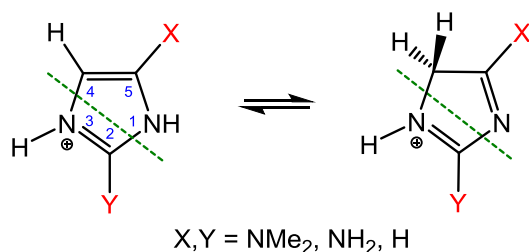


Fig. 1. The tautomerism of protonated imidazoles (1H-Imi+ and 4H-Imi+).

conjugated system is a better medium than its aromatic counterpart in communicating between substituents [9,20], as understandably an aromatic ring tends to retain its aromatic character and thus is rather resistant to the substituent effect. This can be verified by the facts that substituents influence the π electron delocalization of benzene very weakly [21] and perfluorobenzene is as aromatic as benzene [22]. Back to the tautomerism of protonated imidazoles ($X, Y = H$) in Fig. 1, the preference of 1H-Imi+ over 4H-Imi+ seems clear as the aromaticity in 1H-Imi+ has a dominating role, but it is complicated with substituents which change the structural preference.

Imidazole ring and its substituted derivatives have been studied by Chermahini et al. [23,24]. Based on the harmonic oscillator model of aromaticity, or HOMA [25–27], they concluded that the aromaticity character slightly decreased in substituted imidazoles with going from electron withdrawing groups (EWGs) to electron donating ones (EDGs) [23]. This conclusion holds true for protonated imidazoles and imidazole anions, though insightful explanation seems missing. Similar trend has also been found in substituted benzenes by Krygowski et al. [21]. If we focus on the upright side of the dashed line in Fig. 1, the tautomerism of 1H-Imi+ and 4H-Imi+ is actually similar to the enamine-imine tautomerism [28], and existing findings and conclusions for the latter thus would be illuminating for our current study of the former. The effect of various substituents on the imine-enamine tautomerism for $XH_2C-CH=NH$ and $CH_3-CX=NH$ has been examined [29,30]. For $X = BH_2, NO,$ and CN in $XH_2CCH=NH$, the enamines are favored over the imines due to the conjugative interaction between the carbon-carbon double bond and the vacant p orbital on boron or the π^* orbitals in NO and CN [29]. The substituent effect can also be explored with the barrier to intramolecular proton transfer, as the barrier is implicated by differential inductive effects. For instance, EDGs stabilize the transition state structures and lead to low barriers, but EWGs increase the energy barrier with reference to the unsubstituted system of $CH_3-CX=NH$ [30].

In general, much recent attention has been paid not only to neutral molecules, but also to their radical ions such as phenol [31], aniline [32], imidazole [23,33], 4-aminopyrimidine [34], purine [35] and adenine [36]. It has been found that all these neutral, oxidized and protonated molecules behave in a similar manner, but the reduced forms exhibit the reverse correlation. In other words, the order of tautomer stability is changed, and the least aromatic form becomes the dominant tautomer. The forces behind this reversion are yet to be identified. We also note that the solvent-assisted tautomerization has been widely studied [37–44]. The intermolecular factors such as hydrogen bonding formed by substituents with compounds surrounding the substituted molecule, or simply a solvent such as water molecule, may dramatically change the electron distribution of the substituted core [37,38,45,46]. The tautomeric equilibrium is different with the participation of water as water molecules can influence the relative stabilities of tautomers.

In this work, we explored the factors governing the tautomerism between 1H-Imi+ and 4H-Imi+ by using the ab initio valence bond (VB) theory together with the molecular orbital (MO) theory. The uniqueness of the VB theory is its definition of electron-localized states (i.e., resonance or Lewis states). In addition, solvent effect was also studied. Findings from this study are expected to be enlightening for synthetic organic chemists in their design of reactions routes or new molecules related to imidazole or other conjugated rings.

2. Results and discussions

2.1. Substituent effect

Simply look at the equilibrium shown in Fig. 1, one may conclude that the aromatic 1H-Imi+ would be more stable than the nonaromatic 4H-Imi+. However, both calculations and experiments indicate that the substituents X and/or Y play an important role in the isomerization (tautomerism) between 1H-Imi+ and 4H-Imi+. Here we compared the energy changes with different substituents which can be EDGs or EWGs in Table 1. The resonance constant R value, which defines the resonance effect on the average of electron-donating ability and electron-accepting ability of a functional group by Swain-Lupton [47], is also listed for comparison. Table 1 shows that the relative stability of 4H-Imi+ over 1H-Imi+, ΔE , increases along the EDGs (or decreases along the EWGs). With strong EDGs like amino (NH_2) or hydroxyl (OH) substituting the hydrogens at positions 2 and 5, the 4H-Imi+ isomers are even more stable than the 1H-Imi+ isomers.

The electronic effects of substituents are usually composed of two main parts: a field/inductive component and a resonance component [48,49]. Gas-phase proton-transfer equilibria for a variety of reaction series have been studied in order to elucidate the substituent effect. For the tautomerism in Fig. 1, the field/inductive effect are quite similar in both isomers, and the major difference between substituted 1H-Imi+ and 4H-Imi+ is the resonance effect therein. This conclusion can be verified by the good correlations between substituent resonance parameter R and the energy difference ΔE as shown in Fig. 2a. To further quantify the resonance effect in this tautomerism, we performed BLW computations [50–52]. The uniqueness of the BLW method is that we can stepwisely delocalize the π electrons and quantitatively explore the energetic impact of electron delocalization and thus precisely identify the cause of the tautomeric preference. When all π electrons and lone pairs are strictly localized, all the relative energies (ΔE_{Loc}) are negative, indicating that it is the resonance effect that dominates the tautomeric preference.

Starting from the strictly localized state, we delocalize the six π electrons in rings (note that for substituted 4H-Imi+, there are two π electrons from the methylene group originating from the combination of the two CH σ bonds). The subsequent energy change (RE_C as listed in Table 1) reflects the stability due to the aromatic resonance, though the aromaticity in substituted 4H-Imi+ should be weak compared to substituted 1H-Imi+ and largely driven by the positive charge. Indeed, the aromatic resonance stability in 4H-Imi+ is almost unchanged as their energies ($RE_C(4H)$) only slightly fluctuate around 40 kcal/mol. Differently, the aromatic resonance energy ($RE_C(1H)$) increases in substituted 1H-Imi+ with from EDGs to EWGs. For instance, compared to the value 101.27 kcal/mol in unsubstituted 1H-Imi+ (1H-un-Imi+), the resonance energy is reduced to 79.00 kcal/mol in 1H- NH_2 -Imi+, suggesting that the aromaticity reduces when the amino groups are attached to the ring. For those with EWGs, their $RE_C(1H)$ increases to between 104.09 and 116.51 kcal/mol. These data indicate that EDGs have more sensitive influence on the RE_C than the EWGs. Now the

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