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COMMUNICATION

Unusual *para*-substituent effects on the intramolecular hydrogen-bond in hydrazone-based switches[†]

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A "V"-shaped Hammett plot shows that resonance-assisted hydrogen bonding does not dictate the strength of the intramolecular hydrogen bond in the E isomers of hydrazone-based switches because it involves an aromatic pyridyl ring.

Hydrogen bonding is a universal phenomenon that is of particular interest to chemists because of its prevalent influence on chemical reactivity, properties, and processes.1 Although the study of H-bonds has been going on for decades, the nature of H-bonding, especially intramolecular H-bonding, is still intriguing.^{1b} In 1989, Gilli et al. proposed the resonance-assisted hydrogen bonding (RAHB) theory in order to explain the unique strength of the intramolecular H-bond in acetylacetone (HOCR=CR-CR=O) fragments.² Based on this theory π -delocalization in the fragments involved in intramolecular H-bonding can lead to the strengthening of these bonds.³ In recent years RAHB theory has been expanded to include N-H···O,⁴ O-H···S⁵ and $N-H \cdots N^6$ H-bonded systems, thus broadening its impact on H-bonding theory.⁷ Even though the RAHB theory has been widely accepted⁸ and validated in various H-bonding fragments,^{7b} its scope is still not completely defined. For instance, its effect has not been thoroughly assessed in intramolecularly H-bonded fragments involving heterocyclic aromatic groups.9

Our interest in developing hydrazone-based switches¹² has led us to the synthesis of various intramolecularly H-bonded compounds (Scheme 1). What is interesting and unique in these systems is that they not only possess the classical RAHB fragment HN–N=C–C=O in the minor Z isomer, but also feature another six-membered H-bonded network (HN–N=C–C==N) in the major E isomer.¹² The latter involves a heteroatom which is part of the aromatic pyridyl ring. There are only few examples of RAHB studies focused on the N–H···N H-bond fragment,⁶ and none of these involve an aromatic ring. The fact that these molecular switches exist in solution as a mixture of isomers offers us a unique opportunity to directly compare two different intramolecularly H-bonded fragments and study the



Scheme 1 The equilibrium between the *E* and *Z* isomers of the hydrazone-based switches and the corresponding Hammett constants (σ_p) for the *para*-substituents,¹⁰ in addition to the measured pK_a values¹¹ in acetonitrile (CH₃CN). The H-bond fragments HN–N=C–C=N and HN–N=C–C=O are indicated in red.

effect of incorporating an aromatic heterocycle as part of the H-bonded fragment on RAHB.

We therefore decided to systematically investigate the structure–property relationship of a series of *para*-substituted phenylhydrazones in terms of their intramolecular H-bond strength (Scheme 1 and Scheme S1, ESI†). The substituents on the phenyl ring range from typical electron donating groups (EDGs) to typical electron withdrawing ones (EWGs). The electronic properties of these sustituents are usually quantified by the Hammett substituent constant σ (in the case of *para*-substituents, σ_p), which describes their electron-donating or electron-withdrawing capabilities.¹⁰ Generally speaking, the higher the absolute value of σ , the stronger the electron-donating/withdrawing ability of a substituent. The influence of substituents on the H-bond strength is usually used to decipher the nature of the studied bond.

The linear free-energy relationship (LFER)¹³ between H-bond strength and σ has been reported for a few O–H···O¹⁴ and N–H···O^{4a} RAHB systems, reflecting the validity of this type of analysis. In our system, the H-bond strength of HN–N=C–C=O fragments can be characterized and quantified by the chemical shifts of the N–H protons in the Z configuration ($\delta_{N-H,Z}$). Usually the stronger the H-bond the more downfield shifted is the N–H proton signal.^{4a} A plot of $\delta_{N-H,Z}$ of the different derivatives *vs.* the appropriate σ_p values yields an excellent linear relationship ($R^2 = 0.985$, Fig. S1, ESI†) between these two variables (Fig. 1). As can be seen from the plot the N–H chemical shift decreases from 11.85 to 11.16 ppm as σ_p increases. This trend demonstrates that the H-bond becomes weaker as we move from EDGs to EWGs.

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Fig. 1 The plot of $\delta_{N-H,Z}$ (CD₃CN) of the different derivatives (in their Z configuration) *vs.* the corresponding σ_p values, and the resonance structures in the N-H···O RAHB system.

This observation is consistent with RAHB theory, *i.e.*, the resonance structures HN–N=C–C=O \leftrightarrow H⁺N=N–C=C–O⁻ strengthen the H-bonding through π -delocalization.^{4a} The presence of an EDG in the phenyl ring enhances the electron density and increases the H-bond strength, whereas EWGs lead to the opposite effect. On the other hand and without RAHB facilitation, the trend in the change of H-bond strength would have been completely the opposite since EDGs will decrease the acidity of the N–H proton, thus weakening the H-bonding. It is noteworthy that the influence of RAHB is so significant that it surpasses the increase in N–H acidity in the derivatives with EWGs.

On the other hand the plot of the N–H chemical shifts $(\delta_{N-H,E})$ of the HN–N=C–C=N fragment in the *E* isomers *vs*. the appropriate σ_p values affords a "V"-shaped curve instead of a straight trend line (Fig. 2). A decrease from 14.78 to 14.55 ppm is observed when going from *p*-NMe₂ to *p*-H, followed by an increase (14.55 to 14.77 ppm) going from *p*-H to *p*-NO₂. A roughly linear relationship between $\delta_{N-H,E}$ and σ_p is observed in both sections (Fig. S2, ESI†). With *p*-H as the lowest point in the curve, it is clear that both EDGs and EWGs are making the H-bond stronger. This observation is



Fig. 2 The plot of $\delta_{N-H,E}$ (CD₃CN) of the different derivatives (in their *E* configuration) *vs.* the corresponding σ_p values, and the forbidden resonance in the HN–N=C–C=N fragment.

definitely not consistent with RAHB theory! To reaffirm the trend in H-bond strength we examined the crystal structures of several derivatives in their E configuration (Fig. S7, ESI^{\dagger}), since the donor-acceptor atom distance can be used to evaluate the H-bond strength.¹⁵ Derivatives with either EDGs or EWGs have shorter N···N distances compared to that in p-H, indicating that they also have stronger H-bonds. In addition, the $N \cdots N$ distances in these compounds range from 2.603(2) to 2.658(2) Å, which are longer than those in reported N-H···N RAHB systems. The C=N bond lengths in these derivatives range from 1.305(2) to 1.315(4) Å, indicating that they retain their double bond character, while the N-N bond lengths range from 1.316(1) to 1.327(3) Å, affirming their single bond character.⁶ These results rule out RAHB induced hydrazone-azo tautomerization¹⁶ in these systems.¹⁷ Thus, neither ¹H NMR spectroscopy nor X-ray crystallography results show any evidence of RAHB in the HN-N=C-C=N fragment. This observation can be attributed to the relatively high energy of the resonance form, $H^+N = N - C = C = N^-$, in which the aromaticity of the pyridyl group is diminished. This conclusion is not straightforward, especially when one takes into account reported examples in which aromaticity is compromised for the sake of RAHB.9,18 The difference between these systems and ours is the position of the acceptor atom; it is directly attached to the aromatic ring in the former, and is part of the ring in the latter. This distinction seems to be responsible for the observed differences in behavior, and can be important when analyzing RAHB phenomena in heterocyclic systems, such as base pairs.¹⁹

To validate our hypothesis and better understand the unexpected trend observed for the H-bond strength in the *E* isomers, we sought to determine the basicity of the pyridyl group in these derivatives. We first studied the influence of the phenyl ring *para*-substituents on the pyridyl ring by examining the chemical shifts of the pyridyl proton H5 (δ_{H5} , Scheme 1). The LFER in the plot of δ_{H5} vs. σ_p clearly shows that the electronic properties of the substituents on the phenyl ring *p*-NMe₂ to *p*-NO₂ the values increase from 8.68 to 8.75 ppm. The positive slope shows that the EWGs lead to the expected downfield shift. This observation demonstrates that the pyridyl ring is in conjugation with the phenyl one,^{12d} and thus its basicity can be modulated by the *p*-substituents.

The basicities of the molecular switches (p K_a values of their conjugate acids) were determined using the previously described methodology,²⁰ and are presented in Scheme 1 (Table S2, ESI†).¹¹ As shown previously,¹² protonation of the pyridyl group to yield the conjugate acid leads to the switching of the molecule into the protonated Z isomer. The p K_a values show a roughly linear correlation with the σ_p values (Fig. S4, ESI†); however, a "V"-shaped pattern is again observed when these values are plotted against $\delta_{N-H,E}$ (Fig. S5, ESI†). Thus, there is no straightforward relation between the p K_a values of the compounds and the strength of the intramolecular H-bond in the *E* isomer. In order to better understand the nature of the substituent effect in these systems, we looked deeper into the factors that can modulate their H-bond strength, *i.e.*, inductive and resonance effects. When we correlated the p K_a values with the field-inductive $(\sigma_{\rm F})$ and resonance $(\sigma_{\rm R})$ constants of the substituents¹⁰ (Fig. S6, ESI[†]) we obtained the following equation:²¹

$$pK_a = 12.3 - 2.0\sigma_R - 1.1\sigma_F$$
 ($r^2 = 0.97, S = 0.11$) (1)

It can be seen that although both effects are operational, the influence of the resonance effect is almost twice as strong. Combining the pK_a values with the information on the strength of the intramolecular H-bond leads to the conclusion that the *para*-substituents work in two different ways. The EWGs first of all increase the N–H proton acidity, which is more pronounced than the accompanied decrease in the basicity of the pyridyl group leading to a stronger intramolecular H-bond. On the other hand, the EDGs reduce the acidity of the N–H proton; however, they concurrently lead to a larger increase in the basicity of the pyridyl nitrogen, thereby leading to an overall strengthening of the H-bond.

In summary, we have shown that the two H-bond fragments HN-N=C-C=N and HN-N=C-C=O in a series of hydrazone-based switches adopt two distinct H-bonding motifs. The HN-N=C-C=N fragment cannot take advantage of RAHB enhancement, because that will diminish the aromatic character of the pyridyl group. On the other hand, the HN-N=C-C=O fragment follows RAHB theory. By measuring the pK_a values of the pyridyl ring and dissecting its components, we were able to show that both electron donating and withdrawing *p*-substituents strengthen the H-bond in the HN-N=C-C=N fragment by inversely modulating the acidity and basicity of the N-H and pyridyl nitrogens, respectively.

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