

The Role of Through-Bond Stereoelectronic Effects in the Reactivity of 3-Azabicyclo[3.3.1]nonanes

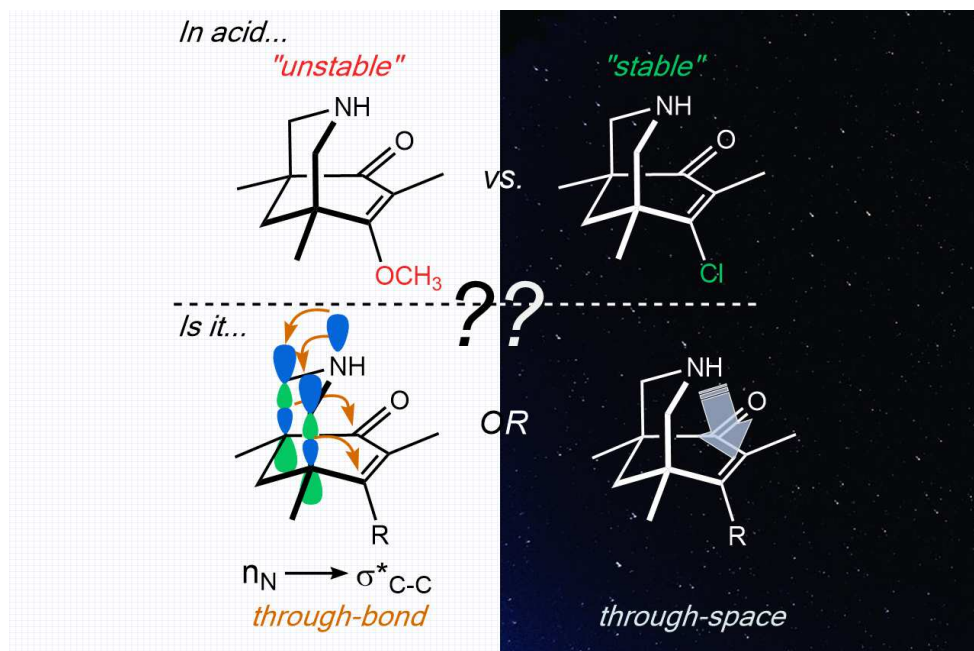
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KEYWORDS. remote stereoelectronic effects; through-bond interactions; heterolytic fragmentation; isodesmic reactions; hydration propensity; basicity

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ABSTRACT. Hyperconjugation/conjugation through-bond stereoelectronic effects were studied with density functional theory (DFT) in the context of 3-azabicyclo[3.3.1]nonanes to unravel puzzling differences in reactivity between a vinylogous chloride (**4**) and a vinylogous ester (**5**). These compounds—whose structures differ only by one substituent—were found to display strikingly different reactivities in hydrochloric acid by Risch and co-workers (*J. Am. Chem. Soc.* **1991**, *113*, 9411–9412). Computational analyses of substituent effects, noncovalent interactions, natural bond orbitals, isodesmic reactions, and hydration propensities lead to a model for which the role of remote, through-bond stereoelectronic effects is key to explaining **4** and **5**'s diverging reactivity.

INTRODUCTION

*Bond, through-bond.*¹ Interactions in chemistry can occur through-space and/or through-bond,^{2–4} both of which have been the subject of intense research in theoretical chemistry^{2,3} and photoelectron spectroscopy.^{5–10} These interactions can affect reactivity/selectivity of molecules because their manifestations are net stabilizing or destabilizing and depend on molecular geometry, hence *stereoelectronic*.^{11–16} For example, many investigations have been sparked by 1-azaadamantane structures (e.g., Scheme 1, **1**) because of its unique, conformationally constrained architecture,^{17–19} rich in hyperconjugation.^{11,20,21} Additionally, 1-azaadamantanes (and derivatives like 1-azaadamantanones) have been synthesized^{22,23} and studied in the past for their tendency to undergo Grob fragmentations,²⁴ for their intramolecular through-bond¹⁶ and charge transfer interactions,²⁵ and for measuring electron spin distribution through a σ -skeleton by ¹³C contact shifts in NMR studies.²⁶ We developed an interest in 1-azaadamantanone structures (e.g.,

1, Scheme 1) and their 3-azabicyclo[3.3.1]nonane fragmentation products (e.g., **4** and **5**, Scheme 1) for their visually appealing²⁷ and unusual structures, which hold functional groups of varying nucleophilicity and electrophilicity in particular orientations. 3-Azabicyclo[3.3.1]nonanes²⁸ are of interest for their pharmaceutical applications^{29,30} and use in molecular recognition chemistry.^{31,32} The 3-azabicyclo[3.3.1]nonane architecture also arises in *Aristotelia* alkaloid natural products (e.g., hobartine and aristoquinoline).^{33,34}

Heterolytic fragmentation reactions (e.g., **2** → **3**) can be useful strategic tools in organic synthesis.^{35–41} When applied successfully, fragmentation reactions can effect ring-expansion^{42,43}—see, for example, the total synthesis of vinigrol.⁴⁴ Examples in which fragmentation reactions have been useful continue to emerge in the literature (e.g., in bioorthogonal self-immolative linkers)⁴⁵ and we suspect their utility will only continue to expand. Nevertheless, sparse mechanistic information hinders their broad use. Somewhat cryptic aspects of fragmentations that computational chemistry is uniquely positioned to address include: (1) directing competing divergent mechanisms to control product outcomes,⁴⁶ (2) connection between the atom-length of a fragmentation and its concertedness, and (3) tendencies of particular groups to sequentially fragment (in stepwise or concerted but asynchronous pathways).²⁴ Basic research⁴⁷ into simple theoretical model systems that investigate the roles of stereoelectronic interactions in fragmentations, and intermediates/products born out of them, would therefore be valuable for future investigations of heterolytic fragmentations. To this aim, we consider here through-bond effects in a 3-azabicyclo[3.3.1]nonane product borne out of a fragmentation reaction⁴⁸—orbital effects that could have promoted its formation and that influence its fate.

Compound **1**, reported by Risch's group, piqued our interest because it was reported that **1** fragments to a "stable" intermediate, **4**.⁴⁸ Here, stable refers to *kinetic* stability (as opposed to *thermodynamic* stability) with respect to hydrolysis. Specifically, diketone **1** yields **2** when refluxed in thionyl chloride. Molecule **2** then fragments to a 3-azabicyclo[3.3.1]nonane derivative, **4**, upon workup [(1) aqueous ammonia, 25%; (2) methanol/NaOH; (3) concentrated hydrochloric acid].⁴⁸ An alternative fragmentation of **2** could generate β,γ -unsaturated ketone **6**, but the authors do not observe **6**. Our calculations are consistent with this result: fragmentation to **6** is kinetically and thermodynamically less favorable than fragmentation to **3** ($\Delta G^\ddagger = 24.3$ kcal mol⁻¹, $\Delta G = 16.4$ kcal mol⁻¹ to **6** versus $\Delta G^\ddagger = 22.2$ kcal mol⁻¹, $\Delta G = 10.2$ kcal mol⁻¹ to **3**; see Supporting Information (SI), Figure S1) Notably, treatment of **4** with CH₃O⁻ was reported to give structure **5**, which "immediately reacts with hydrochloric acid at room temperature"⁴⁸ to form **1**, presumably via initial hydrolysis to the vinylogous acid.

Scheme 1. Unusual reorganization of 3-azabicyclo[3.3.1]nonanes through heterolytic fragmentation.

METHODS

Density functional theory calculations were carried out using *Gaussian 09*.⁵⁰ The Minnesota hybrid functional, M06-2X,⁵¹ was used for geometry optimization and frequency analysis for calculation of Gibbs free energies, as it has been shown to work well for systems involving hyperconjugation and minimizes error associated with extensive electron delocalization.^{52,53} A triple- ζ Pople basis set, 6-311+G(d,p), was used with diffuse and polarization functions for all calculations. Intrinsic reaction coordinate (IRC) calculations were carried out to find the minimum energy pathways downhill in energy and each transition state structure's flanking minima.^{54–56} To check the robustness of our level of theory, we computed amine proton affinities with B3LYP-D3^{57,58} in the gas phase and M06-2X in a polarizable continuum (PCM)⁵⁹ solvation model and compared the results to that in Figure 2 (*vide infra*). The data gleaned from this case study led to consistent qualitative conclusions across the three levels. Thus, we reasoned that M06-2X/6-311+G(d,p) adequately captures qualitative trends for the systems studied here. All computed structures (including coordinates) can be found on the ioChem-BD repository⁶⁰ at the following DOI: <https://doi.org/10.19061/iochem-bd-6-120>. Energies, file names, and lowest frequencies associated with each structure can also be found in the SI.

Basicities were computed by using the proton transfer equilibrium equation (1) and a formula based on electronic energies (2).⁶¹ Relative basicity values (B) obtained from this method establish a reasonable sense of relative basicity for various R-substituted fragmented products (FPs).



$$B = E(FPH^+ + H_2O) - E(FP + H_3O^+) \quad (2)$$

Noncovalent interaction (NCI) plots⁶² were generated using Multiwfn version 3.7 with a medium quality grid.⁶³ Natural bond orbital (NBO) analysis (version 3.1) was carried out in *Gaussian 09* to obtain second-order perturbation NBO energies.^{64,65} Hydration propensities of our substrates were calculated using electronic energies (E) in a formula based on thermodynamic data⁶⁶—hydration data may also be determined kinetically^{67,68}—with the following equations (3 and 4), where E is the non-hydrated species, and E_{hyd} is the hydrated species:

$$\Delta E_{rxn} = E_{hyd} - (E + E_{H_2O}) \quad (3)$$

$$\ln K_{hyd} = -\left(\frac{\Delta E_{rxn}}{RT}\right) \quad (4)$$

RESULTS AND DISCUSSION

Noncovalent Interactions (NCI) Analysis

Structures **4** and **5** are unique in that the amine and π -system are close enough that a through-space interaction could be relevant between the lone pair of the nitrogen (n_N) and the π -system (i.e., $n_N \rightarrow \pi^*_{C=C}$ or $n_N \rightarrow \pi^*_{C=O}$) or between the N-H bond and the π -system. If through-space interactions are operative, then a noncovalent interaction (NCI) analysis should reveal any difference in through-space interactions that exist between **4** and **5**. NCI analysis is a useful tool for qualitatively visualizing intra- and intermolecular noncovalent interactions within (or between) molecules.⁶² The use of NCI analyses in computational organic chemistry studies has become increasingly important to characterize, visualize, and rationalize the role of weak, noncovalent interactions in mechanistic models.^{69–71} Colors in NCI plots indicate the type of

interaction: blue indicates strong attraction on one extreme, and red indicates strong repulsion on the other; green lies in the middle of the two extremes and indicates weak interactions (e.g., dispersion interactions). Figure 1 shows NCI plots for structures **4** and **5**. The green in each plot indicates that weak interactions exist between the amine and the π -system, but the degree to which it changes from **4** to **5** suggests that through-space effects remain effectively the same in **4** and **5** (analogous results were obtained for the *N*-invertomers of **4** and **5**—**4'** and **5'**—and their *N*-protonated forms; see SI). A through-space interaction argument alone is thus insufficient to explain Risch et al.'s observed diverging kinetic stabilities in acid. Though these plots by themselves do not definitively rule out the existence of strong through-space interactions between the amine and the enone moieties, they weigh against through-space effects having a consequential role in the fate of these structures in acid.

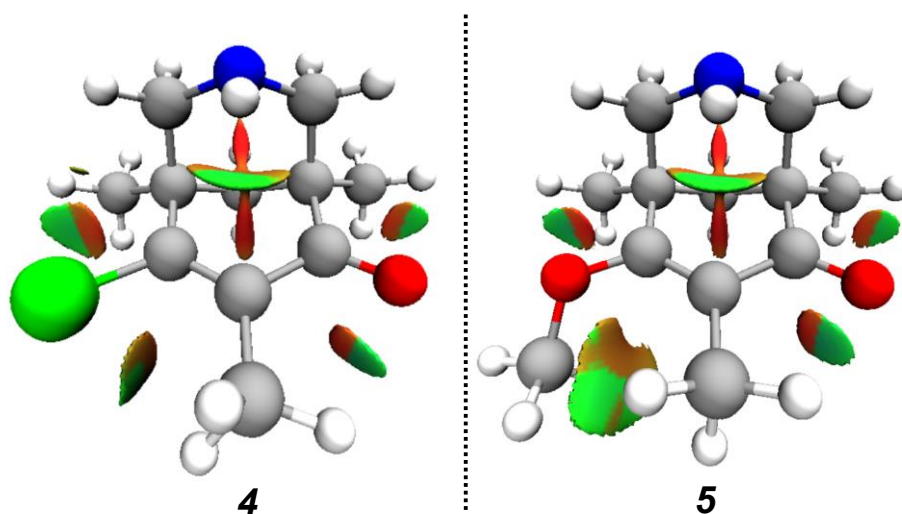


Figure 1. NCI index plots (blue, strong attraction; green, weak interaction; red, strong repulsion; isovalue = 0.5) of structures **4** and **5**.

Basicity of Amine and π -system

If, on the other hand, through-bond effects are important for the stabilities in acid of **4** and **5**, we would expect to see a significant difference in computed basicity for the amine, the most basic site of **4** and **5**. The strong basicity of the amine relative to other groups is reflected in our computed basicities below: in Figures 2a and 2b when R = H, the basicities of the amine and ketone are -61.7 and -45.7 kcal mol⁻¹, respectively.

Both **4** and **5** have local amine functionality and local vinylogous carbonyl derivative functionality. But these local functional groups may communicate with each other by through-bond orbital effects. If this is the case, we would expect to observe changes in amine basicity upon changing the substituent at carbon 6 (C6, Scheme 1); it would not be the first time amine basicity is influenced by remote, neighboring functionality.^{72,73} Figure 2a shows the results of our amine basicity calculations with different C6 substituents plotted against their Hammett σ_{para} constants, which reflect the π electron-donating and -withdrawing ability of R.^{74,75} Though the range of basicity (ca. 10 kcal mol⁻¹) for the amine pales in comparison to the range of computed basicity for the ketone (Figure 2b, ca. 30 kcal mol⁻¹), the correlation in Figure 2a ($R^2 = 0.88$) with σ_{para} values suggest that the amine lone pair is sensitive to the nature of the R group, an observation consistent with a through-bond interaction. Additionally, the difference in basicity values between **4** and **5**, a $\Delta\Delta E = 5.3$ kcal mol⁻¹, suggests that a Cl at C6 (**4**) makes the amine notably less basic than when a methoxy group is at C6 (**5**).

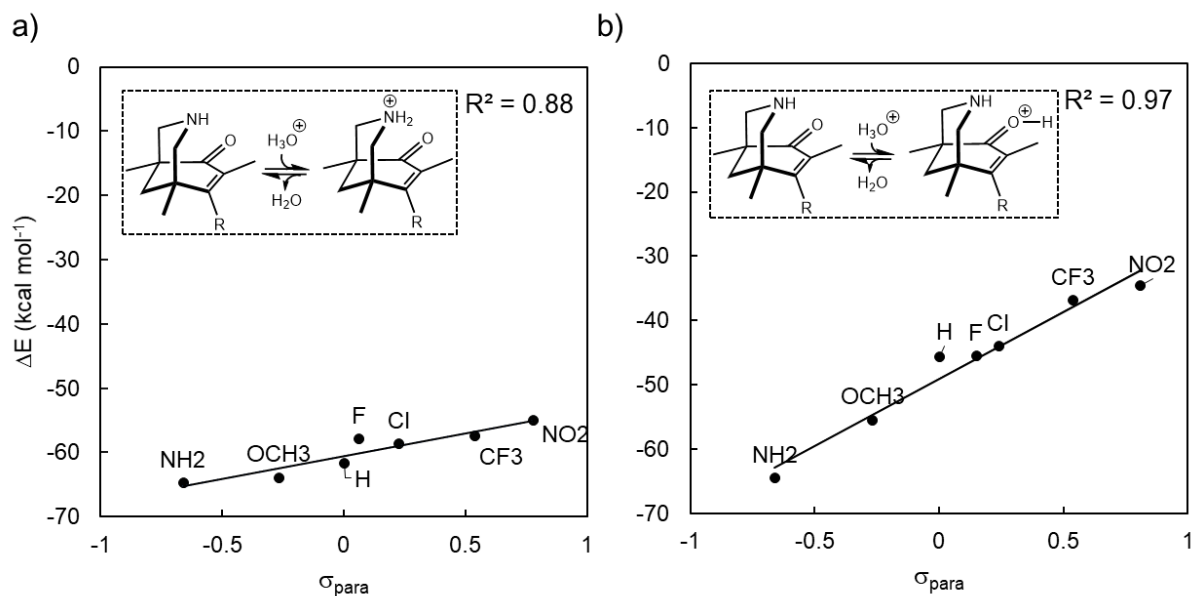


Figure 2. Relationship between R substituent σ_{para} constant and (a) basicity of nitrogen (slope = 7.0) and (b) basicity of carbonyl oxygen (slope = 20.8). The energy (ΔE) axis range in both plots is kept consistent for easy comparison.

The same basicity analysis was applied to the ketone group (Figure 2b). Oxygen basicities are highly correlated with the Hammett σ_{para} value ($R^2 = 0.97$), and more sensitive to R (slope = 20.8 versus slope = 7.0 in Figure 2a), as expected. Compound **5** (R = OCH₃) has a greater ketone oxygen basicity than that of **4** (R = Cl): ΔE 's = -55.5 kcal mol⁻¹ and -44.1 kcal mol⁻¹ for **5** and **4**, respectively. The greater basicity of **5** likely contributes to its greater instability in acidic solution by promoting its activation as an electrophile.

One could consider the above discussion of data up until this point being also consistent with a through-space interaction between the R group and the amine group. But, as we argue in subsequent sections, through-space interactions make up only a minor role in comparison. While we acknowledge it is difficult to decouple through-bond and through-space interactions

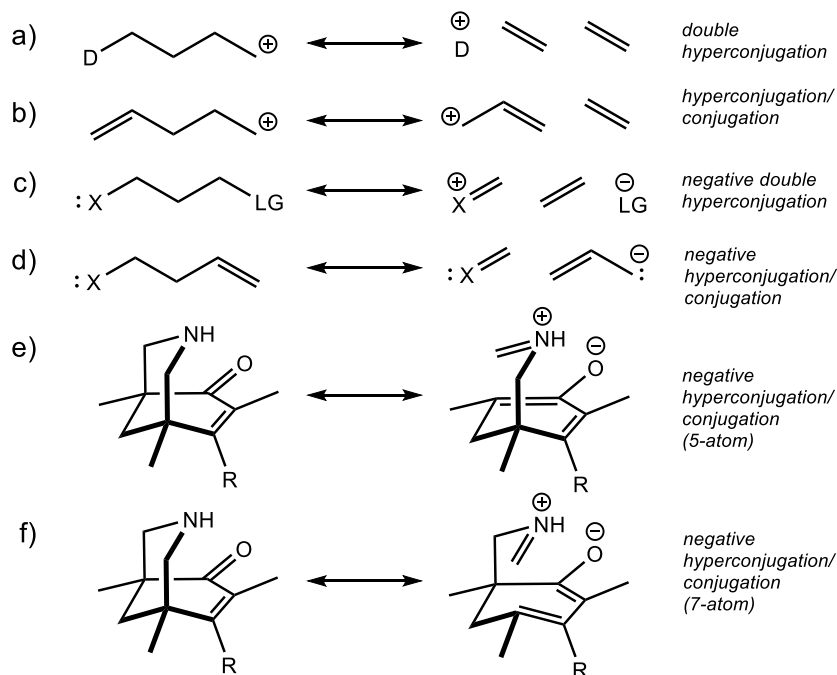
completely, the lack of clear evidence from NCI analysis for through-space interactions, and ample evidence of through-bond interactions, led us to arrive at the considerable role of through-bond interactions in this particular system (*vide infra*).

It Takes Two to Tango—Hyperconjugation/Conjugation Effects

How exactly does changing R influence the basicity of the amine? We surmised based on past literature on 1-azaadamantanones (such as **1**), the precursor to intermediates **4** and **5**, that through-bond interactions may be the major means of modulating amine basicity.^{76,77} Despite the nitrogen lone pair being two bonds away from the carbonyl, it still participates in an interaction resembling that of double hyperconjugation or hyperconjugation/conjugation (Scheme 2).^{78,79} In this particular case, the nitrogen lone pair in 1-azaadamantanones donates electron density into the σ^* orbital of the adjacent C–C bond, while simultaneously, the σ orbital of the C–C bond donates electron density into the $\pi^*_{\text{C=O}}$ (Scheme 2e and 2f).⁸⁰ Both double hyperconjugation (distinct from “two-way” hyperconjugation⁸¹) and hyperconjugation/conjugation are examples of remote stereoelectronic effects inextricably linked by a mediating single-bond bridge, and ample examples of their effects on organic structure and reactivity are documented.^{11,82–86} If intermediates **4** and **5** indeed exhibit through-bond communication between the nitrogen lone pair and the enone substructure, we would expect computed basicities to be sensitive to R’s identity, and that is what is observed (Figure 2).

Scheme 2. Select types of extended hyperconjugation (see ref. 11, Ch. 8 for an in-depth discussion of remote stereoelectronic effects). a) double hyperconjugation, b)

hyperconjugation/conjugation, c) negative double hyperconjugation, d-f) negative hyperconjugation/conjugation



Natural Bond Orbital Analysis

To further explore the possibility of through-bond effects, we computed second-order perturbation NBO energies, an analysis often used to quantify the strength of hyperconjugative donor-acceptor orbital interactions.²⁰ Second-order perturbation NBO energy ($E(2)$, equation 5) analysis measures donor-acceptor electron delocalization that results from filled orbitals interacting with unfilled, antibonding orbitals.⁸⁷ In equation (5), n_σ is the population of σ donor orbitals, F_{ij} is the Fock matrix element between orbitals i and j , and ϵ_σ and ϵ_{σ^*} are the energies of σ and σ^* natural bond orbitals (if, for example, one is computing $E(2)$ energies between σ and σ^* orbitals).

$$E(2) = -n_{\sigma} \frac{\langle \sigma | F | \sigma^* \rangle^2}{\varepsilon_{\sigma^*} - \varepsilon_{\sigma}} = -n_{\sigma} \frac{F_{i,j}^2}{\Delta E}. \quad (5)$$

If through-bond effects are relevant to the stability of **4** and **5**, then we would expect to observe qualitative trends in $E(2)$ NBO energies. Figure 3 plots $E(2)$ NBO energies with Hammett σ_{para} values. In the first case (Figure 3a), sums of $E(2)$ values associated with hyperconjugation from $n_{\text{N}} \rightarrow \sigma_{\text{C-C}}^*$ of both adjacent C–C sigma bonds are plotted against σ_{para} values. A weak correlation ($R^2 = 0.66$) suggests that as the electron-withdrawing ability of the R substituent increases, donation into $\sigma_{\text{C-C}}^*$ antibonding orbitals slightly increases ($\sim 1 \text{ kcal mol}^{-1}$ increase in $E(2)$). In other words, through-bond communication between the nitrogen lone pair and R is non-negligible. The sum of $E(2)$ values corresponding to $n_{\text{N}} \rightarrow \sigma_{\text{C-H}}^*$ hyperconjugation interactions (Figure 3b) are slightly better correlated ($R^2 = 0.72$) with respect to σ_{para} values, but smaller in magnitude (at most, $7.1 \text{ kcal mol}^{-1}$ when $\text{R} = \text{NO}_2$) because $\sigma_{\text{C-H}}^*$ orbitals are worse acceptors, in part, due to their poor orientation for good orbital overlap with respect to the nitrogen lone pair. No correlation between the sum of $E(2)$ values corresponding to $\sigma_{\text{C-C}} \rightarrow \pi_{\text{C=C}}^*$ and $\sigma_{\text{C-C}} \rightarrow \pi_{\text{C=O}}^*$ donor-acceptor interactions and σ_{para} values is observed (Figure 3c). To ensure our NBO analyses were reasonable, we checked whether a correlation is observed between the $\pi_{\text{C=C}} \rightarrow \pi_{\text{C=O}}^*$ donor-acceptor interaction (Figure 3d). Indeed, a strong, negative correlation ($R^2 = 0.90$) exists, which is consistent with electron-withdrawing groups weakening a $\pi_{\text{C=C}} \rightarrow \pi_{\text{C=O}}^*$ interaction.

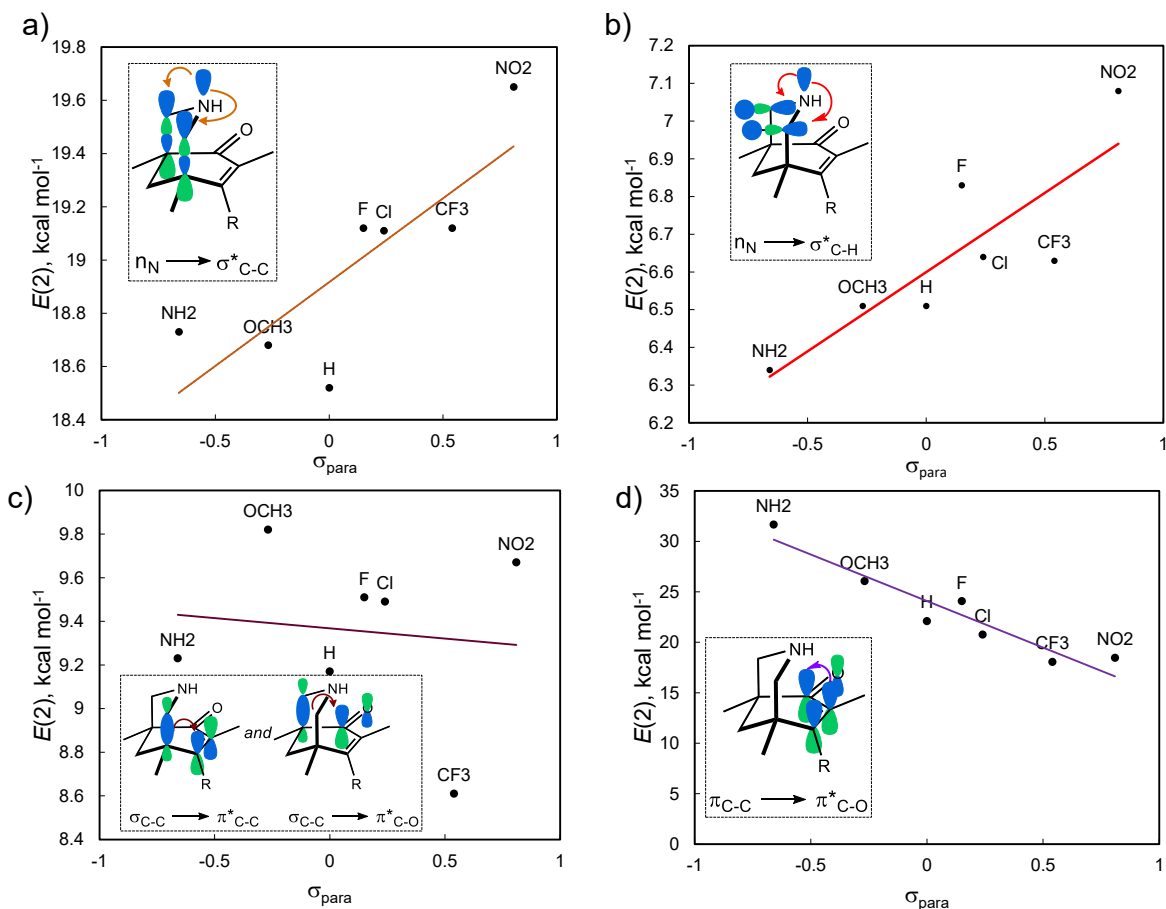


Figure 3. Correlations of second-order perturbation NBO energies, $E(2)$, and Hammett parameter, σ_{para} (proxy for electron-donating and -withdrawing ability of substituent, R). Shown are correlations of $E(2)$ values associated with a) sum of negative hyperconjugation interactions of $n_{\text{N}} \rightarrow \sigma^*_{\text{C-C}}$ of adjacent C-C sigma bonds ($R^2 = 0.66$), b) sum of negative hyperconjugation interactions of $n_{\text{N}} \rightarrow \sigma^*_{\text{C-H}}$ of adjacent C-H sigma bonds ($R^2 = 0.72$), c) sum of $\sigma_{\text{C-C}} \rightarrow \pi^*_{\text{C=C}}$ and $\sigma_{\text{C-C}} \rightarrow \pi^*_{\text{C=O}}$ interactions ($R^2 = 0.01$), and d) $\pi_{\text{C=C}} \rightarrow \pi^*_{\text{C=O}}$ interaction ($R^2 = 0.90$).

In Figure 3a, we observe a slight correlation with the *sum* of $E(2)$ values and π electron-donating and -withdrawing ability, but are the $n_{\text{N}} \rightarrow \sigma^*_{\text{C-C}}$ interactions with adjacent C–C σ -

bonds *evenly distributed between the two bonds*? The range of $E(2)$ values in Figure 4a for the component associated with the “proximal” donor-acceptor interaction (proximal to the R group) is effectively the same as that in 4b for the “distal” interaction (distal to the R group), ~ 0.7 kcal/mol, consistent with an evenly delocalized nitrogen lone pair into (seemingly indistinguishable) empty antibonding orbitals. However, we find that there is no correlation ($R^2 = 0.14$) with respect to the proximal $n_N \rightarrow \sigma_{C-C}^* E(2)$ energy (Figure 4a) and an excellent correlation ($R^2 = 0.98$) with respect to the distal $n_N \rightarrow \sigma_{C-C}^* E(2)$ energy (Figure 4b). The origin of this difference appears to be related to the other partner in the hyperconjugation/conjugation array, i.e., the α,β -unsaturated carbonyl. We observe an unequal distribution of $E(2)$ values for donation from C–C bonds into adjacent π^* -antibonding orbitals, with greater $E(2)$ values for the distal interaction ($\sigma_{C-C} \rightarrow \pi_{C=O}^*$, Figure 4d) than the proximal interaction ($\sigma_{C-C} \rightarrow \pi_{C=C}^*$, Figure 4c), consistent with $\pi_{C=O}^*$ being a better acceptor than is $\pi_{C=C}^*$. In short, the carbonyl modulates communication between the substituent and the distal C–C bond.

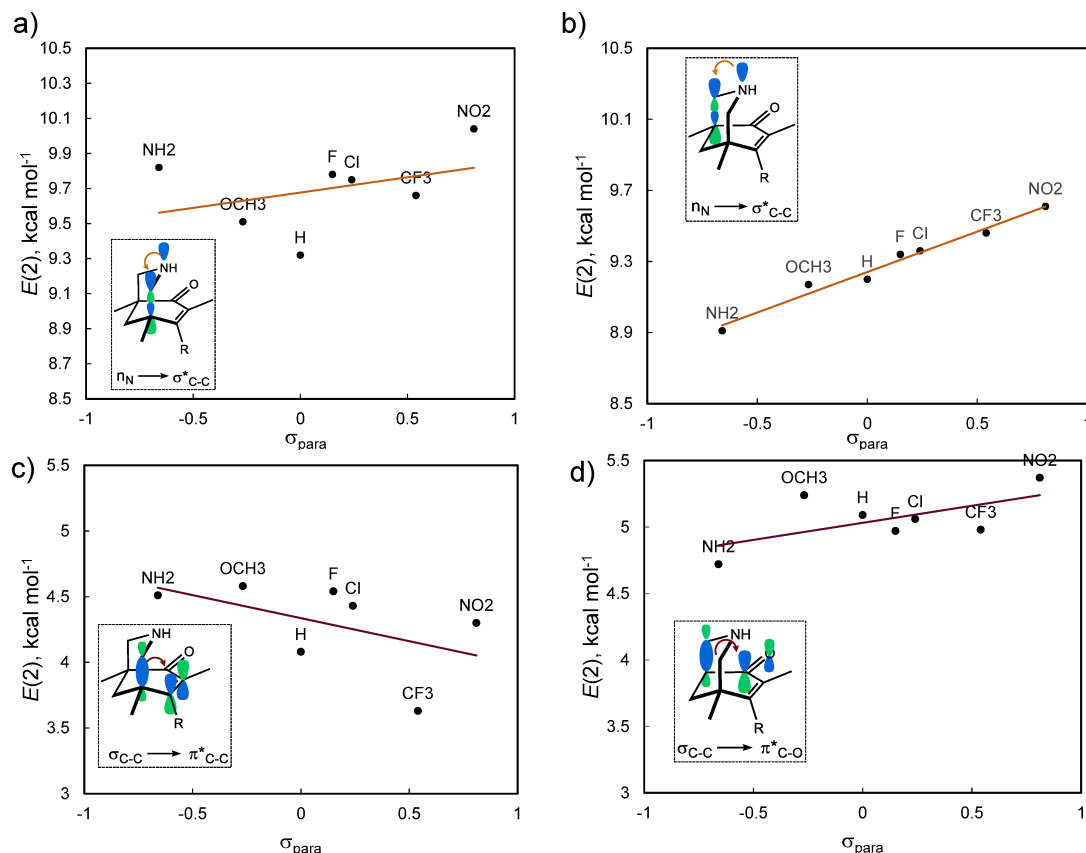


Figure 4. Correlations of second-order perturbation NBO energies, $E(2)$, and Hammett parameter, σ_{para} (a measure for electron-donating/-withdrawing ability of substituent, R). Shown are correlations of $E(2)$ values associated with a) $n_N \rightarrow \sigma^*_{C-C}$ interaction of proximal C-C sigma bonds ($R^2 = 0.14$), b) $n_N \rightarrow \sigma^*_{C-C}$ interaction of distal C-C sigma bonds ($R^2 = 0.98$), c) $\sigma_{C-C} \rightarrow \pi^*_{C=C}$ interaction of proximal C-C sigma bond with $\pi^*_{C=C}$ of enone ($R^2 = 0.25$) and d) $\pi_{C=C} \rightarrow \pi^*_{C=O}$ interaction of distal C-C sigma bond with $\pi^*_{C=O}$ of enone ($R^2 = 0.36$).

Isodesmic Reactions

To isolate key stereoelectronic effects, thermochemical data derived experimentally or computationally are often used in hypothetical reactions (e.g., isogyric, isodesmic,

hypohomodesmotic, homodesmotic, hyperhomodesmotic).⁸⁸ These reactions can provide useful information for deducing how strong a delocalizing stereoelectronic effect is, but they are challenging to implement in practice because achieving an “ideal” reaction requires careful balancing of changes in bond type, charge, hybridization, and steric effects.²⁰ Often, changing a portion of a molecule to probe an effect introduces additional, sometimes undesirable interactions. Figure 5, for example, shows simple isodesmic reactions that switch the lone pair position from equatorial to axial (i.e., **4** → **4'** and **5** → **5'**; **4'** and **5'** are examples of concave bases⁸⁹), a transposition that introduces a $\sigma_{\text{N-H}} \rightarrow \sigma^*_{\text{C-C}}$ interaction at the expense of a $n_{\text{N}} \rightarrow \sigma^*_{\text{C-C}}$ interaction—for both **4** and **5**, the reaction is uphill by at least 1 kcal mol⁻¹. Though this hypothetical reaction seems like a reasonable method for acquiring a qualitative measure of the energetic stabilization due to nitrogen lone pair hyperconjugation, by switching the lone pair's position, we also introduce possible through-space effects between the n_{N} and the π -system (*vide supra*). Like any isodesmic reaction, this one has flaws: the best we can do is asymptotically approach the ‘ideal’ isodesmic reaction.

The energies from Figure 5 reveal that **4'** and **5'** are only 1 to 1.5 kcal mol⁻¹ higher in energy than **4** and **5**, respectively, which suggests that we cannot ignore the relevance of this conformation and possible concomitant through-space interactions contributing to the experimental observation discovered by Risch. However, NCI (SI Figure S3) and NBO analysis on **4'** and **5'** did not provide cogent evidence that through-space effects predominate.

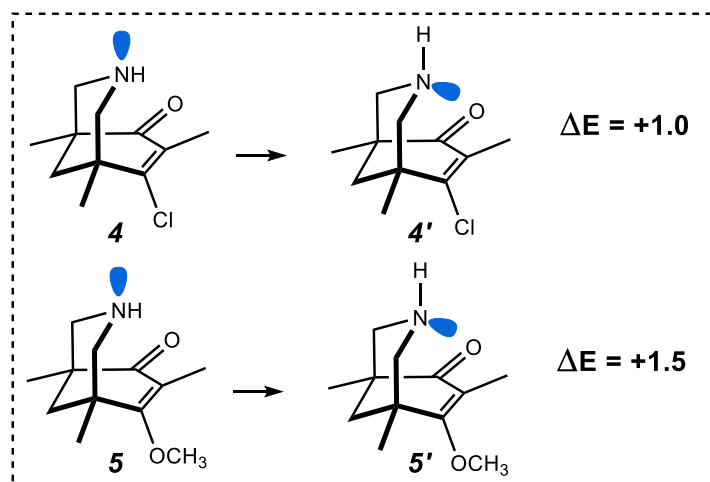


Figure 5. Isodesmic reaction. Amine inversion: lone pair from equatorial (**4** and **5**) to axial position (**4'** and **5'**).

So far, through-*bond* effects appear responsible for **4** and **5**'s kinetic stability in acid, and we have yet to uncover evidence to counter this model. What other isodesmic reactions might we interrogate that would convince us otherwise? Replacing the amine with a methylene (CH_2) group would, in principle, take away any energetic stabilization from the amine lone pair participating in hyperconjugation/conjugation (Figure 6). To keep each side balanced, we added a cyclohexane chair and a piperidine chair on the left and right-hand side, respectively. The ΔE for this reaction is, roughly, a measure of the *difference* between having amine lone pair hyperconjugative stabilization and $\sigma_{\text{C-H}} \rightarrow \sigma^*_{\text{C-C}}$ stabilization from a methylene group, but note that through-space interactions between the π -system and N–H versus C–H bonds are also present (although hopefully not significantly different). Taken together, the reactions shown in Figures 5 and 6a indicate that the net stabilization energy imparted by $n_{\text{N}} \rightarrow \sigma^*_{\text{C-C}}$ interactions in the context of other intermolecular interactions is likely on the order of 1 kcal mol^{-1} for both **4** and **5**, and slightly more so for the latter.

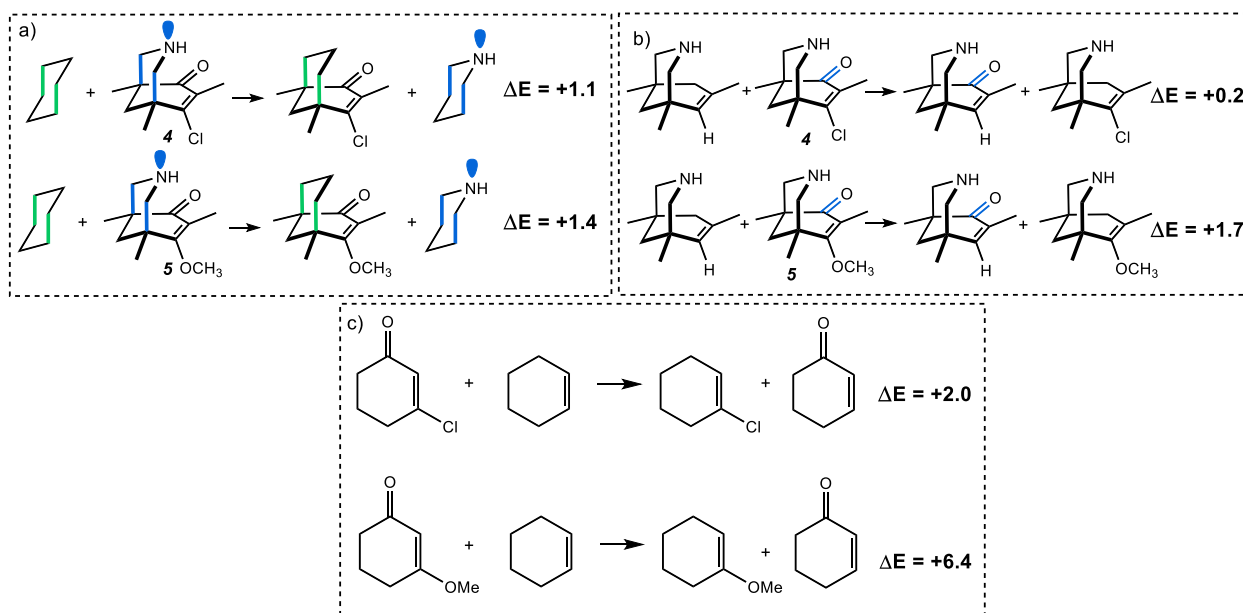


Figure 6. Isodesmic reactions. a) Difference in stabilization energy due to amine lone pair versus C-H hyperconjugation into $\sigma^*_{\text{C-C}}$ antibonding orbital for **4** and **5**. b) and c) “Deletion” of ketone functionality.

Is there an isodesmic reaction that measures the stabilization energy associated with the carbonyl group of the enone? Figure 6b shows that “deleting” the carbonyl group in **4** costs almost nothing (+0.2 kcal mol⁻¹), while “deleting” the carbonyl group in **5** imposes a 1.7 kcal mol⁻¹ energetic penalty, a reasonable reflection of the energetic stabilization due to a donor group at the β position of a carbonyl group. Carbonyl deletion also affects an additional, intertwined stereoelectronic effect: the so-called ‘vinylogous anomeric effect’¹¹ (VAE, originally named the ‘allylic effect’⁹⁰), which results from the in-plane carbonyl oxygen lone pair interacting with the $\sigma^*_{\text{C-R}}$ orbital through the intervening C-C π bond. Contrasting these results to those in Figure 6c suggest that the amine in the bicyclic molecule attenuates the cost imposed by ketone “deletion”,

consistent with the amine reducing the electrophilicity of the carbonyl group via the through-bond interaction described above (here the VAE is still present), i.e., without the amine present, the communication between the Cl/OCH₃ and the carbonyl group through the intervening π -bond is stronger and the penalty for losing that communication is larger (see SI Figure S4 for additional computed isodesmic reactions).

A Closer Look—Trends in Basicity and Hydration Propensity

That the ketone oxygen is more basic in **5** than in **4**, and more sensitive to the substituent at the C6 position, is corroborated by the data in Figure 2b. This result is not surprising. Changes to amine basicity (Figure 2a) were less obvious at the outset, however. Though changes to amine basicity with substituents at the carbonyl β -position are smaller than those to the carbonyl itself, they are substantial (cf. Figure 2). As the electron-withdrawing ability of the C6 substituent increases, the amount of through-bond lone pair delocalization increases (approximated with $E(2)$ in kcal mol⁻¹), and the amine basicity is curtailed (Figure 7).

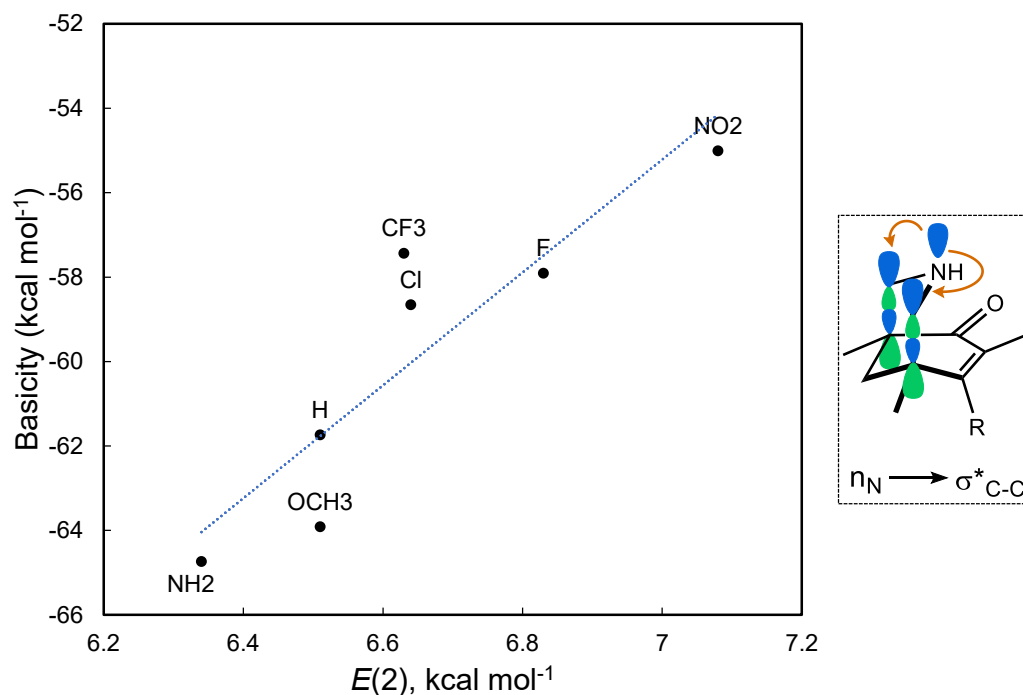
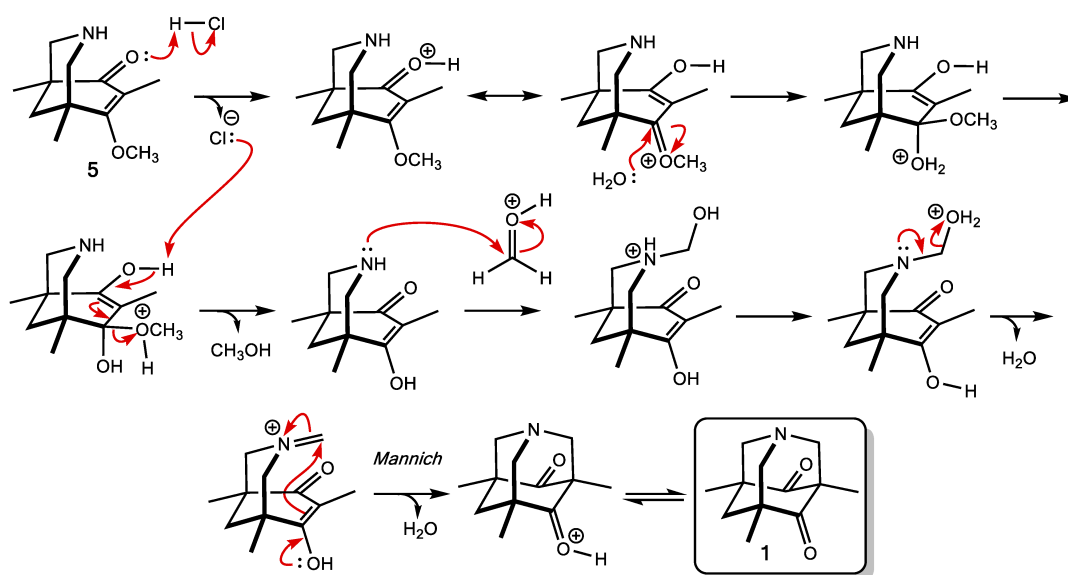


Figure 7. Relation of amine basicity to sum of $E(2)$ NBO energies from $n_N \rightarrow \sigma^*_{C-C}$ interaction; $R^2 = 0.80$.

An increased propensity for carbonyl protonation in **5** versus **4** should lead to increased electrophilicity, more facile attack by water, and more rapid hydrolysis (Scheme 3). But might an increased amine basicity have a similar effect? Covalent hydration propensities ($\ln K_{\text{hyd}}$) were computed for C6-substituted systems with and without the amine protonated to estimate their reactivity towards water in the hydrolysis from **5** to **6** (Scheme 3). The more positive $\ln K_{\text{hyd}}$, the greater the equilibrium lies toward the hydrate, suggesting a greater propensity to be attacked by water.

Scheme 3. Plausible mechanism from **5** to **1** through hydrolysis and a Mannich reaction.⁴⁸



Three hydration sites were considered, for both neutral and *N*-protonated forms of **4** and **5** (a total of six hydration scenarios; see SI Figure S5 for details): (a) hydration at the carbonyl carbon, (b) hydration at C6 (β -position) resulting from water addition from the “bottom” face (i.e., distal with respect to the amine), and (c) hydration at C6 resulting from water addition from the “top” face (i.e., proximal with respect to the amine). In all scenarios, *N*-protonated versions showed overall greater hydration propensities than their non-protonated counterparts. Electron-withdrawing groups at C6 also showed greater hydration propensities (e.g., Figure 8; see SI for other scenarios).

For **4** and **5**, whether hydration is favored at the carbonyl carbon or the β -carbon depends on C6 substitution. In the case of **4**, when the amine is protonated, hydration propensities at all possible sites are approximately equal ($\ln K_{\text{hyd}} \sim 24$). For **5**, when the amine is protonated, hydration at the β -carbon resulting from “bottom” face attack by water (the face distal with respect to the amine) is most favored ($\ln K_{\text{hyd}} = 23.5$). Thus, we proposed a mechanism in Scheme 3 wherein water attacks the β -carbon from the “bottom” face ($\ln K_{\text{hyd}}$ for “top” face water attack

is 17.9). For this hydration scenario, *N*-protonation makes the hydration propensity for **4** ($\ln K_{\text{hyd}} = 23.7$) and **5** about equal ($\ln K_{\text{hyd}} = 23.5$; Figure 8)! An equal susceptibility for water attack such as this is not present when the amines of **4** and **5** are not protonated (see SI, Figure S8); in fact, in that case, **4** is *more* likely to be hydrated ($\ln K_{\text{hyd}} = 10.9$ for **4** versus 7.2 for **5**). In acid, however, the amines are likely protonated.

These hydration propensity results add yet another explanatory (albeit complex) layer to the mix: that is, despite hydration propensities for **4** and **5** being equal once their amines are protonated, **5**'s amine is *more* basic (Figure 7), hence more vulnerable to protonation and subsequent water attack. This result is consistent with the experimental observation that **5** is less kinetically stable under acidic conditions. Though we hesitate to single out any one property responsible for the stability of these molecules, the data is consistent with one overriding message: *through-bond interactions modulate the reactivity of both the amine and enone components of 4 and 5*.

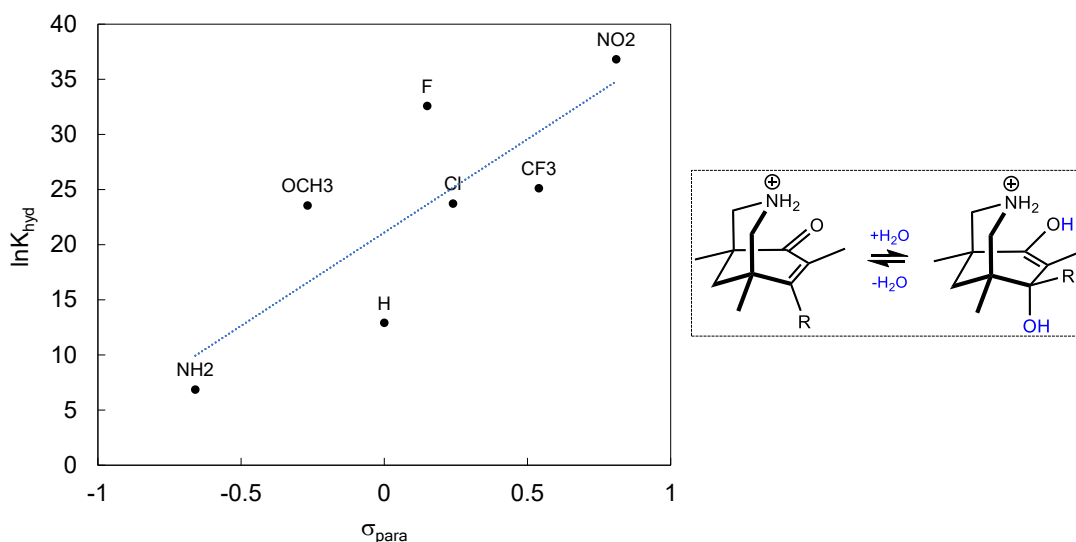


Figure 8. Hydration propensities ($\ln K_{\text{hyd}}$) increase as electron-withdrawing ability of R increases. The greater $\ln K_{\text{hyd}}$ the greater the energetic driving force to be hydrated by H_2O ; $R^2 = 0.63$.

THE UPSHOT—A MODEL FOR THROUGH-BOND EFFECTS IN 3-AZABICYCLO[3.3.1]NONANES

So, why is **5** unstable in acidic solution and **4** stable? First, it should be emphasized, as was stressed in a recent review article by Alabugin et al.,⁵² that “molecular stability always depends on multiple factors. Singling one out of many can be misleading – unless there is a reason.” In this study, we singled out particular stereoelectronic interactions to decide if the strengths of these interactions correlated with the π -donating/withdrawing ability of the substituent at C6. While correlation does not equate to causation,⁹¹ the data gathered up to this point allow us to suggest a working model rooted in through-bond effects. This model hinges on the reactivity of *both* the more-basic amine nitrogen *and* the less-basic ketone oxygen, which communicate with each other through intermediary σ -bonds. This study highlights the importance of remote through-bond effects (specifically, negative hyperconjugation/conjugation) in organic reactivity, an area still rich in opportunity for discovery. To not overlook (or underestimate) the importance of such interactions could make the difference between achieving a working model for explaining divergent reactivity of two (or more) molecules and being left in the dark.

ASSOCIATED CONTENT

Supporting Information. Supporting Data and Figures; Energies and Frequencies of Computed Structures (PDF).

A data set collection of computational results, including geometries and structure coordinates, is available in the ioChem-BD repository and can be accessed via <https://doi.org/10.19061/iochem-bd-6-120>

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