

Why Are Esters and Amides Weaker Carbon Acids than Ketones and Acid Fluorides? Contributions by Resonance and Inductive Effects

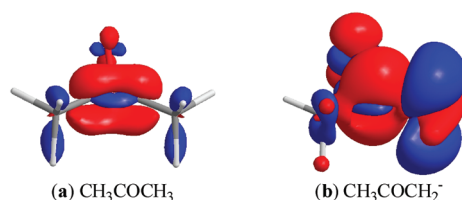
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Electron density difference (EDD) maps showing π resonance in



Two computational methodologies—a vinylogue extrapolation methodology and a block localized wave function (BLW) methodology—were employed to determine the contributions by resonance and inductive effects toward the gas-phase deprotonation enthalpies at the α carbons of acetone, acetamide, acetic acid, and acetyl fluoride, which were taken to be model compounds for ketones, amides, esters, and acid fluorides, respectively. Results from the vinylogue methodology suggest that resonance serves to enhance the gas-phase deprotonation enthalpy of a ketone by 34.3 kcal/mol, an amide by 26.2 kcal/mol, an ester by 30.5 kcal/mol, and an acid fluoride by 30.8 kcal/mol. Comparably, the BLW methodology suggests those numbers to be 42.3, 31.2, 36.1, and 39.7 kcal/mol, respectively. Results from the vinylogue methodology suggest that inductive effects serve to enhance the gas-phase deprotonation enthalpy of a ketone by 11.8 kcal/mol, an amide by 12.7 kcal/mol, an ester by 15.5 kcal/mol, and an acid fluoride by 26.0 kcal/mol, and in the same order, those numbers suggested by the BLW methodology are 3.0, 6.2, 8.5, and 16.3 kcal/mol.

Introduction

Alkanes are among the weakest acids known, owing to the relatively small size and low electronegativity of the carbon atom. Ethane, for example, has a pK_a value of about 50 in solution, and its gas-phase acidity (ΔG^0_{acid}) measures¹ 411.7 ± 2.1 kcal/mol ($\Delta H^0_{\text{acid}} = 420.1 \pm 2.0$ kcal/mol). By contrast, a carbon acid is much stronger when the carbon atom is α to a carbonyl group. An example is acetone, whose pK_a value is 19.3² and whose ΔG^0_{acid} is 361.9 ± 2.0 kcal/mol ($\Delta H^0_{\text{acid}} = 369.1 \pm 2.1$ kcal/mol).³ This stronger acidity is extremely important in organic chemistry because it allows α carbons to be deprotonated rather easily, producing enolate anions—enolate anions are strong carbon nucleophiles that are key

intermediates in a number of staple organic reactions, including α halogenations, α alkylations, and aldol condensations. Thus, it becomes important to understand precisely why α carbons are dramatically more acidic than alkane carbons.

The two main factors that contribute to the enhanced acidity of an α carbon are resonance effects and inductive effects. Resonance allows the negative charge to be delocalized over both the α carbon and the carbonyl oxygen (Figure 1a), which decreases the concentration of negative charge that develops, and therefore lowers the energy of the enolate anion. Inductive effects, on the other hand, arise from the relatively high electronegativity of the carbonyl oxygen. Thus, electron density is drawn away from the α carbon through the bonds that connect the carbonyl oxygen to the α carbon (Figure 1b). This decrease in charge concentration on the α carbon also contributes to the stability of the enolate anion.

Although it is understood that resonance and inductive effects both contribute to the enhancement of an α carbon, it is intrinsically difficult to distinguish them at the ab initio

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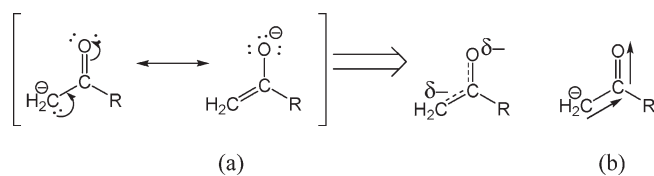


FIGURE 1. (a) Resonance structures of the enolate anion of a ketone are shown inside the square brackets. The resonance hybrid is shown to the right of the brackets, illustrating that the negative charge in the enolate anion is shared over both the α carbon and the carbonyl oxygen. (b) Inductive effects in the enolate anion of a ketone. The relatively high electronegativity of the oxygen atom draws electron density away from the α carbon.

level. The present study actually is very similar to the controversy over the origin of the enhanced acidity of carboxylic acids compared to aliphatic alcohols. While conventionally π electron delocalization was claimed to be the culprit,⁴ this explanation was challenged by Siggel et al.,^{5,6} who attributed the difference in acidity to electrostatic interactions. The controversies continued^{7–9} due, in large part, to the lack of absolute data to support either side. A significant leap forward in our understanding of the issue, however, came with the study by Hiberty and Byrman,¹⁰ who used ab initio valence bond (VB) calculations to directly determine the stabilization energy due to π electron delocalization in the carboxylate anion. Similarly, one of our main goals of this paper is to quantify the contributions by both resonance and inductive effects in the acidity of ketones.

A second goal of this paper is to determine how those contributions are affected when a heteroatom is also attached to the carbonyl carbon, as in amides, esters, and acid fluorides. In such cases, the lone pair of electrons on the heteroatom can participate in resonance with the carbonyl group, and to the extent that it does, charge delocalization on carbon will be diminished (Figure 2a). Thus, the anion will not be as stable, and the result will be a weakening of the carbon acidity relative to a ketone. On the other hand, the electronegativity of the heteroatom is expected to increase the inductive electron withdrawal, thus contributing to a decrease in charge concentration on the α carbon and a strengthening of the carbon acidity (Figure 2b).

Rablen and Bentrup¹¹ have previously carried out a study on the contributions by resonance and inductive effects toward the gas-phase acidities of amides, esters, and acid fluorides, relative to ketones. Their aim, however, was simply to determine whether or not electrostatic effects (i.e., inductive effects) by the OR and NR₂ groups of esters and amides, respectively, contribute toward enhancing carbon acidity. Using an empirical methodology, they determined that electrostatics do indeed contribute.

The methodology that Rablen and Bentrup implemented further allowed them to quantify the resonance and inductive effects that the heteroatoms impose on carbon acidity in an amide, ester, and acid fluoride, relative to a ketone. However, we believe that their results are inaccurate.

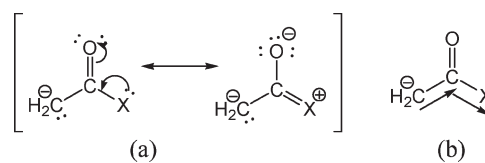


FIGURE 2. (a) In an amide ($X = \text{NR}_2$), ester ($X = \text{OR}$), or acid fluoride ($X = \text{F}$), the lone pair of electrons on the heteroatom can participate in resonance with the carbonyl group. To the extent that it does, charge delocalization on carbon will be diminished. (b) The relatively high electronegativity of the heteroatom draws electron density away from the α carbon, which helps decrease the concentration of negative charge.

Namely, the inductive effects they proposed for all three species are overestimated, most substantially by a factor of about 2 for esters. Also, the resonance effects they put forth for esters and acid fluorides are too high by a factor of about 2–3. Moreover, we believe that their results incorrectly suggest that the resonance effect by the heteroatom in an ester is greater than that by the nitrogen atom in an amide.

Our above assertions stem from two fundamentally different computational methodologies we have employed in this study—a vinyllogue extrapolation methodology and a block-localized wave function methodology (both methodologies will be described below). These methodologies agree that resonance serves to strengthen ketones, amides, esters, and acid fluorides as carbon acids by 34–42, 26–31, 31–36, and 31–40 kcal/mol, respectively, relative to alkanes. Inductive effects also serve to strengthen these compounds as carbon acids by 3–12, 6–13, 9–16, and 16–26 kcal/mol, respectively, relative to alkanes. Relative to ketones, resonance in amides, esters, and acid fluorides serves to *weaken* the acids by 8–11, 4–6, and 3–4 kcal/mol, respectively, whereas inductive effects serve to *strengthen* the acids by about 1–3, 4–6, and 13–14 kcal/mol, respectively. Overall, then, amides are weaker acids than ketones, primarily due to resonance, whereas acid fluorides are stronger acids than ketones, primarily due to inductive effects. The two effects are similar in esters, giving esters and ketones similar acid strengths.

Computational Methodologies

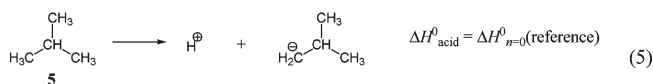
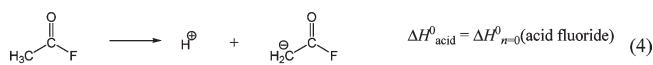
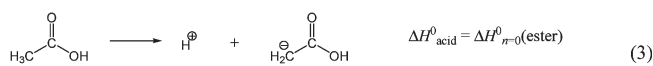
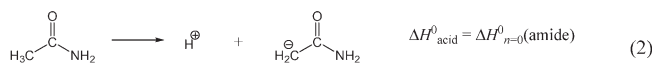
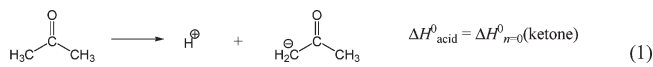
The vinyllogue extrapolation¹² and block localized wave function^{13–15} methodologies have been described in detail elsewhere. Here we simply provide general aspects of these methodologies.

Vinyllogue Extrapolation Methodology. For this study, acetone (**1**) was chosen as a representative ketone. Its deprotonation enthalpy (ΔH_{acid}^0) is the enthalpy change upon dissociation of a proton from an α carbon (eq 1), which we define as $\Delta H_{n=0}^0(\text{ketone})$. As models for an amide, ester, and acid fluoride, we chose acetamide (**2**), acetic acid (**3**), and acetyl fluoride (**4**), respectively. Although for acetamide and acetic acid the most acidic proton is on the heteroatom, we computed the gas-phase deprotonation enthalpies at the α carbon (eqs 12–14), which we define as $\Delta H_{n=0}^0(\text{amide})$, $\Delta H_{n=0}^0(\text{ester})$, and $\Delta H_{n=0}^0(\text{acid fluoride})$, respectively. We chose **2** and **3** as models for two reasons. First, these molecules, being very similar in size

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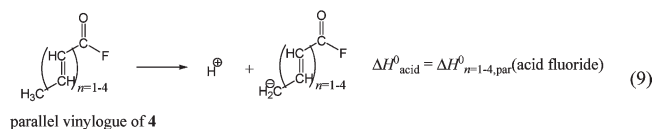
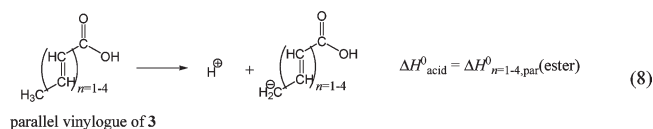
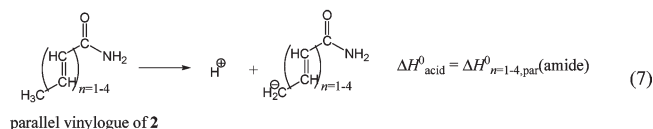
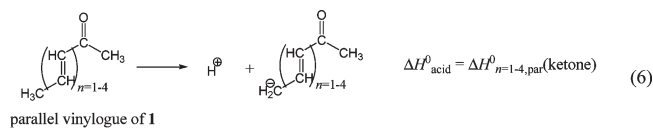
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to **1**, have similar polarizabilities as well. Polarizability matching is important in order to avoid large differences in the internal solvation of an ion, which could otherwise have a significant impact on the heat of a reaction in which it is involved.¹⁶ The second reason for choosing these molecules as models was to minimize the sizes of their corresponding vinylogues (described below) and thus minimize computational time.



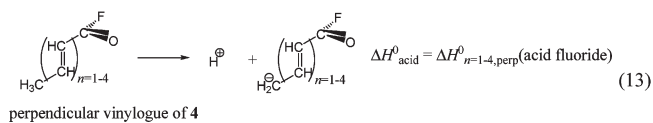
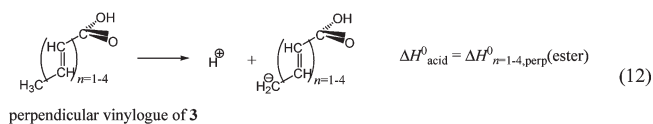
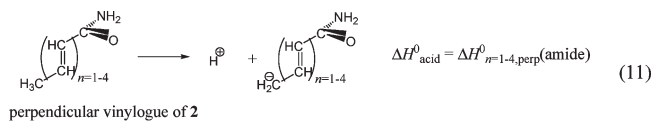
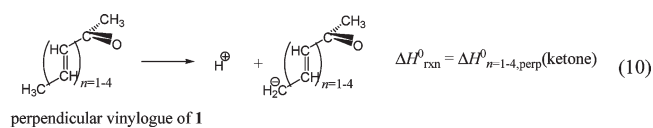
Our vinylogue methodology also requires a suitable reference molecule, which, for this study, is methylpropane (**5**). Methylpropane is similar in size and shape to **1–4**, but its gas-phase deprotonation enthalpy, which we define as $\Delta H_{n=0}^0(\text{reference})$, has essentially no contribution from resonance or inductive effects. Thus, the strengthening of **1–4** as acids, relative to **5**, corresponds to the sum of the resonance and inductive contributions toward $\Delta H_{\text{acid}}^0(\mathbf{1})$, $\Delta H_{\text{acid}}^0(\mathbf{2})$, $\Delta H_{\text{acid}}^0(\mathbf{3})$, and $\Delta H_{\text{acid}}^0(\mathbf{4})$, respectively.

Vinylogues of **1–5** were constructed by inserting up to four vinyl groups (i.e., $-\text{CH}=\text{CH}-$) between the acidic carbon and the adjacent carbon. Due to the ensuing conjugation, the vinylogues of **1–4** are most stable with the vinyl groups coplanar with the carbonyl group (eqs 6–9). These are called “parallel” vinylogues, and their gas-phase deprotonation enthalpies are denoted as $\Delta H_{n=1-4,\text{par}}^0(\text{ketone})$, $\Delta H_{n=1-4,\text{par}}^0(\text{amide})$, $\Delta H_{n=1-4,\text{par}}^0(\text{ester})$, and $\Delta H_{n=1-4,\text{par}}^0(\text{acid fluoride})$, respectively, where the value of n refers to the number of vinyl groups inserted.

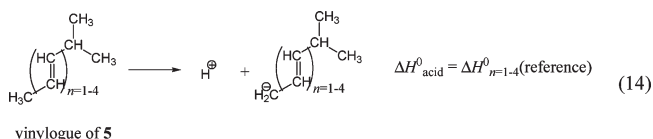


We also constructed “perpendicular” vinylogues of **1–4**, in which the vinyl chain is perpendicular to the carbonyl group (eq 10–13). Their gas-phase deprotonation enthalpies are

denoted as $\Delta H_{n=1-4,\text{perp}}^0(\text{ketone})$, $\Delta H_{n=1-4,\text{perp}}^0(\text{amide})$, $\Delta H_{n=1-4,\text{perp}}^0(\text{ester})$, and $\Delta H_{n=1-4,\text{perp}}^0(\text{acid fluoride})$, respectively.



Finally, “reference” vinylogues were constructed (eq 14). Gas-phase deprotonation enthalpies of these species are denoted $\Delta H_{n=1-4}^0(\text{reference})$.



Knowing the gas-phase deprotonation enthalpies of the various parallel, perpendicular, and reference vinylogues, we can calculate the contributions by resonance and inductive effects toward each parallel vinylogue. For example, as shown for the case of a ketone in eq 15, the resonance contribution by the carbonyl group toward the deprotonation enthalpy of a parallel vinylogue, $\text{Res}_{n=1-4}(\text{ketone})$, is the difference in deprotonation enthalpy between corresponding parallel and perpendicular vinylogues. This is because the perpendicularity excludes the carbonyl group from participating in resonance with vinyl chain, while inductive effects are maintained. On the other hand, as shown in eq 16, the carbonyl group’s inductive effect, $\text{Ind}_{n=1-4}(\text{ketone})$, is the difference in deprotonation enthalpy between corresponding perpendicular and reference vinylogues. This is because the deprotonation enthalpy of a perpendicular vinylogue includes inductive effects but not resonance effects, whereas the reference vinylogue’s deprotonation enthalpy includes neither resonance nor inductive effects.

$$\text{Res}_{n=1-4}(\text{ketone}) = \Delta H_{n=1-4,\text{par}}^0(\text{ketone}) - \Delta H_{n=1-4,\text{perp}}^0(\text{ketone}) \quad (15)$$

$$\text{Ind}_{n=1-4}(\text{ketone}) = \Delta H_{n=1-4,\text{perp}}^0(\text{ketone}) - \Delta H_{n=1-4}^0(\text{ref}) \quad (16)$$

The same relationships hold for the amide, ester, and acid fluoride vinylogues as well. Once the contributions by resonance and inductive effects are calculated for the $n = 1-4$ vinylogues, we arrive at the contributions in the parent molecule (i.e., molecules **1–4**) by extrapolation of the observed trend back to $n = 0$.

Block-Localized Wave Function (BLW) Methodology. The BLW method^{13–15} can be regarded as the simplest variant of

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the ab initio VB theory,^{17–25} which defines individual electron-localized resonance structures in terms of Heitler–London–Pauling–Slater (HLPS) functions. For example, for resonance structure L, where two electrons in orbitals φ_i and φ_j form a chemical bond (here we assume closed-shell cases, making N an even number), its HLPS can be expressed as

$$\Phi_L = N_L \hat{A} \{ (\varphi_1 \varphi_2 \varphi_3 \cdots \varphi_N) \prod_{ij} [\alpha(i)\beta(j) - \beta(i)\alpha(j)] \} \quad (17)$$

where N_L is the normalization constant and \hat{A} is an antisymmetrizer. While the overall wave function Ψ for the ground state is a superposition of all independent resonance structures, the delocalization energy can be generally “obtained by subtracting the actual energy of the molecule in question from that of the most stable contributing structure.”^{26–28} Realize that eq 17 can be expanded into $2^{N/2}$ Slater determinants; thus, the electron correlation is taken into account.

The BLW method reduces eq 17 into one Slater determinant by adopting doubly occupied (i.e., $\varphi_i = \varphi_j$ in eq 17) but block-localized molecular orbitals (BL-MOs).

$$\Phi_L = N_L \hat{A} \{ \Omega^1 \Omega^2 \cdots \Omega^K \} \quad (18)$$

Corresponding to the resonance structure L (eq 18), all primitive orbitals and electrons are partitioned into K blocks (or groups), and each MO is allowed to expand only in one block. While BL-MOs in the same block are constrained to be orthogonal, BL-MOs between different blocks are nonorthogonal. Thus, both the advantages of VB theory (nonorthogonality for chemical bonding) and MO theory (orthogonality for efficient computations) have been taken in the BLW method. In eq 18, Ω^A is a successive product of n_A occupied spin-orbitals in subgroup A:

$$\Omega^A = \psi_1^A \alpha \psi_1^A \beta \cdots \psi_{n_A/2}^A \beta \quad (19)$$

If we allow all orbitals to expand in the whole space of primitive orbitals, eq 18 will be equal to the much familiar Hartree–Fock (or Kohn–Sham with the density functional theory) wave function Ψ^{Del} , corresponding to a delocalized, adiabatic state, which is implicitly a superposition of all electron-localized states. If we choose the resonance structure L as the most stable resonance structure, the energy difference between Φ_L and Ψ^{Del} is generally defined as the delocalization energy, DE (or resonance energy, RE).

$$\text{DE} = E(\Phi_L) - E(\Psi^{\text{Del}}) \quad (20)$$

Computational Details

Vinylogue Extrapolation Methodology. All deprotonation enthalpies reported here were calculated using the Gaussian 03

software package.²⁹ Input geometries were constructed using GaussView 4³⁰ and were optimized with density functional theory (DFT) at the B3LYP level of theory³¹ using the 6-31+G* basis set. This is the same level of theory and basis set we used in our previous vinylogue studies,^{12,32,33} which have proven to be in excellent agreement with available reaction thermodynamics as well as with other resonance studies. Furthermore, we have shown that the enthalpy differences calculated at that level are in excellent agreement with those obtained at the G2 level of theory.¹²

The parallel and reference vinylogues were fully optimized, whereas the perpendicular vinylogues were optimized with the restriction that the carbonyl-containing group is perpendicular to the conjugated chain. Frequency calculations were performed on the geometry-optimized structures in order to obtain enthalpies thermally corrected to 298 K, as well as to ensure that the energy-minimized geometries were appropriate. Namely, all perpendicular vinylogues were observed to have one imaginary frequency, corresponding to the transition state for rotation about the single bond connecting the carbonyl carbon to an adjacent carbon. All other species were observed to have no imaginary frequencies.

All double bonds in the vinylogues were constructed in the *E* configuration, for two reasons. First, working with the all-*E* configuration ensures that electrostatic and steric repulsions were kept to a minimum. Second, it ensures that any errors introduced in calculating deprotonation enthalpies will largely cancel when taking enthalpy differences.

BLW Methodology. The BLW method is applied to the evaluation of stabilization energies in neutral acetone, acetamide, acetic acid, acetyl fluoride, and their corresponding deprotonated anions due to π electron delocalization. All BLW calculations were carried out at the B3LYP/6-31+G* level using a modified version of GAMESS.^{15,34}

Results

Table 1 contains the calculated gas-phase deprotonation enthalpies of **1** and its $n = 1–4$ vinylogues, along with the calculated deprotonation enthalpies of **4** and its $n = 1–4$ vinylogues. The resonance and inductive contributions by the carbonyl group toward each parallel vinylogue,

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TABLE 1. Contributions by Resonance and Inductive Effects toward the Gas-Phase Deprotonation Enthalpies of 1 and Its Vinylogues, Calculated at the B3LYP/6-31+G* Level of Theory

| n | $\Delta H_{n,\text{par}}^0$ (ketone) (kcal/mol) | $\Delta H_{n,\text{perp}}^0$ (ketone) (kcal/mol) | ΔH_n^0 (reference) (kcal/mol) | Res _{<i>n</i>} (ketone) ^a (kcal/mol) | Ind _{<i>n</i>} (ketone) ^b (kcal/mol) |
|-----|---|--|--|--|--|
| 0 | 367.1 | | 413.5 | (34.3) ^c | (11.8) ^c |
| 1 | 354.7 | 377.9 | 388.1 | 23.2 | 10.2 |
| 2 | 346.3 | 363.7 | 372.8 | 17.4 | 9.1 |
| 3 | 340.5 | 354.3 | 362.1 | 13.8 | 7.8 |
| 4 | 336.0 | 347.7 | 354.4 | 11.7 | 6.7 |

^aCalculated from eq 15. ^bCalculated from eq 16. ^cExtrapolated from the $n = 1-4$ vinylogues.

calculated according to eqs 15 and 16, are also included. The extrapolated resonance and inductive contributions to the parent molecule (see below) appear in parentheses. Analogous results for 2–4 and their corresponding vinylogues are provided in Tables 2–4, respectively.

Figures 3 and 4 are plots constructed in order to extrapolate the resonance and inductive effects in the respective $n = 1-4$ vinylogues back to $n = 0$. In Figure 3, the DFT-calculated resonance contributions are plotted against the corresponding Hückel resonance parameters, described below. In Figure 4, the natural logarithms of the inductive contributions are plotted against n .

In order to extrapolate contributions for the $n = 1-4$ vinylogues back to $n = 0$, we employed Hückel molecular orbital theory. Hückel theory is ideally suited to aid in carrying out such an extrapolation because it produces molecular orbitals of π symmetry only, excluding the σ framework. Therefore, Hückel energies derive from the delocalization of π electrons and exclude inductive effects.

Specifically, we used Hückel theory to compute what we call Hückel resonance parameters. The Hückel resonance parameter for a given n th vinylogue was calculated³⁵ as the change in total Hückel energy (in units of β) of the deprotonated $n+1$ st vinylogue when the vinyl chain is isolated from the carbonyl group—i.e., when the matrix elements that couple the carbonyl carbon to the α carbon are set to zero. In essence, then, the Hückel resonance parameter is the resonance contribution by the carbonyl group of the deprotonated $n+1$ st vinylogue toward the total Hückel energy. The reason we use the energy difference of the $n+1$ st vinylogue instead of the n th vinylogue is described elsewhere.³³ Briefly, however, it is because simple Hückel theory does not take into account charge repulsion and, therefore, increasingly overestimates relative resonance contribution as the conjugated chain becomes shorter.

We note that even though simple Hückel theory is not reliable for *absolute* energies,^{36,37} it is reliable for *relative* energies in a homologous series. For example, in UV–vis spectroscopy, the λ_{max} of linear conjugated polyalkenes, $\text{H}_2\text{C}=\text{CH}-(\text{CH}=\text{CH})_n-\text{CH}=\text{CH}_2$, tracks very well with that predicted by simple Hückel MO theory; the value of R^2 is greater than 0.99 for $n = 0-4$. Moreover, notice that in Figure 3 the lowest R^2 value is 0.996.

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TABLE 2. Contributions by Resonance and Inductive Effects toward the Gas-Phase Deprotonation Enthalpies of 2 and Its Vinylogues, Calculated at the B3LYP/6-31+G* Level of Theory

| n | $\Delta H_{n,\text{par}}^0$ (amide) (kcal/mol) | $\Delta H_{n,\text{perp}}^0$ (amide) (kcal/mol) | ΔH_n^0 (reference) (kcal/mol) | Res _{<i>n</i>} (amide) ^a (kcal/mol) | Ind _{<i>n</i>} (amide) ^b (kcal/mol) |
|-----|--|---|--|---|---|
| 0 | 375.4 | | 413.5 | (26.2) ^c | (12.7) ^c |
| 1 | 359.1 | 377.2 | 388.1 | 18.1 | 10.9 |
| 2 | 349.7 | 363.2 | 372.8 | 13.5 | 9.6 |
| 3 | 343.3 | 354.0 | 362.1 | 10.7 | 8.1 |
| 4 | 338.5 | 347.4 | 354.4 | 8.9 | 7.0 |

^aCalculated from eq 15. ^bCalculated from eq 16. ^cExtrapolated from the $n = 1-4$ vinylogues.

TABLE 3. Contributions by Resonance and Inductive Effects Toward the Gas-Phase Deprotonation Enthalpies of 3 and its Vinylogues, Calculated at the B3LYP/6-31+G* Level of Theory

| n | $\Delta H_{n,\text{par}}^0$ (ester) (kcal/mol) | $\Delta H_{n,\text{perp}}^0$ (ester) (kcal/mol) | ΔH_n^0 (reference) (kcal/mol) | Res _{<i>n</i>} (ester) ^a (kcal/mol) | Ind _{<i>n</i>} (ester) ^b (kcal/mol) |
|-----|--|---|--|---|---|
| 0 | 368.2 | | 413.5 | (30.5) ^c | (15.5) ^c |
| 1 | 354.3 | 374.8 | 388.1 | 20.5 | 13.3 |
| 2 | 345.9 | 361.2 | 372.8 | 15.3 | 11.6 |
| 3 | 340.1 | 352.3 | 362.1 | 12.2 | 9.8 |
| 4 | 335.1 | 345.9 | 354.4 | 10.8 | 8.5 |

^aCalculated from eq 15. ^bCalculated from eq 16. ^cExtrapolated from the $n = 1-4$ vinylogues.

TABLE 4. Contributions by Resonance and Inductive Effects toward the Gas-Phase Deprotonation Enthalpies of 4 and Its Vinylogues, Calculated at the B3LYP/6-31+G* Level of Theory

| n | $\Delta H_{n,\text{par}}^0$ (acid fluoride) (kcal/mol) | $\Delta H_{n,\text{perp}}^0$ (acid fluoride) (kcal/mol) | ΔH_n^0 (reference) (kcal/mol) | Res _{<i>n</i>} (acid fluoride) ^a (kcal/mol) | Ind _{<i>n</i>} (acid fluoride) ^b (kcal/mol) |
|-----|---|--|---|--|--|
| 0 | 356.7 | | 413.5 | (30.8) ^c | (26.0) ^c |
| 1 | 345.3 | 366.1 | 388.1 | 20.8 | 22.0 |
| 2 | 338.4 | 354.3 | 372.8 | 15.9 | 18.5 |
| 3 | 333.5 | 346.5 | 362.1 | 13.0 | 15.6 |
| 4 | 329.8 | 340.9 | 354.4 | 11.1 | 13.5 |

^aCalculated from eq 15. ^bCalculated from eq 16. ^cExtrapolated from the $n = 1-4$ vinylogues.

The reason Figure 4 plots the natural logarithm of the calculated inductive contribution against n is that inductive effects are generally believed to fall off exponentially with distance.^{12,38–44} Thus, the logarithm of an inductive effect is expected to fall off linearly with distance. Indeed, the lowest R^2 value in Figure 4 is 0.995.

Table 5 contains results from the BLW methodology. Resonance contributions are calculated as the difference in deprotonation enthalpy between corresponding localized and delocalized structures. Inductive contributions are calculated by subtracting the resonance contribution from the difference in deprotonation enthalpy between the delocalized structure and that of methylpropane, the reference acid.

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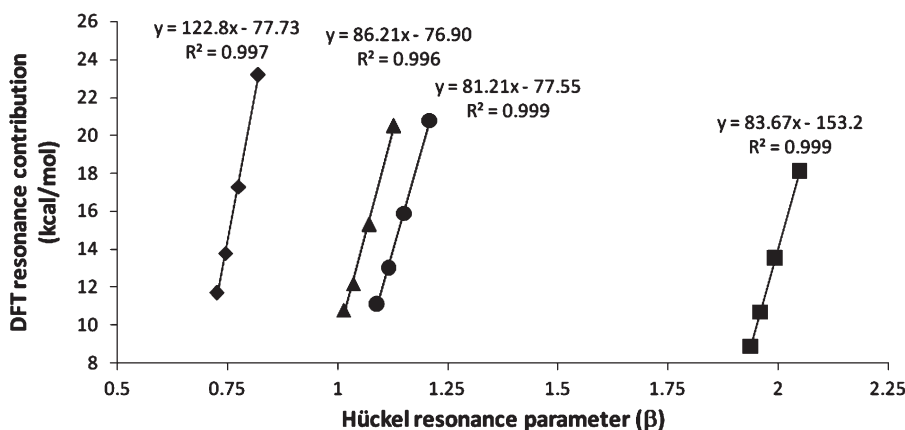


FIGURE 3. Contributions by resonance effects toward the gas-phase deprotonation enthalpies of the $n = 1-4$ vinylogues of **1-4**. Diamonds (◆) correspond to the ketone vinylogues; squares (■) correspond to the amide vinylogues; triangles (▲) correspond to the ester vinylogues; circles (●) correspond to the acid fluoride vinylogues. For each data series, n increases from right to left.

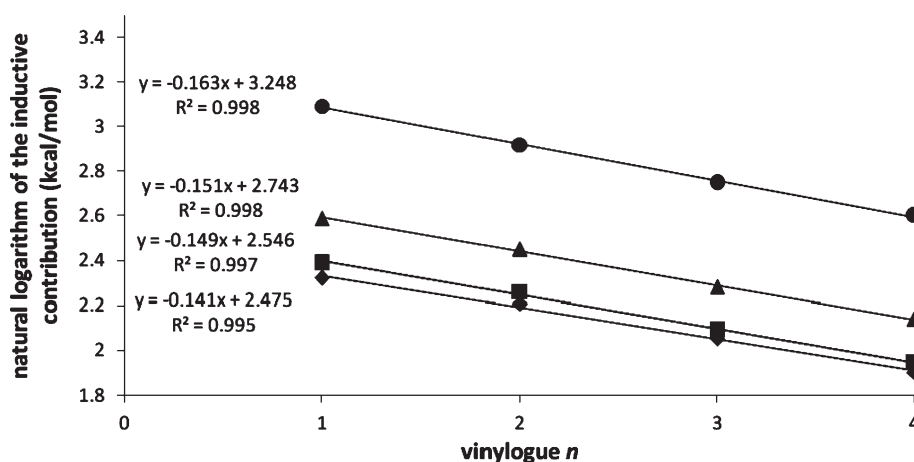


FIGURE 4. Contributions by inductive effects toward the gas-phase deprotonation enthalpies of the $n = 1-4$ vinylogues of **1-4**. Diamonds (◆) correspond to the ketone vinylogues; squares (■) correspond to the amide vinylogues; triangles (▲) correspond to the ester vinylogues; circles (●) correspond to the acid fluoride vinylogues.

TABLE 5. Calculated (B3LYP/6-31+G*) Gas-Phase Deprotonation Enthalpies of Delocalized and Localized Forms of **1-4** and the Derived Contributions by Resonance and Inductive Effects

| species | deprotonation enthalpy of delocalized structure ^a (kcal/mol) | deprotonation enthalpy of localized structure (kcal/mol) | resonance contribution (kcal/mol) | inductive contribution ^b (kcal/mol) |
|----------|---|--|-----------------------------------|--|
| 1 | 367.2 | 409.5 | 42.3 | 3.0 |
| 2 | 375.1 | 406.3 | 31.2 | 6.2 |
| 3 | 368.0 | 404.1 | 36.1 | 8.5 |
| 4 | 356.5 | 396.2 | 39.7 | 16.3 |

^aThe enthalpies computed with GAMESS are slightly different (< 0.3 kcal/mol) from those in Tables 1–4 computed with Gaussian. ^bComputed as the difference between the deprotonation enthalpies of the localized structure and the reference (**5**), whose calculated deprotonation enthalpy is 412.5 kcal/mol.

Discussion

The calculated deprotonation enthalpies of **1-5** can be compared to experimental gas-phase deprotonation enthalpies and are in very good agreement. The experimental gas-phase deprotonation enthalpy of **1** is 369.1 ± 2.1 kcal/mol,³ and its calculated deprotonation enthalpy is 367.1 kcal/mol using Gaussian and 367.2 kcal/mol using GAMESS. Those numbers for **2** are 373 ± 3 ,⁴⁵ 375.4, and 375.1 kcal/mol; those for **3** are 368.3 ± 3 ,⁴⁶ 368.2, and 368.0 kcal/mol; those for **4**

are 355.9 ± 3.8 ,⁴⁷ 356.7, and 356.5 kcal/mol; and those for **5** are 412.9 ± 2 ,¹ 413.5, and 412.5 kcal/mol.

Even though our calculations are in good agreement with experimental numbers, our vinylogue extrapolation methodology is not terribly concerned with absolute deprotonation enthalpies. Rather, it is concerned essentially exclusively with *relative* gas-phase deprotonation enthalpies—recall that the calculated resonance and inductive contributions are *differences* in deprotonation enthalpy of like species. Therefore, the numbers that we extrapolate are expected to be even more precise than the above discrepancies because

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TABLE 6. Contributions by Resonance and Inductive Effects toward the Gas-Phase Deprotonation Enthalpies of Molecules 1–4

| species | vinylogue methodology | | | | BLW methodology | | |
|----------|---|----------------------------------|----------------------------------|--------------------------------|---|----------------------------------|----------------------------------|
| | total effect ^a (kcal/mol) | Res _{n=0} (kcal/mol) | Ind _{n=0} (kcal/mol) | sum ^b (kcal/mol) | total effect ^c (kcal/mol) | Res _{n=0} (kcal/mol) | Ind _{n=0} (kcal/mol) |
| 1 | 46.4 | 34.3 | 11.8 | 46.1 | 45.3 | 42.3 | 3.0 |
| 2 | 38.1 | 26.2 | 12.7 | 38.9 | 37.4 | 31.2 | 6.2 |
| 3 | 45.4 | 30.5 | 15.5 | 46.0 | 44.6 | 36.1 | 8.5 |
| 4 | 56.8 | 30.8 | 26.0 | 56.8 | 56.0 | 39.7 | 16.3 |

^aDeprotonation enthalpy enhancement relative to methylpropane, Gaussian. ^bSum of the extrapolated values of Res_{n=0} and Ind_{n=0}. ^cDeprotonation enthalpy enhancement relative to methylpropane, using GAMESS.

any errors that would appear in the calculated deprotonation enthalpy of one species would largely cancel in computing deprotonation enthalpy differences.

The results in Tables 1–4 exhibit a number of trends. One trend is that the vinylogues are stronger acids with increasing *n*, which is explained by the increasing resonance stabilization of the negatively charged conjugate base. Second, each perpendicular vinylogue is a weaker acid than its corresponding parallel vinylogue. This is because the resonance stabilization in the negatively charged conjugate base is decreased when the vinyl chain is perpendicular to the carbonyl group. Third, each perpendicular vinylogue is a stronger acid than the corresponding reference vinylogue, confirming that inductive effects by the carbonyl-containing group serve to strengthen the acid.

Also, notice that both the resonance and inductive contributions in the parallel vinylogues decrease with increasing value of *n*. With increasing *n*, the resonance contribution by the carbonyl-containing group accounts for a smaller fraction of the total resonance. In other words, with sufficiently long conjugated vinyl chains, a saturation of the resonance effect is observed. Inductive effects, on the other hand, decrease with increasing *n* due to the increasing distance between the acidic carbon and the electron-withdrawing carbonyl group.

From the data in Tables 1–4, the resonance and inductive contributions toward the gas-phase deprotonation enthalpies of 1–4 are obtained by extrapolating the plots in Figures 3 and 4 back to *n* = 0. The resulting extrapolated values were previously shown separately in parentheses in Tables 1–4 and are shown together in Table 6. Also included in Table 6 are the corresponding resonance and inductive contributions obtained from the BLW methodology.

Notice from Table 6 that the results from the vinylogue extrapolation methodology are internally consistent. For each molecule 1–4, the resonance and inductive contributions were derived independently. In each case, the “sum” of those effects is very close to the deprotonation enthalpy enhancement relative to **5**, listed as the “total effect” in Table 6. The largest discrepancy is only 0.8 kcal/mol (for **2**), where the total effect is 38.1 kcal/mol and the sum of the extrapolated resonance and inductive effects is 38.9 kcal/mol. This internal consistency throughout provides validation to the extrapolation methodology.

Moreover, our results for **1** are comparable to those obtained by Silva,⁴⁸ who performed a similar vinylogue study on the gas-phase acidity of acetaldehyde. He determined that the inductive contribution is 12.8 kcal/mol, which differs by only 1.0 kcal/mol from the inductive contribution we obtained for **1**. However, the resonance contribution he

obtained for acetaldehyde is 41.9 kcal/mol, which is 7.6 kcal/mol greater than the resonance contribution we obtained for **1**. This large difference might be due to geometrical constraints imposed on the perpendicular vinylogue structures. The numbers we report for the perpendicular structures are of their optimized geometries, consistent with notion that acidities are equilibrium processes. It is not clear that Silva carried out the same optimizations. If he did not, then the resonance contribution he reports will be artificially high.

Table 6 also shows that the results from the vinylogue methodology and the BLW methodology are in good agreement quantitatively. Discrepancies among the derived resonance and inductive contributions are all less than 10 kcal/mol, even though the magnitude of the effects reach roughly 40 kcal/mol. Significantly, the relative resonance and inductive contributions are in perfect agreement qualitatively. Both methodologies suggest that the resonance contribution increases in the order **2** < **3** < **4** < **1**, and both methodologies suggest that the inductive contribution increases in the order **1** < **2** < **3** < **4**.

Obviously, differences in these effects arise from the fact that in 1–4 different groups are attached to the carbonyl carbon on the side opposite the acidic carbon. That group attached in **1** is CH₃, the one attached in **2** is NH₂, the one attached in **3** is OH, and the one attached in **4** is F. From Table 6, we can see that both the vinylogue extrapolation methodology and the BLW methodology suggest that relative to CH₃, the NH₂, OH, and F groups serve to weaken the acid via resonance but strengthen it via inductive effects. According to the vinylogue methodology, the NH₂ group weakens the acid via resonance by 8.1 kcal/mol and strengthens it via inductive effects by 0.9 kcal/mol. The OH group weakens the acid via resonance by 3.8 kcal/mol and strengthens it via inductive effects by 3.7 kcal/mol. The F atom weakens the acid via resonance by 3.5 kcal/mol and strengthens it via inductive effects by 14.2 kcal/mol. According to the BLW methodology, the NH₂ group weakens the acid via resonance by 11.1 kcal/mol and strengthens the acid via inductive effects by 3.2 kcal/mol, the OH group weakens the acid via resonance by 6.2 kcal/mol and strengthens it via inductive effects by 5.5 kcal/mol, and the F atom weakens the acid via resonance by 2.6 kcal/mol and strengthens it via inductive effects by 13.3 kcal/mol. These results are summarized in Table 7.

The relative resonance and inductive effects in an amide, ester, and acid fluoride can be understood straightforwardly by the electronegativities of N, O, and F. The resonance structure with the positive charge on X in Figure 2a decreases in stability in the order NH₂ > OH > F. This is because with X = OH, that positive charge is on O, whereas with X = NH₂, that positive charge is on N. Therefore, N, being less electronegative than O, can accommodate the positive

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TABLE 7. Resonance and Inductive Contributions toward Gas-Phase Deprotonation Enthalpies Relative to Acetone

| functional group | resonance contribution (kcal/mol) | | | | inductive contribution (kcal/mol) | | | |
|------------------|-----------------------------------|------------------|-----------------|-----------------|-----------------------------------|------------------|-----------------|-----------------|
| | vinyllogue ^a | BLW ^b | RB ^c | SL ^d | vinyllogue ^a | BLW ^b | RB ^c | SL ^d |
| amide | -8.1 | -11.1 | -11.5 | -15.1 | 0.9 | 3.2 | 4.4 | 7.6 |
| ester | -3.8 | -6.2 | -12.8 | -10.6 | 3.7 | 5.5 | 8.8 | 9.3 |
| acid fluoride | -3.5 | -2.6 | -7.5 | -1.4 | 14.2 | 13.3 | 15.4 | 15.1 |

^aDerived from the vinyllogue methodology, this work. ^bDerived from the block-localized wave function methodology, this work. ^cRablen and Bentrup, ref 11. ^dDerived from the Swain–Lupton parameters.

charge better. Consequently, the carbonyl group in **3**, being less tied up in resonance with X, is more available for resonance with the enolate carbon. For similar reasons, the carbonyl group in **4** is less tied up in resonance with X than it is in **3**, giving **4** the more stable enolate anion.

By contrast, the greater electronegativity of O than N gives the opposite result for inductive effects. With the greater electronegativity of the heteroatom, the OH group is more electron-withdrawing inductively. As illustrated previously in Figure 2b, this inductive electron withdrawal stabilizes the enolate anion. Therefore, the enolate anion of **3** is more stabilized by inductive effects than is the enolate anion of **2**, making the inductive contribution toward deprotonation enthalpy greater in **3** than in **2**. For the same reason, the inductive contribution toward the deprotonation enthalpy of **4** is greater than it is for **3**.

For comparison, we also calculated the relative resonance and inductive contributions toward the deprotonation enthalpies of **2–4** using the empirical relationship proposed by Swain and Lupton as shown in eq 21.⁴⁹

$$\log(K/K_0) = \rho(F+rR) \quad (21)$$

Here, F and R are the field/inductive and resonance parameters, which are characteristic of a particular substituent. The products ρF and ρR can be viewed as the reaction's sensitivity to field/inductive and resonance effects, respectively. We evaluated these products by obtaining a least-squares fit of the Swain–Lupton equation to calculated (B3LYP/6-31+G*) relative gas-phase deprotonation enthalpies of several acids of the form $\text{CH}_3\text{C}(\text{O})-\text{X}$, where $\text{X} = \text{CH}_3, \text{NH}_2, \text{OH}, \text{F}, \text{Cl}, \text{CF}_3, \text{CN},$ and NO_2 . Relative to $\text{X}=\text{H}$, the respective calculated deprotonation enthalpies are 3.25, 11.55, 4.35, -7.15, -18.95, -17.53, -23.23, and -28.28 kcal/mol.

From the fit of these data, we determined that $\rho F = -20.7 \pm 4.0$ kcal/mol and $\rho R = -7.5 \pm 2.1$ kcal/mol. Substituting in the values of F and R for the various substituents, we determined that the NH_2 , OH , and F groups strengthen the acids via inductive effects by 7.6, 9.3, and 15.1 kcal/mol, respectively. Their resonance contributions weaken the acids by 15.1, 10.6, and 1.4 kcal/mol. These numbers are included in Table 7. As can be seen, results from the Swain–Lupton equation are in perfect qualitative agreement with those from the vinyllogue and BLW methodologies. However, they are not in very good quantitative agreement for the NH_2 and OH groups. Namely, the resonance contributions predicted by the Swain–Lupton equation for NH_2 and OH are each greater than the values predicted in this work by 4–7 kcal/mol. Moreover, the inductive contributions of these two groups are predicted by the Swain–Lupton equation to

be greater than the values predicted in this work by 4–7 and 4–6 kcal/mol, respectively.

The quantitative discrepancies between the predictions from the Swain–Lupton equation and the results from this work are not surprising. The Swain–Lupton substituent parameters are derived from systems in which the substituent and the reaction center are relatively far apart. For the reaction considered in this work, the substituents are only two bond lengths away from the reaction center, so effects other than simply resonance and inductive effects, such as steric effects, can play significant roles. In addition, establishing the Swain–Lupton substituent parameters required certain assumptions to be made and was met with scrutiny by a number of authors.^{50–52} For instance, they assumed that the resonance contribution by the trimethylammonium substituent, $(\text{CH}_3)_3\text{N}^+$, is zero. The validity of such an assumption is to be questioned, however, especially given the fact that the magnitude of the resonance parameter for the isoelectronic *tert*-butyl group, $(\text{CH}_3)_3\text{C}^-$, is 28% of the magnitude of the resonance parameter for a methoxy group, CH_3O^- .

In the introduction to this paper, we mentioned that the motivation for our study stems from the fact that results by Rablen and Bentrup¹¹ are in error both quantitatively and qualitatively. They report that, relative to a ketone, the inductive contribution by the NR_2 group in an amide strengthens the acid by 4.4 kcal/mol, the inductive contribution by the OR group in an ester strengthens the acid by 8.8 kcal/mol, and the inductive contribution by F in an acid fluoride strengthens the acid by 15.4 kcal/mol. These numbers are presented in Table 7, alongside results from our current work. Notice that the inductive contributions obtained by Rablen and Bentrup are all greater than the numbers we have obtained. Notably, for an ester, the inductive contribution they obtained exceeds our numbers by roughly a factor of 2. Their numbers are, however, in qualitative agreement with ours, insofar as F strengthens the acid via inductive effects more than does the OH/OR group, which, in turn, strengthens the acid via inductive effects more than does the NH_2/NR_2 group.

Similarly, the resonance contributions obtained by Rablen and Bentrup for the OR and F groups are not in very good quantitative agreement with our numbers. Specifically, their numbers for these substituents are a factor of about 2–3 greater than ours. More problematic is the fact that their resonance numbers are in qualitative disagreement with ours. Their results suggest that the OR group in an ester has a greater contribution via resonance than does the NR_2

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group in an amide. Not only is this contrary to our results, but furthermore is counterintuitive, given our previous argument—that oxygen cannot accommodate a positive charge as well as a nitrogen atom can.

The reason for the discrepancies between our results and those by Rablen and Bentrup are not entirely clear, but could stem from two flaws in the empirical relationship they applied in order to derive their numbers. That empirical relationship is shown in eq 22.

$$\Delta E_{\text{electrostatic}} = (11 \text{ kcal/mol})\Sigma(\chi_i - \chi_j) \quad (22)$$

Here, χ_i and χ_j are the electronegativities of the atoms α and β to the acidic site.

One flaw of this equation is that it is derived from the enthalpies of isodesmic reactions involving σ bonds only.⁹ The reactions in question in this study, however, involve π bonds connecting atoms α and β to the acidic carbon—namely, the C–O π bond of the carbonyl group. Therefore, to apply eq 22 toward the acidities of ketones, esters, and amides, one must assume that inductive effects are transmitted through π bonds no differently than they are through σ bonds. This, however, is not an appropriate assumption. As Bowden⁵³ showed, the transmission factor through a carbonyl carbon is 0.43, whereas that through an sp^3 -hybridized carbon is 0.48. This is consistent with the fact that an ether oxygen (with only σ bonds) is estimated to be about 12% more polarizable than is a carbonyl oxygen (with one σ bond and one π bond).⁵⁴ Thus, Rablen and Bentrup's model would overestimate the contribution by inductive effects.

The second flaw of eq 22 is that the only data used to derive it were reactions taking place at O and N atoms. The molecules in this study, however, involve reactions at a C atom.

Conclusions

Contributions by resonance and inductive effects toward deprotonation enthalpy were determined for compounds **1–4** at the α carbon, employing both a vinylogue extrapolation methodology and a block-localized wave function (BLW) methodology. With the vinylogue methodology, gas-phase deprotonation enthalpies were calculated for the $n = 1–4$ vinylogues of **1–4**, both in their parallel and perpendicular conformations, as well as for the $n = 1–4$ vinylogues of **5**. Comparisons of these acidities were made

among corresponding (i.e., same n) vinylogues to obtain the resonance and inductive contribution in each parallel vinylogue. Those contributions were extrapolated back to $n=0$ to obtain resonance and inductive contributions for the parent molecules **1–4**. With the BLW methodology, resonance and inductive contributions were obtained in a more direct fashion by comparing calculated deprotonation enthalpies involving delocalized structures to calculated deprotonation enthalpies involving specific resonance structures.

The two methodologies were in good agreement both qualitatively and quantitatively. Using the vinylogue methodology, the resonance contribution by the carbonyl-containing group of **1** was determined to be 34.3 kcal/mol, and using the BLW methodology, it was determined to be 42.3 kcal/mol. For **2**, those numbers are 26.2 and 31.2 kcal/mol, respectively; for **3**, those numbers are 30.5 and 36.1 kcal/mol, respectively; and for **4**, those numbers are 30.8 and 39.7 kcal/mol. Using the vinylogue methodology, the inductive contribution by the carbonyl-containing group of **1** was determined to be 11.8 kcal/mol, and using the BLW methodology, it was determined to be 3.0 kcal/mol. For **2**, those numbers are 12.7 and 6.2 kcal/mol, respectively; for **3**, those numbers are 15.5 and 8.5 kcal/mol, respectively, and for **4**, those numbers are 26.0 and 16.3 kcal/mol, respectively.

By comparison to the effects in **1**, the NH_2 group in **2** serves to weaken the acid via resonance by 8.1–11.1 kcal/mol, but serves to strengthen the acid via inductive effects by 0.9–3.2 kcal/mol. The OH group in **3** serves to weaken the acid via resonance by 3.8–6.2 kcal/mol but serves to strengthen the acid via inductive effects by 3.7–5.5 kcal/mol. The F atom in **4** serves to weaken the acid via resonance by 2.6–3.5 kcal/mol but strengthens the acid via inductive effects by 13.3–14.2 kcal/mol.

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Supporting Information Available: Optimized Cartesian coordinates, energies, zero-point energy corrections, and enthalpies at 298 K. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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