

## Are the Enolates of Amides and Esters Stabilized by Electrostatics?

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**Abstract:** The fact that amides and esters form less stable enolates than ketones might be seen as evidence that electrostatic stabilization is unimportant in these anions. However, *ab initio* molecular orbital calculations show that electrostatic stabilization does in fact lie beneath the competing resonance effect that causes the decrease in acidity. The electrostatic contribution is revealed by examining torsionally twisted amide and ester structures in which the  $\pi$  resonance interactions are largely inhibited. These twisted amides and esters have greater enolate acidity than the corresponding ketones. Qualitatively similar behavior is observed with respect to protonation, such that twisted amides and esters are generally less basic than the reference ketones, in striking contrast to their behavior in the normal geometries.

### Introduction

The greater acidity of carboxylic acids relative to alcohols has most often been attributed to resonance stabilization of the carboxylate anion.<sup>1,2</sup> However, during the last two decades, this point of view has increasingly been questioned, and alternative electrostatic explanations have been offered. The electrostatic hypothesis states that the primary role of the carbonyl oxygen is to increase the positive charge on carbon.<sup>3,4</sup> The positive charge stabilizes the increase in negative charge on the adjacent hydroxy oxygen atom that occurs when a proton is lost.<sup>5</sup> Alternatively, one can look upon the additional positive charge at carbon as repelling the hydroxy proton in the neutral acid. While these two perspectives differ in detail, they are similar in broad outlook. Both predict the same increase in acidity and ascribe this increase to preexisting polarization of the carbonyl bond.

To avoid confusion, a few words about definitions are in order at this point. The electrostatic contribution described in the preceding paragraph might instead be considered an inductive effect. Furthermore, the electrostatic effect has sometimes been defined as that component of the energy change upon deprotonation that is obtained by merely removing the proton and not allowing relaxation of either the electron density or the geometry of the remaining anion. This perspective has in fact been applied very productively to the case of carboxylic acids by a number of authors, including most recently Bökman.<sup>6</sup>

However, a somewhat different meaning of the term electrostatic is intended here, corresponding to a usage common among organic chemists, in which atoms are viewed as having partial charges that mutually interact. The *inductive* effect is taken to mean the polarization of electron density in bonds, caused primarily by electronegativity differences. This polarization can be viewed, in a highly approximate sense, as resulting in partial charges on the atoms of a molecule. For instance, in the current example, the inductive effect causes accumulation of positive charge on the carbonyl carbon and of negative charge on the carbonyl oxygen. The *electrostatic* effect is viewed as the interaction *between* these partial atomic charges in various parts of a molecule; or, in the case of a comparison, as the energetic *consequence* of the inductive polarization for some other perturbation.<sup>7</sup>

Again, to use the present context as an example, the electrostatic effect corresponds to the interaction of the C=O bond dipole (i.e., the partial charges on C and O) with the OH group in the neutral acid or with the negatively charged oxygen atom in the anion. The electrostatic contribution to the differential acidity of an alcohol compared to a carboxylic acid corresponds to the change in the energy required to remove the hydroxy proton, depending on whether or not the C=O dipole is present. The C=O bond dipole—i.e., the additional positive charge on carbon, beyond that characteristic for an alcohol, and also the more distant negative charge on the carbonyl oxygen—strongly influences the electrostatic energies of the neutral and deprotonated forms of the hydroxy oxygen!<sup>8</sup>

While the electrostatic effect is viewed by the authors as transmitted through space (i.e., a field effect), one could also view it as transmitted through bonds, and the analysis would

(1) Wheland, G. W. *Resonance in Organic Chemistry*; Wiley: 1955; p 345.

(2) Pauling, L. *Nature of the Chemical Bond*, 2nd ed.; Cornell University Press: Ithaca, NY, 1960; p 276.

(3) Siggel, M. R.; Thomas, T. D. *J. Am. Chem. Soc.* **1986**, *108*, 4360–4363.

(4) (a) Wiberg, K. B. *Acc. Chem. Res.* **1999**, *32*, 922–929. (b) Wiberg, K. B. *J. Chem. Educ.* **1996**, *73*, 1089–1095.

(5) In this perspective, the electron density previously shared by the oxygen and the proton is viewed as now residing purely on oxygen, thereby increasing the negative charge on oxygen. Electrostatic stabilization results from the interaction of this increased negative charge with the electron density distribution of the remainder of the molecule, which is viewed as remaining unchanged.

(6) Bökman, F. *J. Am. Chem. Soc.* **1999**, *121*, 11217–11222.

(7) In this way of thinking, the interaction between the “ordinary” partial charges on atoms bonded to each other is ignored, however, since it is assumed to be part of the normal bond energy.

not change.<sup>9</sup> Strictly speaking, treatment of a field effect requires taking into account the consequences of relative orientation. However, for the short-range 1,2 and 1,3 interactions of interest here, there is very little room for geometric variation, and so these orientation effects can be safely ignored.

Numerous previous studies have attempted to determine to what extent the acidity of carboxylic acids can be attributed to either resonance or electrostatic effects.<sup>3,4</sup> Some of the major published points of view are summarized briefly in the antecedent to this study,<sup>10</sup> and in the interest of brevity that summary is not repeated here. This previous study concluded, however, that electrostatic considerations accounted for roughly two-thirds of the enhanced acidity of acetic acid relative to *tert*-butyl alcohol and that resonance stabilization of the anion contributed only one-third. This finding was in qualitative agreement with the conclusions reached by several previous studies, such as those of Hiberty and Byrman,<sup>11</sup> of Taft and co-workers,<sup>12</sup> and of Wiberg, Streitwieser, Thomas, and colleagues.<sup>13</sup> It was based upon a systematic comparison of the relative gas-phase acidities and proton affinities of acetic acid and a variety of comparison structures, evaluated by use of isodesmic reaction energies calculated at high levels of ab initio molecular orbital (MO) theory. Furthermore, the electrostatic contribution to differential acidity and basicity in the gas phase was found to be well described by eq 1 for the class of structures examined:

$$\Delta E_{\text{electrostatic}} = (11 \text{ kcal/mol})(S) \sum_{\text{bonds}} (\chi_i - \chi_j) \quad (1)$$

In this equation, *S* takes on the value of +1 or -1, depending only on whether a cation or an anion is under consideration, and the electronegativity differences are derived from Allred-Rochow electronegativities.  $\sigma$  and  $\pi$  bonds are treated independently and equally in this approach (e.g., a double bond is equivalent to two single bonds). Equation 1 indicates that on average each C-F bond contributes 15 kcal/mol, each C-O bond contributes 9 kcal/mol, and each C-N bond contributes 4 kcal/mol to differential acidity and basicity. Full details about the application of eq 1 appear in ref 10.

Subsequent to this study, Exner and Cársky have contributed another perspective.<sup>14</sup> Exner and Cársky emphasize the resonance explanation for the behavior of carboxylic acids and also

**Table 1.** Enthalpies of Isodesmic Reactions<sup>a</sup>

| reaction | CBS-4 <sup>b</sup> | CBS-Q <sup>b</sup> | B3LYP <sup>c</sup> | MP2 <sup>c</sup> | B3/MP2 <sup>d</sup> |
|----------|--------------------|--------------------|--------------------|------------------|---------------------|
| 1.1      | -7.8               | -7.1               | -8.4               | -7.4             | -7.9                |
| 1.2      | -3.5               | -4.0               | -3.6               | -4.2             | -3.9                |
| 1.3      | +7.5               | +7.9               | +9.6               | +7.8             | +8.7                |
| 2.1      | +6.8               | +5.3               | +4.9               | +5.3             | +5.1                |
| 2.2      | +3.8               | +3.8               | +4.2               | +3.9             | +4.0                |
| 2.3      | +1.9               | +2.7               | +3.7               | +3.3             | +3.5                |
| 3.1      | +24.0              | +24.3              | +21.5              | +24.0            | +22.7               |
| 3.2      | +1.1               | +1.9               | +1.0               | +1.8             | +1.4                |
| 3.3      | -22.2              | -22.0              | -22.7              | -21.7            | -22.2               |
| 4.1      | -1.2               | -0.4               | 0.0                | -0.9             | -0.4                |
| 4.2      | -3.2               | -1.5               | -1.2               | -1.7             | -1.4                |
| 4.3      | +2.1               | +1.8               | +1.1               | +2.1             | +1.6                |
| 5.1      | +9.5               | +8.4               | +8.2               | +8.7             | +8.4                |
| 5.2      | -3.3               | -3.9               | -3.5               | -3.1             | -3.3                |
| 5.3      | -1.7               | -1.6               | -3.0               | -2.3             | -2.7                |

<sup>a</sup> All enthalpies are given in kilocalories per mole. <sup>b</sup> Enthalpy at 0 K. <sup>c</sup> Using the 6-311+G(2df,p) basis set, at the B3LYP/6-31+G\*\* optimized geometry, and with the B3LYP/6-31+G\*\* zero point vibrational energy (scaled by 0.97) included. <sup>d</sup> Average of B3LYP and MP2 values.

point out some of the inherent difficulties in ever conclusively settling the issue. They also make the very interesting point that even if electrostatic considerations play a dominant role in the gas phase, resonance still might play the more important role in solution, since the solution environment is expected to attenuate electrostatic effects more strongly than resonance effects.

Another challenge to the importance of electrostatic considerations might seem to arise from the well-known fact that amides and esters exhibit lower enolate acidity than do ketones.<sup>15-18</sup> This phenomenon has long been attributed to attenuated resonance stabilization in the enolates of esters and amides relative to their neutral forms. In a ketone enolate, resonance stabilization occurs without hindrance. In the amide and the ester enolates, however, resonance stabilization of the negative charge can only be accomplished by relinquishing the resonance interaction of the lone pair on nitrogen or oxygen with the carbonyl—an interaction that strongly stabilizes the neutral molecule. This explanation is almost undoubtedly correct. However, it is shown here that the behavior of esters and amides nonetheless does not contradict the important role of electrostatics. In fact, amides and esters obey eq 1 about as well as one would expect. To the extent that the resonance contribution can be eliminated, the electrostatic effects are still evident.

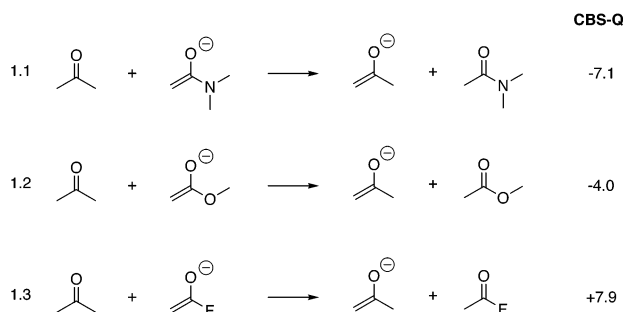
## Results

The primary data used in this study consist of calculated enthalpy changes at zero Kelvin for a series of isodesmic reactions. The reactions themselves are listed in Schemes 1–5, and the corresponding energies are listed in Table 1. For the sake of consistency, the same four levels of theory that were used in the previous structural comparison<sup>10</sup> were selected for the present application: CBS-4, CBS-Q, B3LYP/6-311++G-(2df,p)/B3LYP/6-31+G\*\*, and MP2/6-311++G(2df,p)/B3LYP/6-31+G\*\*. CBS-4 and CBS-Q are compound procedures developed by Petersson and Ochterski and have been shown to reproduce proton affinities of neutral and anionic species, among

- (8) The two definitions of the electrostatic effect might at first appear completely different, but in fact they are quite similar. The definition of the electrostatic effect described here corresponds to the energy associated with adding or removing a proton and leaving both the geometry and the electron density distribution of the remainder of the molecule unchanged, with only one minor exception: the atom actually experiencing protonation or deprotonation is viewed as undergoing a localized relaxation of its electron density distribution. That is, in a deprotonation, the electrons originally in the X-H bond are assumed to relax into a lone pair on X (in analogy to the traditional arrow-pushing of electrons by organic chemists). The physical chemist's definition and the organic chemist's definition of the electrostatic contribution are consequently not so different as they at first appear.
- (9) For a discussion of inductive and electrostatic effects, and transmission through bonds and through space, see (a) Exner, O. *J. Phys. Org. Chem.* **1999**, *12*, 265–274. (b) Charton, M. *J. Phys. Org. Chem.* **1999**, *12*, 275–282.
- (10) Rablen, P. R. *J. Am. Chem. Soc.* **2000**, *122*, 357–368 and references therein.
- (11) Hiberty, P. C.; Byrman, C. P. *J. Am. Chem. Soc.* **1995**, *117*, 9875–9880.
- (12) Taft, R. W.; Koppel, I. A.; Topsom, R. D.; Anvia, F. *J. Am. Chem. Soc.* **1990**, *112*, 2047–2052.
- (13) (a) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1987**, *109*, 5935–5943. (b) Thomas, T. D.; Siggel, M. R. F.; Streitwieser, A., Jr. *J. Mol. Struct. (THEOCHEM)* **1988**, *165*, 309–318. (c) Siggel, M. R. F.; Streitwieser, A., Jr.; Thomas, T. D. *J. Am. Chem. Soc.* **1988**, *110*, 8022–8028. (d) Wiberg, K. B.; Ochterski, J.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 8291–8299.
- (14) Exner, O.; Cársky, P. *J. Am. Chem. Soc.* **2001**, *123*, 9564–9570.

- (15) Bruice, P. Y. *Organic Chemistry*; Prentice Hall: Englewood Cliffs, NJ, 2001; p 829.
- (16) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 3129–3141.
- (17) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327–4331.
- (18) Richard, J. P.; Williams, G.; O'Donoghue, A. C.; Amyes, T. L. *J. Am. Chem. Soc.* **2002**, *124*, 2957–2968, and references therein.

## Scheme 1

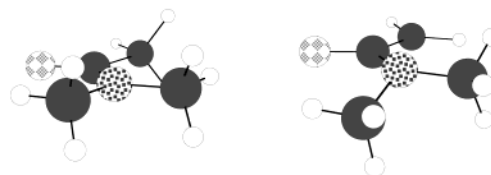


other properties, with high accuracy.<sup>19</sup> The latter two procedures are recommended for calculation of proton affinities by Turecek, who has found that the average between these MP2 and B3LYP energies gives excellent agreement with the highest levels of ab initio theory.<sup>20</sup> The energies marked B3/MP2 correspond to this average. The energies of the individual species, in hartree units, appear in Table S2 in the Supporting Information.

It is readily apparent from Table 1 that the four levels of calculation agree very closely. The excellent accord between the various calculations lends confidence to the computational approach. Experimental comparisons are only available for four of the reactions, but Table 1 confirms that the calculated reaction energies agree to within the fairly large experimental uncertainties ( $\pm 3$  to  $\pm 6$  kcal/mol) in at least three of the four cases.<sup>21</sup> It is also worth noting that all levels of calculation reproduce the 15.8 kcal/mol experimentally determined barrier to rotation of the amino group in *N,N*-dimethylacetamide<sup>22</sup> to within less than 1.5 kcal/mol. Henceforth the CBS-Q energies are used for discussion. However, none of the conclusions that follow would change in any significant manner if the CBS-4, B3LYP, or MP2 energies were used instead. It has been amply demonstrated elsewhere that the CBS-4, CBS-Q, and B3/MP2 procedures yield calculated enthalpic properties for ordinary organic molecules that correspond closely with gas-phase experimental values.<sup>19,20</sup>

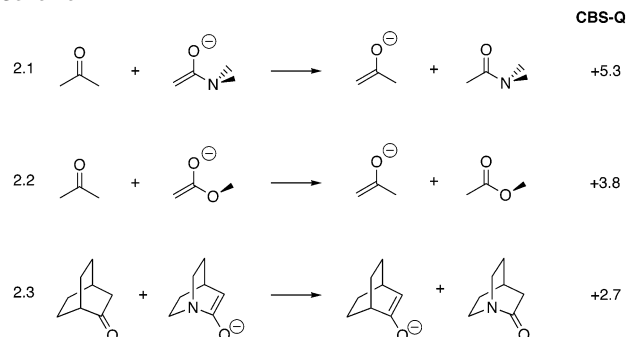
## Discussion

Isodesmic reactions 1.1 and 1.2 in Scheme 1 illustrate the classic phenomenon that esters and amides are more difficult to deprotonate than ketones. The magnitude of the effect in the gas phase is 7.1 kcal/mol for *N,N*-dimethylacetamide and 4.0 kcal/mol for methyl acetate, in both cases measured relative to acetone. The traditional explanation is supported by the calculated geometries, which show, for instance, that the degree of pyramidalization at the amide nitrogen is markedly increased in the enolate as compared to the neutral amide (Figure 1). Reaction 1.3, however, already suggests that resonance does not by itself control the acidity: acetyl fluoride is considerably *more* acidic than acetone. While a resonance argument would predict the acidity of acetyl fluoride to be *diminished* relative to that of acetone, the positive enthalpy observed for reaction



**Figure 1.** B3LYP/6-31+G\*\* optimized structures of *N,N*-dimethylacetamide (left) and the corresponding enolate (right). The neutral amide is planar, but the nitrogen becomes strongly pyramidalized in the enolate.

## Scheme 2



1.3 is easily understood in terms of electrostatic and/or inductive stabilization of the anion by fluorine.

In reactions 1.1 and 1.2, it is entirely plausible to propose that the ester oxygen and the amide nitrogen provide similar stabilization of the corresponding enolates. The negative enthalpies for these reactions merely show that the traditional resonance contribution, which stabilizes the neutrals relative to the anions, is more important. The relatively small magnitudes of the energies for reactions 1.1 and 1.2 make this suggestion particularly reasonable. For instance, the rotational barrier in *N,N*-dimethylacetamide (DMA) is about 16 kcal/mol.<sup>22</sup> Insofar as the rotational barrier serves as an estimate of the strength of the resonance stabilization of the neutral amide, one might naively have expected the amide to be about 16 kcal/mol less acidic than the ketone. The actual difference is less than half as great.

Pugh and Streitwieser<sup>23</sup> have recently shown by NMR that the barrier to rotation in the lithium enolate of DMA lies below 10 kcal/mol and have calculated the barrier to be in the neighborhood of 5–7 kcal/mol. The 10 kcal/mol lowering of the barrier in the enolate compared to the neutral amide confirms the expectation that interaction of the nitrogen lone pair with the carbonyl  $\pi$  system is strongly attenuated in the enolate. This difference in the barrier between anion and neutral provides an even more precise estimate of the resonance contribution to the differential acidity of acetone and DMA than does the barrier in neutral DMA by itself. The actual acidity difference of only 7 kcal/mol still suggests that some other factor must be partially counteracting resonance.

The reactions in Scheme 2 attempt to quantify the tension between resonance and electrostatic contributions by examining the carbon acidity of species in which  $\pi$  resonance stabilization is eliminated or at least strongly attenuated. Reaction 2.1 compares acetone to the transition state for rotation about the C–N bond in DMA, a structure in which the nitrogen lone pair

(19) Ochterski, J. W.; Petersson, G. A.; Montgomery, J. A., Jr. *J. Chem. Phys.* **1996**, *104*, 2598–2619.

(20) Turecek, F. *J. Phys. Chem. A* **1998**, *102*, 4703–4713.

(21) The calculated energy for reaction 3.1 might fall outside the experimental range, depending on the assessment one makes of the experimental uncertainty. However, another source of discrepancy between the calculated and experimental values is that the calculated values correspond to zero Kelvin, while the experimental values are for higher temperatures.

(22) (a) Ross, B. D.; True, N. S.; Matson, G. B. *J. Phys. Chem.* **1984**, *88*, 2675–2678. (b) Feigel, M. *J. Phys. Chem.* **1983**, *87*, 3054–3058. (c) Feigel, M. *J. Chem. Soc., Chem. Commun.* **1980**, 456.

(23) (a) Pugh, J. K.; Streitwieser, A. *J. Org. Chem.* **2001**, *66*, 1334–1338. (b) Kim, Y.-J.; Streitwieser, A.; Chow, A.; Fraenkel, G. *Org. Lett.* **1999**, *1*, 2069–2071.

**Table 2.** Comparison of Reaction Energies to Estimates from the Electrostatic Model<sup>a</sup>

| compound class | charge state | CBS-Q isodesmic reaction energy <sup>b</sup> |                  |                         |                        |
|----------------|--------------|--|------------------|-------------------------|------------------------|
|                |              | normal geometry                              | twisted geometry | prediction <sup>c</sup> | reactions <sup>d</sup> |
| amide          | anion        | -7.1   | +5.3 or +2.7     | +4.4                    | 1.1, 2.1, 2.3          |
|                | cation       | +24.3  | -0.4 or +1.8     | -4.4                    | 3.1, 4.1, 4.3          |
| ester          | anion        | -4.0   | +3.8             | +8.8                    | 1.2, 2.2               |
|                | cation       | +1.9   | -1.5             | -8.8                    | 3.2, 4.2               |
| imine          | cation       | +8.4   | -3.9 or -1.6     | -4.4                    | 5.1, 5.2, 5.3          |
| acid fluoride  | anion        | +7.9   | N/A              | +15.4                   | 1.3                    |
|                | cation       | -22.0  | N/A              | -15.4                   | 3.3                    |

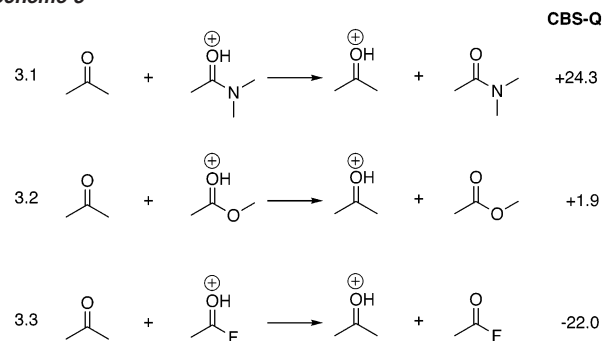
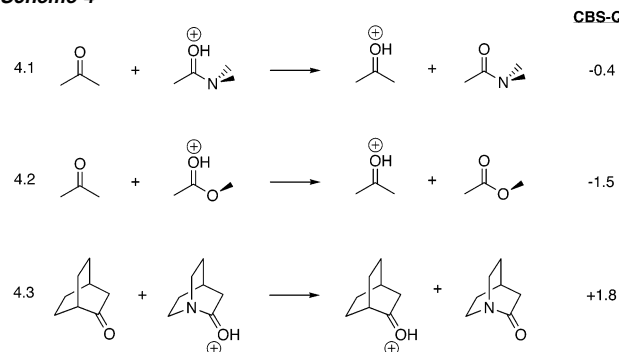
<sup>a</sup> Reaction energies are given in kilocalories per mole. <sup>b</sup> CBS-Q isodesmic reaction energy (repeated from Table 1). <sup>c</sup> Predicted electrostatic contribution from eq 1. Electronegativity differences:  $\chi_{\text{O}} - \chi_{\text{C}} = 0.8$ ;  $\chi_{\text{N}} - \chi_{\text{C}} = 0.4$ ;  $\chi_{\text{F}} - \chi_{\text{C}} = 1.4$  ( $\chi_{\text{C}} = 2.6$ ;  $\chi_{\text{N}} = 3.0$ ;  $\chi_{\text{O}} = 3.4$ ;  $\chi_{\text{F}} = 4.0$ ). The isodesmic reaction energies from the twisted geometries are in at least qualitative agreement with the electrostatic predictions, while the reaction energies from the normal geometries are not. <sup>d</sup> Reactions used to provide the values in columns 3 and 4.

is orthogonal to the  $\pi$  system. The calculated reaction enthalpy of +5.3 kcal/mol shows that the DMA transition state is in fact *more* acidic than acetone. Thus when the consequences of resonance stabilization are removed, the electrostatic stabilization of the enolate by nitrogen is revealed. Furthermore, the magnitude of the acidity enhancement relative to acetone—5.3 kcal/mol—lies very close to the 4.4 kcal/mol predicted by eq 1 (see Table 2). The bicyclic amide in reaction 2.3 illustrates the same point.

Reaction 2.2 shows a similar situation for methyl acetate. Although in its minimum energy conformation the ester is less acidic than acetone, in its transition state for bond rotation it is more acidic than acetone. The magnitude of the acidity enhancement (3.8 kcal/mol) is considerably smaller than the prediction from eq 1 (8.8 kcal/mol; see Table 2), but that is hardly surprising: even in the torsional transition state, one of the lone pairs on the ester oxygen can still interact at least weakly with the carbonyl  $\pi^*$  orbital. The  $\pi$  resonance interaction is only attenuated in the transition state, rather than eliminated entirely as with the amide.

In the forerunner to this study, eq 1 was found to apply to protonated, cationic species as well as to deprotonated, anionic species.<sup>10</sup> Applying the same logic as before, one would expect resonance contributions to enhance the carbonyl basicity of amides and esters relative to that of ketones. In the normal, planar conformations, positive charge can be delocalized away from the carbonyl oxygen via resonance, resulting in stabilization. On the other hand, electrostatic factors would be expected to attenuate the basicity of amides and esters relative to ketones. The additional positive charge at the carbonyl carbon, resulting from inductive electron withdrawal by the nitrogen or oxygen, should disfavor protonation of the carbonyl oxygen.

Reaction 3.1 in Scheme 3 clearly shows that resonance stabilization of the protonated amide far outweighs the electrostatic considerations, such that DMA is almost 25 kcal/mol more easily protonated than acetone. With an ester, the balance is more delicate: the proton transfer from protonated methyl acetate to acetone (reaction 3.2) is close to thermoneutral. With fluorine, not surprisingly, the electrostatic factor dominates, to the extent that proton transfer from protonated acetyl fluoride to acetone (reaction 3.3) is exothermic by 22 kcal/mol. These trends correspond closely with the findings of Wiberg et al.<sup>24</sup>

**Scheme 3****Scheme 4**

for neutral carbonyls. They found that acetamide, acetic acid, and acetyl fluoride are all about equally stabilized relative to acetone, but for quite different reasons:  $\pi$  resonance dominates the stabilization in acetamide;  $\pi$  resonance and electrostatic stabilization are in approximate parity for acetic acid; and the stabilization in acetyl fluoride is almost purely electrostatic in nature.

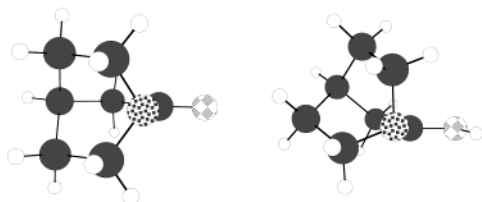
Scheme 4 reveals what happens when torsionally twisted structures are used to eliminate or attenuate the  $\pi$  resonance contribution. Reaction 4.1 shows that the transition state for bond rotation in DMA is in fact less basic than acetone, not more basic, although by only a very small amount. Nonetheless, the 25 kcal/mol decrease in basicity relative to the planar structure is striking. The torsional transition state for methyl acetate likewise is less easily protonated than acetone. With the resonance contributions largely removed, basicity differences for both amides and esters thus revert to the direction predicted by electrostatic arguments.

The basicity enhancement of 1.5 kcal/mol that is observed for the methyl acetate transition-state structure seems rather paltry compared to the 8.8 kcal/mol that would be expected from eq 1 in the absence of resonance stabilization. However, the protonated transition-state structure adopts a somewhat flattened geometry at the ester oxygen, suggesting a significant degree of interaction of one of the lone pairs on oxygen with the carbonyl  $\pi$  system. In the B3LYP/6-31+G\*\* optimized structure, for instance, the COC angle is 130.9°, rather a far cry from the canonical 109.5° for an  $\text{sp}^3$  oxygen, or even of 120° for an  $\text{sp}^2$  oxygen. This leakage of resonance stabilization into the protonated transition state structure accounts for the lack of quantitative agreement with eq 1.

The bicyclic amide shown in reaction 4.3 is more easily protonated than the corresponding ketone, although by only 1.8

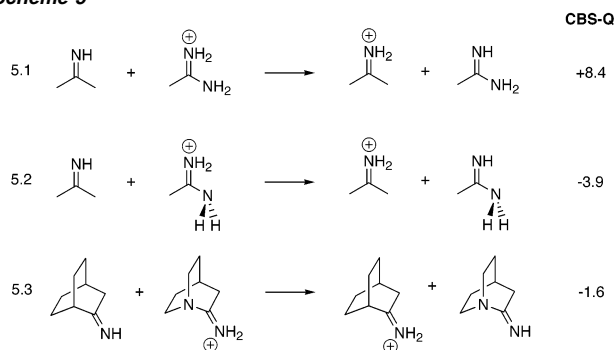
(24) Wiberg, K. B.; Hadad, C. M.; Rablen, P. R.; Cioslowski, J. *J. Am. Chem. Soc.* **1992**, *114*, 8644–8654.





**Figure 2.** Comparison of the B3LYP/6-31+G\*\* optimized geometries of 2-quinuclidine (left) and its protonated form (right). The view corresponds closely to a Newman projection looking down the amide C–N bond. While the neutral amide is not distorted, the protonated form is, allowing some degree of interaction of the nitrogen lone pair with the carbonyl  $\pi$  system.

### Scheme 5



kcal/mol. At first, this observation appears to contradict the argument being developed. However, the protonated bicyclic amide adopts a distorted geometry, accepting a certain amount of strain in return for the ability to achieve some degree of resonance stabilization (Figure 2). The neutral amide, by contrast, adopts an undistorted,  $C_s$  symmetric geometry. The protonated amide thus evades, to some extent, the original intention of the comparison in reaction 4.3. It is in fact not surprising, then, that some small residue of the 24 kcal/mol basicity enhancement of a normal, planar amide relative to a ketone remains in evidence.

Qualitatively, the reactions in Scheme 4 do seem to reveal underlying electrostatic destabilization of the protonated amide and ester. However, the apparent electrostatic contributions are very weak, and yield poor agreement with eq 1. At least to some degree, the lack of agreement results from incomplete removal of the  $\pi$  resonance interactions in the twisted structures. However, other factors might also contribute to the apparent inapplicability of eq 1.

One complication that might contribute to the failure of eq 1 concerns the position of protonation. With the twisted amide in reaction 4.3 and the twisted ester in reaction 4.2, protonation of the carbonyl occurs preferentially on the position syn to the nitrogen/oxygen. In this position, however, the nitrogen or ester oxygen lone pair can exert a direct through-space stabilization, confounding the analysis of the electrostatic contribution. If the slightly less stable anti protonated structures are used instead, the corresponding reaction enthalpies are  $-2.9$  kcal/mol for reaction 4.2 and  $-0.3$  kcal/mol for reaction 4.3. Another complication perhaps arises from the ambiguity in the amides as to whether the positive charge resides on oxygen, as is implicitly assumed in the act of applying eq 1, or on nitrogen.

The imines, however, present a cleaner case, as shown in Scheme 5. Reaction 5.1 demonstrates that resonance stabilization makes acetamide more basic than the imine of acetone, despite the counteracting electrostatic destabilization. Reaction 5.2,

however, reveals the underlying electrostatic destabilization by using the twisted transition-state structure in which  $\pi$  resonance stabilization is not possible. The twisted acetamide is less basic than the imine, by 3.9 kcal/mol—very close to the value of 4.4 kcal/mol predicted by eq 1. The bicyclic structures in reaction 5.3 illustrate the same point, although yielding slightly poorer agreement with eq 1.

### Conclusion

While amide and ester enolates are indeed more difficult to form than ketone enolates, this observation does not indicate an absence of electrostatic stabilization. The traditional resonance argument correctly explains the lower carbon acidity of amides and esters relative to ketones, but this resonance effect is actually diminished by an electrostatic factor operating in the reverse direction. The enhanced carbon acidity of acetyl fluoride, relative to acetone, already demonstrates the importance of the electrostatic factor. Furthermore, the resonance factor can be largely eliminated by examining the behavior of twisted amide or ester structures that prohibit, or at least attenuate,  $\pi$  resonance interactions. Transition states for bond rotation in esters and amides can be used for this purpose, as can the bicyclic amide 2-quinuclidine, which has a twisted geometry even at its energy minimum. In either case, the underlying electrostatic effect is observed, such that the twisted amides and esters exhibit greater carbon acidity than the corresponding ketones. Qualitatively similar behavior is observed with respect to protonation. While *N,N*-dimethylacetamide and methyl acetate are considerably more basic than acetone, acetyl fluoride is less basic than acetone. Furthermore, twisted amide and ester structures are in most cases less basic than the reference ketones, although the magnitude of the electrostatic destabilization of these positively charged species is less than one might have expected.

### Calculations

The Gaussian 98<sup>25</sup> package was used to carry out all ab initio calculations. Standard Pople-type basis sets were employed.<sup>26</sup> For molecules with rotatable bonds, all possible rotamers were investigated at the lower levels of theory. The lowest-energy conformer was then carried through to higher level calculations.<sup>27</sup> All structures were verified as minima via HF/6-31G\* frequency calculations (i.e., no imaginary frequencies).<sup>28</sup> CBS-4 and CBS-Q calculations were carried out by use of the corresponding keywords. B3LYP/6-31+G\*\* geometry optimizations and frequency calculations were also performed, followed by B3LYP/6-311+G(2df,p) and MP2/6-311+G(2df,p) single-point cal-

- (25) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98* (Revision A.6); Gaussian, Inc., Pittsburgh, PA, 1998.
- (26) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
- (27) In cases where the HF/3-21G\* energies of one or more rotamers were similar, HF/6-31G\* optimizations were used to verify which conformer was of lowest energy.
- (28) There were two minor exceptions: at the B3LYP/6-31+G\*\* level only, acetone and the enolate anion of *Z*-methyl acetate each had one imaginary frequency in a planar,  $C_s$  symmetric geometry. However, magnitudes of these frequencies were so small that the planar structures were used anyway.

culations. Table S2 in the Supporting Information tabulates the CBS-4,<sup>16</sup> CBS-Q,<sup>16</sup> B3LYP,<sup>29</sup> and MP2<sup>30</sup> energies. The CBS-4 and CBS-Q values include zero-point energy (ZPE) corrections by definition. The B3LYP, MP2, and B3/MP2 energies in Table 1 include ZPEs calculated at B3LYP/6-31+G\*\* and scaled by 0.97.<sup>31</sup>

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- (29) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (c) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200–206.
- (30) (a) Möller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618–622. (b) Head-Gordon, M.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett.* **1988**, *153*, 503–506. (c) Frisch, M. J.; Head-Gordon, M.; Pople, J. A. *Chem. Phys. Lett.* **1990**, *166*, 275–280. (d) Frisch, M. J.; Head-Gordon, M.; Pople, J. A. *Chem. Phys. Lett.* **1990**, *166*, 281–289. (e) Head-Gordon, M.; Head-Gordon, T. *Chem. Phys. Lett.* **1994**, *220*, 122–128. (f) Sæbo, S.; Almlöf, J. *Chem. Phys. Lett.* **1989**, *154*, 83–89.
- (31) For the determination of 0.97 as a scaling factor for B3LYP zero-point energies, see Rablen, P. R.; Lockman, J. W.; Jorgensen, W. L. *J. Phys. Chem. A* **1998**, *102*, 3782–3797.

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**Supporting Information Available:** Descriptions of molecular geometries (Table S1); energies in hartrees (Table S2); graphical representations of the B3LYP/6-31+G\*\* optimized structures; and Cartesian coordinates and some Z-matrixes for B3LYP/6-31+G\*\* optimized structures (100 pages, print/PDF). This information is available free of charge via the Internet at <http://pubs.acs.org>.

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