JOC The Journal of Organic Chemistry

Featured Article

pubs.acs.org/joc

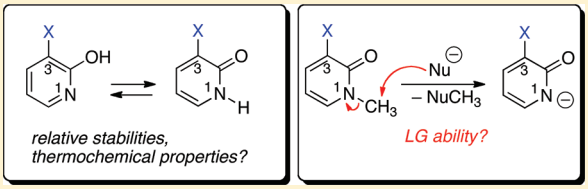
2-Pyridone and Derivatives: Gas-Phase Acidity, Proton Affinity, Tautomer Preference, and Leaving Group Ability

Anna Zhachkina Michelson, Aaron Petronico, and Jeehiun K. Lee*

Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, New Brunswick, New Jersey 08901, United States

Supporting Information

ABSTRACT: The fundamental properties of the parent and substituted 2-pyridones (2-pyridone, 3-chloro-2-pyridone, and 3-formyl-2-pyridone) have been examined in the gas phase using computational and experimental mass spectrometry methods. Newly measured acidities and proton affinities are reported and used to ascertain tautomer preference. These particular substrates (as well as additional 3-substituted pyridones) were chosen in order to examine the correlation between leaving group ability and acidity for moieties that allow resonance delocalization versus those that do not, which is discussed herein.



INTRODUCTION

We have long been interested in the leaving group ability of nucleobases, particularly damaged ones, in relation to the mechanism of the enzymes that remove such bases from DNA. Many of our recent studies have focused on uracil, which is an RNA base that can be mutagenic when it occurs in DNA.[1−5]

Uracil is removed from the genome by the enzyme uracil DNA glycosylase, which has been shown to involve N1-deprotonated uracil as the leaving group (Figure 1).[1,2] In

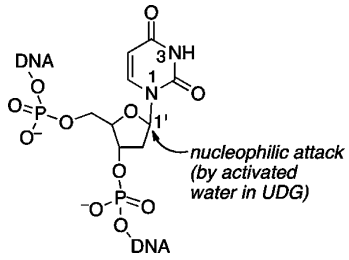


Figure 1. Uracil is removed from genome by uracil DNA glycosylase (UDG).

previous work, we examined the properties of uracil in the gas phase; with a dielectric of 1, the gas phase is an "ultimate" nonpolar environment and can therefore potentially lend insight into reactivity in other nonpolar media, including enzyme active sites.[3−5]

We found that the intrinsic, gas-phase acidity of uracil is comparable to that of hydrochloric acid. Since acid strength of an acid and leaving group ability of its conjugate base are generally correlated, the implication is that in the gas phase, deprotonated uracil might be a very good leaving group, comparable to chloride.

However, when we examined hydrochloric acid and 3-methyluracil in the gas phase, we found that despite similar acidities, chloride is a better leaving group than N1-deprotonated 3-methyluracil (Figure 2).[5,6] We proposed that the reason for the disparity between acidity and leaving group ability could be due to the resonance delocalization in the N1-deprotonated 3-methyl uracil anion versus the lack thereof in the chloride ion. Deprotonated 3-methyluracil is thermodynamically stable due to delocalization by resonance (Figure 2c); however, that delocalization might not be fully realized in an S_N2 transition state. Therefore, the stabilizing benefit of resonance delocalization is not as evident in leaving group ability, and deprotonated 3-methyl uracil is not as good a leaving group as chloride ion.

To further probe this hypothesis, we would need a model system where we could systematically compare resonance-stabilized and nonresonance-stabilized anionic leaving groups. We would expect a closer correlation between acidity and leaving group ability for the nonresonance-stabilized anions than the resonance-stabilized anions. Toward that end, we decided to examine the effect of substitution on a series of 2-pyridones (Figure 3). We chose the pyridone system for various reasons, including simplicity, resemblance to uracil, and the plan that changing substituent "X" would allow us to probe effects systematically.

Although understanding the substituent effects on leaving group ability was the initial motivation for this study, pyridones are also of interest in their own right. The keto−enol tautomerism of the parent 2-pyridone has been much studied in the last century; pyridone/hydroxypyridine is considered a prototypical model for hydrogen bonding, tautomerization, and proton shuttling in both chemical and biological systems,

Received: September 26, 2011
Published: November 23, 2011

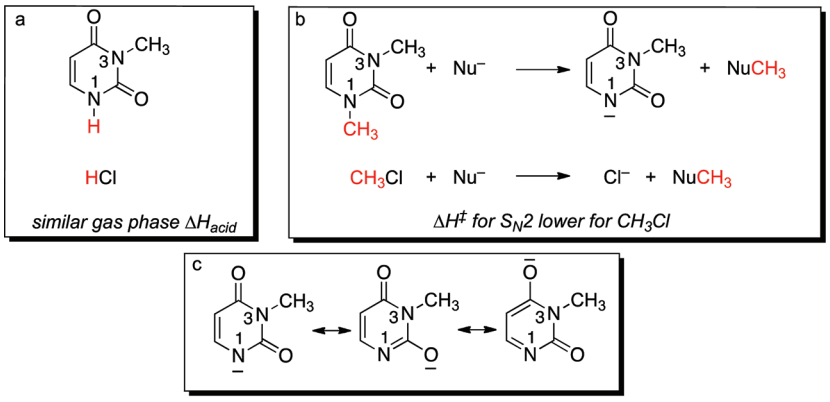


Figure 2. Comparison of (a) acidity and (b) leaving group ability for 3-methyluracil and hydrogen chloride. Resonance delocalization in N1-deprotonated 3-methyluracil anion is also shown (c).

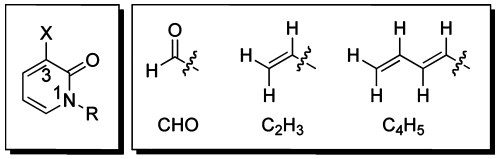
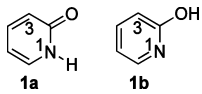


Figure 3. 2-Pyridone and 3-substituted derivatives studied herein.

including those involving nucleobases.[7−11] Aqueous studies point to the keto form (**1a**); gas phase studies indicate a mixture, but with a 2-hydroxypyridine (**1b**) preference.[12−18] In this study, we measure the acidity and proton affinity of various derivatives not heretofore examined, which establishes



fundamental properties as well as giving insight to tautomer presence.

RESULTS AND DISCUSSION

The substrates we considered are shown in Figure 3. We chose substitution at the 3-position as this allowed for a negative charge on N1 to resonate into resonance-stabilizing groups ($-C_2H_3$, $-C_4H_5$, $-$CHO). Chloride and bromide serve as electron-withdrawing groups into which charge cannot delocalize by resonance.

Our first goal was to benchmark calculations by examining the commercially available parent, 3-chloro-, and 3-formyl-2-pyridones experimentally and theoretically. These three were chosen as models for substrates with no substitution, substitution with a moiety that does not provide resonance delocalization for an anion at N1, and substitution with a resonance-stabilizing group, respectively.

2-Pyridone. *i. Calculations: 2-Pyridone Tautomers, Acidity, and Proton Affinity.* The keto−enol tautomerism of the parent pyridone system has been theoretically examined quite extensively in the past several decades.[10] The two tautomers, 2-pyridone (PY, **1a**) and 2-hydroxypyridine (HP, **1b**), appear to have less than a 1 kcal mol^{-1} difference in stability in the gas phase (with HP being more stable), which makes it a challenging computational system to examine.

Although DFT methods generally are known to reverse the PY/HP tautomer relative energies, they do generate reliable molecular structures.[19−25] The incorrect DFT energies have been shown to arise from the exchange potentials.[19]

Because we are interested not just in the relative tautomer stabilities but also the thermochemical properties (proton affinity and acidity, which in our previous studies of nucleobases are well calculated by DFT methods), we calculated the possible tautomers of pyridone using B3LYP/6-31+G(d) (Figure 4).[3,4,26−33] As expected, B3LYP/6-31+G(d)

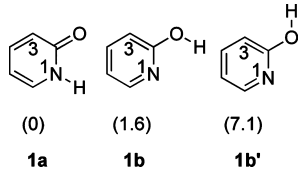


Figure 4. Pyridone calculations at B3LYP/6-31+G(d). Values in parentheses are relative stabilities. All are ΔH_{298} values, in kcal mol^{-1}.

incorrectly predicts that PY tautomer **1a** should be more stable than the HP tautomer **1b** (Figure 4). (The other possible enol structure **1b′** is 7 kcal mol^{-1} less stable than **1a**, Figure 4).

We also calculated the pyridone stabilities and properties using M06-2X/6-311+G(2df,2p) (Figure 5).[34−36] Tautomerism

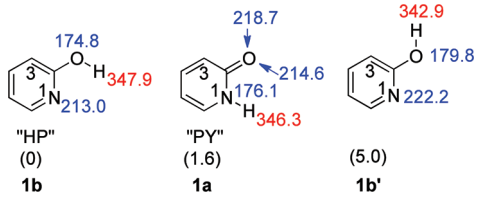


Figure 5. 2-Pyridone calculations at M06-2X/6-311+G(2df,2p). Values in parentheses are relative stabilities. Proton affinity values are in blue; acidity values are in red. All are ΔH_{298} values, in kcal mol^{-1}.

of PY/HP has not been examined by this relatively new suite of density functionals. Because recent papers have shown the accuracy of this method for predicting a wide range of chemistry, we wished to probe whether it could serve as a reasonable method for predicting stability and thermochemical properties in these systems.[34−36] M06-2X/6-311+G(2df,2p)

dx.doi.org/10.1021/jo201991y | J. Org. Chem. 2012, 77, 1623−1631

correctly predicts the higher stability of the enol form HP (**1b**, Figure 5). (The other possible enol structure, with the proton pointing "toward" C3 (**1b′**), is 5 kcal mol^{-1} less stable than **1b** at this level). The relative energy of the keto (PY) form **1a** (+1.6 kcal mol^{-1}) is slightly higher than that found by gas-phase experiments (which predict less than 1 kcal mol^{-1}) but is still a fairly reasonable calculational estimate.[11,13,37,38] More computationally intensive methods (G3, G4, CBS-APNO) yield more accurate values, but the faster M06-2X method is surprisingly quite comparable to CBS-APNO (which gives a relative stability of HP to PY as 1.3 kcal mol^{-1}).[10]

The acidity (ΔH_{acid}) and proton affinity (PA, which is $-\Delta H$ for protonation)[39] of the 2-pyridone structures at M06-2X/6-311+G(2df,2p) are also shown in Figure 5. In terms of acidity, the more stable enol **1b** and the keto structure **1a** have similar values (347.9 versus 346.3 kcal mol^{-1}). The PAs, however, may allow for differentiation between the two tautomers: the most basic site of enol **1b** is calculated to be 213.0 kcal mol^{-1}, while for keto **1a** it is 218.7 kcal mol^{-1}.[40] The enol **1b′** is significantly higher in energy than the other two structures and is unlikely to be present.

ii. Experiments: 2-Pyridone Acidity. We measured the acidity of 2-pyridone using acidity bracketing (details in the Experimental Section).[41] In the bracketing experiment (Table 1),

Table 1. Summary of Results for Acidity Bracketing of 2-Pyridone (1)

		proton transfer[b]	
ref compd	ΔH_{acid}[a]	ref acid	conjugate base
i-propylthiol	354.6 ± 0.5	−	+
n-pentanethiol	352.5 ± 2.3	−	+
m-cresol	349.6 ± 2.1	−	+
acetic acid	347.4 ± 0.5	+	+
butyric acid	346.8 ± 2.0	+	−
formic acid	346.0 ± 0.5	+	−
2,4-pentanedione	343.8 ± 2.1	+	−

[a] ΔH_{acid} is in kcal mol^{-1}.[39,42] [b] A "+" indicates the occurrence and a "−" indicates the absence of proton transfer.

a proton transfer occurs from acetic acid (ΔH_{acid} = 347.4 ± 0.5 kcal mol^{-1}) to deprotonated pyridone; the opposite reaction also occurs (that is, acetate deprotonates 2-pyridone), placing the acidity (ΔH_{acid}) of 2-pyridone at 347 ± 3 kcal mol^{-1}.

iii. Experiments: 2-Pyridone Proton Affinity. We measured the proton affinity (PA) of 2-pyridone using two complementary methods: PA bracketing and the Cooks kinetic method (details in the experimental section). In the bracketing experiment, the reaction is found to proceed in both directions for *N*-methylaniline (PA = 219.1 ± 2.0 kcal mol^{-1}), yielding a PA of 219 ± 3 kcal mol^{-1} (Table 2).

Using the Cooks kinetic method with reference bases 4-methylpyrazole (PA = 216.7 ± 2.0 kcal mol^{-1}), *N*,*N*-dimethylacetamide (PA = 217.0 ± 2.0 kcal mol^{-1}), *N*-benzylamine (PA = 218.3 ± 2.0 kcal mol^{-1}), *N*-methylaniline (PA = 219.1 ± 2.0 kcal mol^{-1}), L-phenylalanine (PA = 220.6 ± 2.0 kcal mol^{-1}), and cyclohexylamine (PA = 223.3 ± 2.0 kcal mol^{-1}) yields a PA of 218 ± 3 kcal mol^{-1}.

iv. Tautomer Composition: 2-Pyridone. Therefore, our experiments indicate a ΔH_{acid} of 347 kcal mol^{-1}. At M06-2X/6-311+G(2df,2p), both the keto (**1a**) and enol (**1b**) tautomers have acidities close to this value (346.3 and 347.9 kcal mol^{-1}),

Table 2. Summary of Results for Proton Affinity Bracketing of 2-Pyridone (1)

		proton transfer[b]	
ref compd	PA[a]	ref base	conjugate acid
N-ethylaniline	221.0 ± 2.0	+	−
n-butylamine	220.2 ± 2.0	+	−
N-methylaniline	219.1 ± 2.0	+	+
3-methylpyrazole	216.5 ± 2.0	−	+
2-chloropyridine	215.3 ± 2.0	−	+
o-toluidine	212.9 ± 2.0	−	+
pyrrole	209.2 ± 2.0	−	+

[a] PA is in kcal mol^{-1}.[39] [b] A "+" indicates the occurrence and a "−" indicates the absence of proton transfer.

so the experimental acidity cannot be used to ascertain what tautomers are present.

The M06-2X/6-311+G(2df,2p) calculated PA for the enol tautomer **1b** is 213.0 kcal mol^{-1} (for the most basic site, which is the ring nitrogen); for the keto tautomer **1a**, the computed PA (at the carbonyl) is 218.7 kcal mol^{-1}. We find that calculated proton affinities using this same method and level for a series of model compounds whose PAs are well-known experimentally (cyclohexanone, *N*-methyl-2-pyridone, *N*-methylacetamide, 3,5,5-trimethyl-2-cyclohexen-2-one) are accurate to within 1 kcal mol^{-1} (Supporting Information).[39] Therefore, the bracketed PA value of 219 kcal mol^{-1} implies that under our conditions, the keto tautomer is present.

As mentioned earlier, previous gas-phase experiments indicate a mixture of the keto and enol tautomers. In the PA bracketing experiment, as long as the neutral keto tautomer **1a** is present, it will deprotonate protonated reference bases with PAs around 219 kcal mol^{-1} and lower ("+" in the rightmost column of Table 2). We cannot know whether the enol **1b** is also present; the enol may contribute to the "+" reactivity at lower PA values, but there is no way to discern that.[43] In the opposite direction, we find that *only* bases with PAs of 219 kcal mol^{-1} and higher deprotonate protonated 2-pyridone. This experimental result implies the presence of the protonated structure **2** but not **3** (Figure 6), since if **3** were present, one

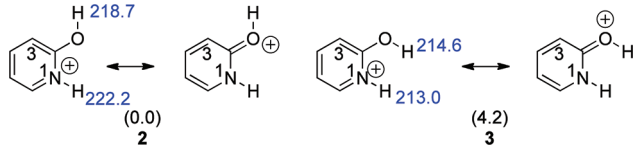
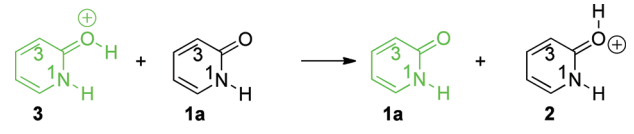


Figure 6. Possible structures for protonated 2-pyridone. Values in parentheses are relative stabilities. Enthalpy required to deprotonate protons are in blue. All are ΔH_{298} values, in kcal mol^{-1}, calculated at M06-2X/6-311+G(2df,2p).

would expect reference bases in the 213−215 kcal mol^{-1} range to deprotonate the protonated 2-pyridone. At M06-2X/6-311+G(2df,2p), **2** is more stable than **3** by 4.2 kcal mol^{-1}. Presumably, once 2-pyridone is protonated, reaction (Scheme 1)

Scheme 1



dx.doi.org/10.1021/jo201991y | J. Org. Chem. 2012, 77, 1623−1631

or rearrangement to the more stable form **2** may occur, leading to deprotonation only by bases with PAs higher than 219 kcal mol^{-1}.[3] Practically speaking, we bracket the more basic tautomer present and cannot be sure that the tautomer with a lower PA is not also present.

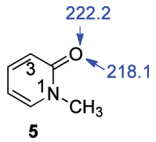
The Cooks kinetic experiment is interesting as a complementary method in that the pyridone is not vaporized; rather, a proton-bound dimer of the pyridone and reference base (**4**) is electrosprayed from aqueous (20% methanol, 80% water) solution. The proton-bound dimer is then isolated in the mass spectrometer, and energy is applied (collision-induced dissociation, CID, details in the Experimental section). The measured PA value of 218 kcal mol^{-1} implies that we measure the proton affinity on the "C3 side" (the face of the oxygen facing C3, not N1) of the keto structure **1a**.[40] Because the proton-bound dimer is electrosprayed from a water solution, this result indicates that pyridone probably exists as the keto tautomer in aqueous solution, which is consistent with previous solution-phase experimental data.[10−12,44,45]

$$[\text{pyridinone}\cdots\text{H}\cdots\text{reference base}]^{\oplus}$$

4

Thus, in our experiments, whether we vaporize 2-pyridone from the solid phase or electrospray a proton-bound dimer of 2-pyridone with a reference base, we measure a PA that is consistent with the calculated PA of the keto structure. This result does not discount the possibility of a keto−enol mixture; we can only say that the keto form is present.

In order to validate the comparison of calculations to experiment, we also calculated the PA of *N*-methyl-2-pyridone (**5**) at M06-2X/6-311+G(2df,2p); methylation of the N removes the possibility of multiple tautomers and "locks" the pyridone into keto form. The calculated PA of the most basic site is 222.2 kcal mol^{-1}. The literature value is 221.3 ± 2.0 kcal mol^{-1},[39,46] which we also confirmed by bracketing the PA in our FTMS (Supporting Information). The calculated and measured values are therefore consistent and support our conclusion for the *parent* (N−H) 2-pyridone: the measured PA of 219 kcal mol^{-1} corresponds to the keto form (calculated PA of 218.7 kcal mol^{-1}).



5

3-Chloro-2-pyridone. *i. Calculations: 3-Chloro-2-Pyridone Tautomers, Acidity, Proton Affinity.* The calculated values at M06-2X/6-311+G(2df,2p) for the acidity and proton affinity for the possible tautomers of 3-chloro-2-pyridone are shown in Figure 7. As with the parent pyridone, calculations predict that the more stable enol tautomer (**6b**, with the proton "pointing" toward N1) will be slightly more stable than the keto **6a**, by 1.2 kcal mol^{-1}. Both tautomers have similar acidity (338−339 kcal mol^{-1}), but the proton affinities of the most basic sites differ by 8 kcal mol^{-1} (208.0 (enol) versus 215.9 kcal mol^{-1} (keto)). There is also the other enol structure (with the proton "pointing" toward C3, **6b′**) that is 2.1 kcal mol^{-1} less stable than the enol tautomer **6b**; its PA and acidity are comparable to the keto form. In the parent pyridone, the analogous enol form (H "pointing" toward C3, **1b′**) is not particularly stable. However, in this 3-chloro compound, a

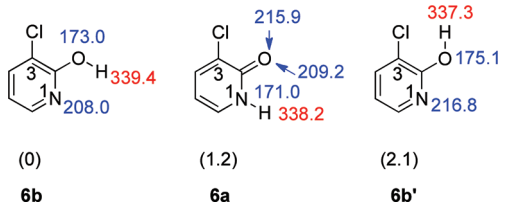


Figure 7. 3-Chloro-2-pyridone calculations at M06-2X/6-311+G(2df,2p). Values in parentheses are relative stabilities. Proton affinity values are in blue; acidity values are in red. All are ΔH_{298} values, in kcal mol^{-1}.

stabilizing interaction between the 3-Cl and the 2-OH exists (calculated Cl−H distance is 2.4 Å), stabilizing the tautomer.

ii. Experiments: 3-Chloro-2-Pyridone Acidity. Acidity. We measured the acidity of 3-chloro-2-pyridone using both bracketing and the Cooks kinetic method. In the bracketing experiment (Table 3), the reaction between the deprotonated

Table 3. Summary of Results for Acidity Bracketing of 3-Chloro-2-pyridone (6)

		proton transfer[b]	
ref compd	ΔH_{acid}[a]	ref acid	conjugate base
formic acid	346.0 ± 0.5	−	+
2,4-pentanedione	343.8 ± 2.1	−	+
methyl cyanoacetic acid	340.8 ± 0.6	−	+
trifluoro-*m*-cresol	339.3 ± 2.1	+	+
2-chloropropionic acid	337.0 ± 2.1	+	−
malononitrile	335.8 ± 2.1	+	−
pyruvic acid	333.5 ± 2.9	+	−

[a] ΔH_{acid} is in kcal mol^{-1}.[39,42] [b] A "+" indicates the occurrence and a "−" indicates the absence of proton transfer.

3-chloro-2-pyridone and trifluoro-*m*-cresol (ΔH_{acid} = 339.3 ± 2.1 kcal mol^{-1}) proceeds, as does the reaction in the opposite direction (trifluoro-*m*-cresolate with neutral 3-chloro-2-pyridone), yielding a ΔH_{acid} value of 339 ± 3 kcal mol^{-1}.

Using the Cooks kinetic method and reference acids anthranilic acid (ΔH_{acid} = 337.3 ± 2.2 kcal mol^{-1}), 2,6-dimethylbenzoic acid (ΔH_{acid} = 338.4 ± 2.1 kcal mol^{-1}), trifluoro-*m*-cresol (ΔH_{acid} = 339.3 ± 2.1 kcal mol^{-1}), benzoic acid (ΔH_{acid} = 340.1 ± 2.2 kcal mol^{-1}), and methoxyacetic acid (ΔH_{acid} = 341.9 ± 2.1 kcal mol^{-1}) gives a ΔH_{acid} of 340 ± 3 kcal mol^{-1}.

iii. Experiments: 3-Chloro-2-Pyridone Proton Affinity. 3-Methylpyrazole (PA = 216.5 ± 2.0 kcal mol^{-1}) deprotonates protonated 3-chloro-2-pyridone, but 2-chloropyridine (PA = 215.3 ± 2.0 kcal mol^{-1}) does not (Table 4). In the opposite direction, 3-chloro-2-pyridone deprotonates protonated 2-chloropyridine, but not protonated 3-methylpyrazole. Therefore, the bracketed PA of 3-chloro-2-pyridone is 216 ± 3 kcal mol^{-1}.

In the Cooks kinetic method experiment, reference bases 2-chloropyridine (PA = 215.3 ± 2.0 kcal mol^{-1}), anthranilic acid (PA = 215.5 ± 2.0 kcal mol^{-1}), 3-methyl pyrazole (PA = 216.5 ± 2.0 kcal mol^{-1}), 4-methylpyrazole (PA = 216.7 ± 2.0 kcal mol^{-1}), and *N*,*N*-dimethylacetamide (PA = 217.0 ± 2.0 kcal mol^{-1}) were used, yielding a PA of 216 ± 3 kcal mol^{-1}.

iv. Tautomer Composition: 3-Chloro-2-pyridone. The ΔH_{acid} of 3-chloro-2-pyridone, regardless of method used, is measured to be 339−340 kcal mol^{-1}. Since the calculated

dx.doi.org/10.1021/jo201991y | J. Org. Chem. 2012, 77, 1623−1631

Table 4. Summary of Results for Proton Affinity Bracketing of 3-Chloro-2-pyridone (6)

ref compd	PA[a]	proton transfer[b] ref base	proton transfer[b] conjugate acid
N-methylaniline	219.1 ± 2.0	+	−
N,*N*-dimethylacetamide	217.0 ± 2.0	+	−
3-methylpyrazole	216.5 ± 2.0	+	−
2-chloropyridine	215.3 ± 2.0	−	+
m-toluidine	214.7 ± 2.0	−	+
o-toluidine	212.9 ± 2.0	−	+
pyrrole	209.2 ± 2.0	−	+

[a]PA is in kcal mol^{-1}.[39] [b]A "+" indicates the occurrence and a "−" indicates the absence of proton transfer.

acidity of the enol and keto tautomers are in the same range (337−339 kcal mol^{-1} for the three different structures **6a**, **6b**, **6b′**), the acidity is not indicative of which tautomers may be present. The bracketed PA is 216 kcal mol^{-1}. As with the parent pyridone, when compared to calculations, the measured PA does not correspond to the most stable enol tautomer **6b**. In this case, the bracketed PA is consistent with either the keto form **6a** or the less stable enol form **6b′**. The latter is calculated to be 2.1 kcal mol^{-1} less stable than the more stable enol **6b**; if this estimate is accurate, this particular form should constitute a relatively small portion of the tautomer mixture. In the following discussion, therefore, we will focus on the keto form **6a** and the enol form **6b**.

In the bracketing experiment, the neutral 3-chloro-2-pyridone is able to deprotonate conjugate acids of reference bases with PAs 215 kcal mol^{-1} and lower (rightmost column, Table 4). This is consistent with the PA of keto form (calculated PA = 215.9 kcal mol^{-1}), indicating the presence of the keto tautomer **6a**. At PAs less than 208 kcal mol^{-1}, the enol tautomer **6b** could also be reacting, but we would not be able to discern its contribution to the overall reactivity. In the opposite direction, reference bases below 216.5 kcal mol^{-1} cannot deprotonate protonated 3-chloro-2-pyridone. This would imply the presence of structure **7**, but not of structure **8**. As with the parent pyridone, we speculate that if **8** is present, it converts under our conditions to the more stable protonated form **7** (more stable than protonated **8** by 6.7 kcal mol^{-1}) (Figure 8).

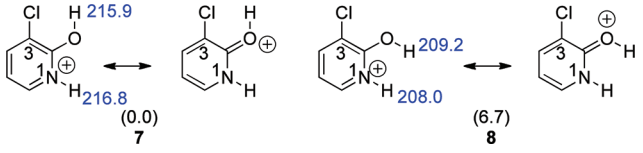


Figure 8. Possible structures for protonated 3-chloro-2-pyridone. Values in parentheses are relative stabilities. Enthalpy required to deprotonate protons are in blue. All are ΔH_{298} values, in kcal mol^{-1}, calculated at M06−2X/6-311+G(2df,2p).

As with the parent pyridone, therefore, we can conclude that the keto (**6a**) tautomer is present but cannot discount a mixture that possibly also includes enol tautomer (**6b**), since the nature of the experiment dictates that we bracket only the most basic tautomer. Given that calculations indicate a roughly 1 kcal mol^{-1} difference in stability for **6a** versus **6b**, a mixture is probable.

The Cooks kinetic PA value is also 216 kcal mol^{-1}, which indicates that we are measuring the carbonyl O (on the "C3" side or face) of **6a**, implying the keto form dominates in solution.[40,45]

3-Formyl Pyridone. *i. Calculations: 3-Formyl-2-pyridone Tautomers, Acidity, Proton Affinity.* 3-Formylpyridone is somewhat more complicated in that several different structures are possible due to both the formyl and the enol moieties. The three lowest energy structures at M06-2X/6-311+G(2df,2p) are shown in Figure 9. (The remaining

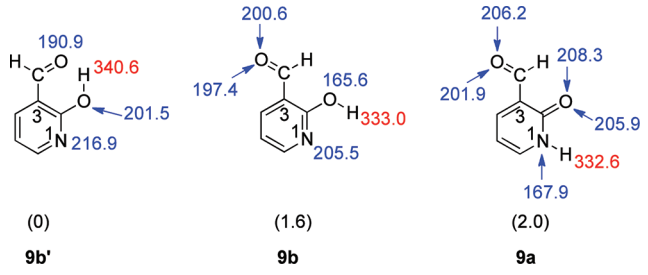


Figure 9. 3-Formyl-2-pyridone calculations at M06-2X/6-311+G(2df,2p). Values in parentheses are relative stabilities. Proton affinity values are in blue; acidity values are in red. All are ΔH_{298} values, in kcal mol^{-1}.

structures are over 4 kcal mol^{-1} less stable than the most stable tautomer **9b′**; all can be found in the Supporting Information.) As with the parent and 3-chloro-2-pyridone, an enol structure (**9b′**) is predicted to be most stable in the gas phase. However, in this case, the proton of the most stable enol is pointing "toward" the C3. This is in contrast to the parent and 3-chloro derivatives, where the analogous structures (**1b′** and **6b′** for the parent and 3-chloro, respectively) were the least stable. The high stability of this structure is due to the internal hydrogen bond that exists between the enol H and the carbonyl O (calculated distance of 1.8 Å). The parent pyridone has no such hydrogen bond, so structure **1b′** is quite unstable, relative to **1b** (Figure 5). In the 3-chloro-2-pyridone, the analogous structure **6b′** is somewhat stabilized by a weak internal hydrogen bond (calculated Cl−H distance of 2.4 Å). Interestingly, with the formyl system, the stabilities are reversed and **9b′** becomes the most stable structure. The calculated acidities and proton affinities are also shown in Figure 9 for the three tautomers.

ii. Experiments: 3-Formyl-2-pyridone Acidity. Acidity. Using the bracketing method, we find that deprotonated 3-formyl pyridone does not deprotonate 2-chloropropionic acid (ΔH_{acid} = 337.0 ± 2.1 kcal mol^{-1}); the opposite reaction occurs (Table 5). Deprotonated 3-formylpyridone does deprotonate

Table 5. Summary of Results for Acidity Bracketing of 3-Formyl-2-pyridone (9)

ref compd	ΔH_{acid}[a]	proton transfer[b] ref acid	proton transfer[b] conjugate base
methyl cyanoacetate	340.8 ± 0.6	−	+
trifluoro-*m*-cresol	339.3 ± 2.1	−	+
2-chloropropionic acid	337.0 ± 2.1	−	+
malononitrile	335.8 ± 2.1	+	−
pyruvic acid	333.5 ± 2.9	+	−
difluoroacetic acid	331.0 ± 2.2	+	−
1,1,1-trifluoro-2,4-pentanedione	328.3 ± 2.9	+	−

[a]ΔH_{acid} is in kcal mol^{-1}.[39] [b]A "+" indicates the occurrence and a "−" indicates the absence of proton transfer.

malononitrile but deprotonated malononitrile does not deprotonate 3-formyl pyridone. We thus bracket 3-formylpyridone to be ΔH_{acid} = 336 ± 3 kcal mol^{-1}.

dx.doi.org/10.1021/jo201991y | J. Org. Chem. 2012, 77, 1623−1631

We also measured the acidity of 3-formyl-2-pyridone using the Cooks kinetic method. Five reference acids were used: 2-chloropropionic acid (ΔH_{acid} = 337.0 ± 2.1 kcal mol^{-1}), 2-bromopropionic acid (ΔH_{acid} = 336.8 ± 2.1 kcal mol^{-1}), *p*-hydroxybenzoic acid (ΔH_{acid} = 335.9 ± 2.1 kcal mol^{-1}), 2-chlorobenzoic acid (ΔH_{acid} = 335.1 ± 2.1 kcal mol^{-1}), and pyruvic acid (ΔH_{acid} = 333.5 ± 2.9 kcal mol^{-1}). The experiments yield an acidity of 335 ± 3 kcal mol^{-1}.

iii. Experiments: 3-Formyl-2-pyridone PA. When bracketing the PA of 3-formyl-2-pyridone, we find that the reaction proceeds in both directions for 3-methylpyrazole (PA = 216.5 ± 2.0 kcal mol^{-1}) and *N,N*-dimethylacetamide, placing the PA = 217 ± 3 kcal mol^{-1} (Table 6).

Table 6. Summary of Results for Proton Affinity Bracketing of 3-Formyl-2-pyridone (9)

		proton transfer[b]	
ref compd	PA[a]	ref base	conjugate acid
n-butylamine	220.2 ± 2.0	+	−
N-methylaniline	219.1 ± 2.0	+	−
N,N-dimethylacetamide	217.0 ± 2.0	+	+
3-methylpyrazole	216.5 ± 2.0	+	+
2-chloropyridine	215.3 ± 2.0	−	+
o-toluidine	212.9 ± 2.0	−	+
pyrimidine	211.7 ± 2.0	−	+
aniline	210.9 ± 2.0	−	+
pyrrole	209.2 ± 2.0	−	+
m-chloroaniline	207.5 ± 2.0	−	+

[a]PA is in kcal mol^{-1}.[39] [b]A "+" indicates the occurrence and a "−" indicates the absence of proton transfer.

Six reference bases were used to measure PA via Cooks kinetic method: *n*-butylamine (PA = 220.2 ± 2.0 kcal mol^{-1}), *N*-methylaniline (PA = 219.1 ± 2.0 kcal mol^{-1}), *N*-benzylamine (PA = 218.3 ± 2.0 kcal mol^{-1}), *N,N*-dimethylacetamide (PA = 217.0 ± 2.0 kcal mol^{-1}) 3-methylpyrazole (PA = 216.5 ± 2.0 kcal mol^{-1}), and 2-chloropyridine (PA = 215.3 ± 2.0 kcal mol^{-1}). These yield a PA of 217 ± 3 kcal mol^{-1}.

iv. Tautomer Composition: 3-Formyl-2-pyridone. The measured acidity is 335−336 kcal mol^{-1}, with a ± 3 kcal mol^{-1} error bar. Because this value is right "in between" and could correspond to any of the various acidities of the three low energy structures (enol **9b′** has a calculated ΔH_{acid} of 340.6 kcal mol^{-1}; the other enol **9b** and the ketone **9a**, both around 333 kcal mol^{-1}), the acidity cannot be used to discriminate among the possible tautomers.

The measured proton affinity of 217 kcal mol^{-1} (by both bracketing and Cooks) corresponds to the calculated PA for the most stable enol tautomer **9b′**: in this case, the most basic site and the most stable tautomer are consistent. Again, the other enol **9b** could also be present (as could, to a lesser extent, the least stable keto **9a**) as a mixture, but we can conclude that we do have enol **9b′** present, whether bracketing or Cooks conditions are used.

S_N2 Studies. As stated previously, the initial motivation for this study was to examine the correlation between acidity and leaving group ability for resonance-stabilized versus non-resonance-stabilized anionic leaving groups. However, characterization of the model system—substituted pyridones—is of interest in its own right, as described in much of this paper. In this section, we wish to briefly report computational results comparing the acidity (ΔH_{acid}) and S_N2 barrier ($\Delta H^{\ddagger}$ for the S_N2 reaction using formate as a nucleophile) for a series of 3-substituted pyridones (Figure 3, Scheme 2, Table 7). The

Scheme 2

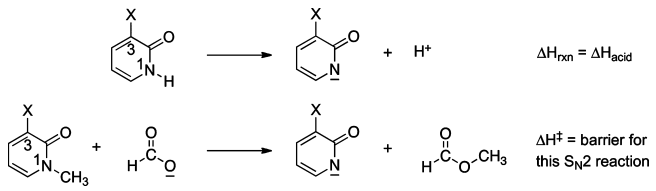


Table 7. M06-2X/6-311+G(2df,2p) Calculations of Acidity and S_N2 Barrier for a Series of 3-Substituted-2-Pyridonones (Structure Shown in Figure 3, R = H)

X	ΔH_{acid},[a] kcal mol^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}[b]	$\Delta\Delta H^{\ddagger}/\Delta\Delta H_{acid}$
H	346.3 (0)	18.4	−
C_2H_3	342.3 (4.0)	16.1 (2.3)	0.575
C_4H_5	339.2 (7.1)	14.5 (3.9)	0.549
HCO	332.6 (13.7)	9.6 (8.8)	0.642
Cl	338.2 (8.1)	13.1 (5.3)	0.654
Br	337.1 (9.2)	12.7 (5.7)	0.620

[a]The values in parentheses are the differences in ΔH_{acid} ($\Delta\Delta H_{acid}$) for the various X substituents, relative to the parent pyridone (X = H) [ΔH_{acid}(parent) − ΔH_{acid}(substituted)]. [b]The values in parentheses are the differences in $\Delta H^{\ddagger}$ ($\Delta\Delta H^{\ddagger}$) for the various X substituents, relative to the parent pyridone (X = H) [$\Delta H^{\ddagger}$(parent) − $\Delta H^{\ddagger}$(substituted)].

parent 2-pyridone is X = H. The moieties C_2H_3, C_4H_5, and HCO were chosen as groups that can delocalize by resonance an anion at N1. Groups that do not allow for resonance delocalization stabilization are X = Cl and Br.[5] In Table 7, "$\Delta\Delta H_{acid}$" represents the difference in ΔH_{acid} between the parent 2-pyridone and a given substituted pyridone. "$\Delta\Delta H^{\ddagger}$" represents the difference in $\Delta H^{\ddagger}$ between the parent 2-pyridone and a given substituted pyridone. The ratio of $\Delta\Delta H^{\ddagger}/\Delta\Delta H_{acid}$ (last column of Table 7) indicates the relationship between the effect an X group has on acidity versus the effect of that same X group on the S_N2 enthalpic barrier. The "better" the correlation between acidity and the S_N2 barrier, the closer to 1 this value should be. We hypothesize that groups that stabilize the N1-anion by resonance delocalization will have a weaker correlation (smaller value) because that delocalization will enhance acidity more than it will lower the S_N2 barrier. The argument is that in the S_N2 transition state, the N1-anion is not fully formed so the full benefit of the resonance delocalization is not realized.[5] The trends in Table 7 do appear to support the hypothesis: the resonance-delocalized groups C_2H_3 and C_4H_5 have a smaller $\Delta\Delta H^{\ddagger}/\Delta\Delta H_{acid}$ value (0.575 and 0.549) than do the halide substituents (0.654 and 0.620 for Cl and Br, respectively). The formyl group is an interesting data point as its correlation is quite high (0.642) for a resonance-delocalized group. We speculate that HCO may not be a good model since the oxygen is inductively electron withdrawing, making the HCO not strictly a resonance delocalization moiety. Hammett σ values support this theory: the σ_m values, which reflect inductive ability, are similar for Br, Cl and HCO (0.39, 0.37, and 0.35, respectively).[47−49] In contrast, the σ_m value for C_2H_3 is very small: 0.05. The comparison of C_2H_3 and HCO is particularly useful, as the groups differ by the"exchange" of a CH2 for an O

dx.doi.org/10.1021/jo201991y | J. Org. Chem. 2012, 77, 1623−1631

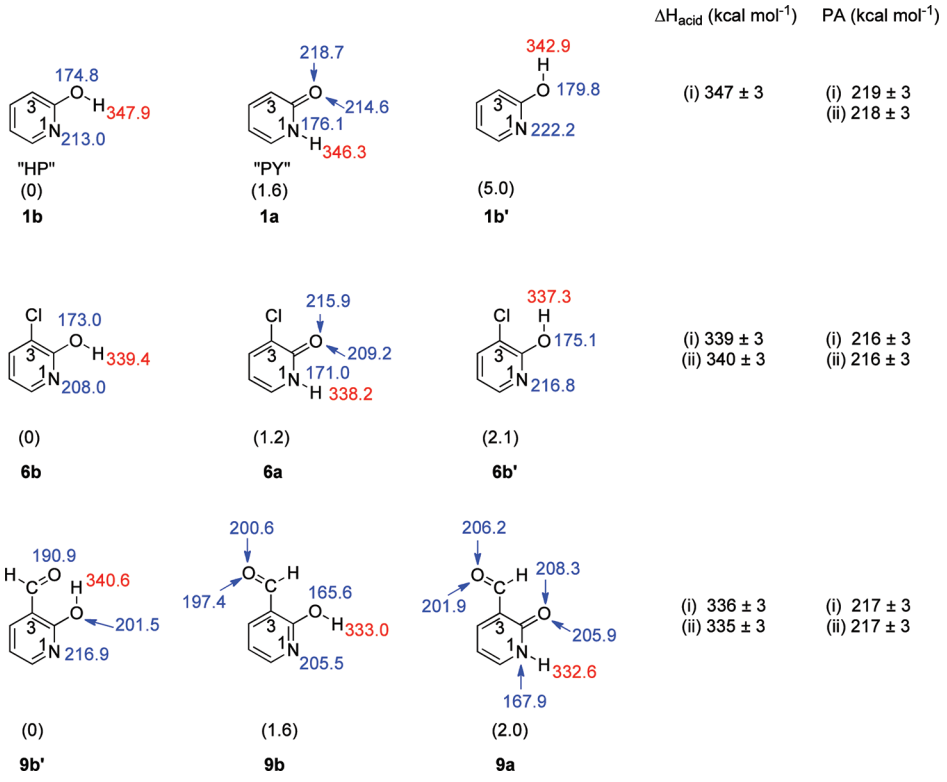


Figure 10. Summary of gas-phase computational (M06−2X/6-311+G(2df,2p)) and experimental data for the pyridones studied herein. Calculated relative stabilities are in parentheses; values in blue are calculated PAs and values in red are calculated acidities. All are ΔH_{298} values. For the experimental data, (i) indicates use of the bracketing method; (ii) indicates Cooks kinetic method measurement.

($H_2C{=}CH_2$ versus $H_2C{=}O$). Both provide resonance stabilization through the double bond, but HCO is also stabilizing via induction, which means it is not a strictly resonance-stabilizing group.

CONCLUSIONS

In summary, we have characterized the acidity and proton affinities of 2-pyridone, 3-chloro-2-pyridone, and 3-formyl-2-pyridone (Figure 10). For 2-pyridone, we find that gas-phase calculations at M06-2X/6-311+G(2df,2p) correctly indicate that the keto and enol forms (**1a** and **1b**) are close in energy, with the enol being slightly more stable. Comparison of calculated and measured PAs indicate that the keto form is present. Most likely, the more stable enol form is also present: we do not bracket its PA as it is less basic. Interestingly, measurement of the PA using the Cooks kinetic method, which vaporizes the pyridone from aqueous solution, indicates the keto tautomer. This is consistent with the solution phase preference for the keto structure.

For the 3-chloro-2-pyridone, which has not heretofore been studied, calculations indicate that the keto **6a** and enol **6b** are close in energy, with the enol being slightly more stable (much like the parent pyridone). The PA measurements point to the keto structure, again because the bracketing experiment targets the more basic tautomer. The more stable enol tautomer is probably also present, in a mixture of keto and enol. The alternate enol structure **6b′** is somewhat stabilized by a weak internal hydrogen bond between the Cl and H, but is still the least stable structure and if present, will be a small component in the mixture. As with the parent 2-pyridone, the Cooks kinetic experiment indicates the keto tautomer, which is probably more stable in solution.

The 3-formyl derivative, which also has not been studied, has an enol conformation with an internal hydrogen bond (between the aldehyde O and the enol H) that renders **9b′** as the most stable tautomer. The PA measurements confirm the presence of this enol form (both with bracketing and the Cooks kinetic method). This particular derivative is interesting as the presence of the formyl group reverses the relative stability of the two enol tautomers (compared to the parent and 3-chloro compounds). Different substitution can therefore allow one to "tune" for tautomer preference.

In terms of the substituted pyridones as a model system for testing acidity-leaving group correlations, our calculations indicate that leaving groups that allow for resonance delocalization of the product anion (pyridones substituted with X = C_2H_3, C_4H_5 (Figure 3)) do show less correlation than nonresonance-stabilizing groups (X = Cl, Br). That is, anions that are stabilized by resonance may be stable conjugate bases (thus their conjugate acids are acidic), but may not be correspondingly good leaving groups since that stabilization is not fully felt in the S_N2 transition state. More studies to test this hypothesis are underway.

EXPERIMENTAL SECTION

All pyridones as well as reference acids and bases are commercially available and were used as received.

Acidity and proton affinity bracketing experiments were conducted using a Finnigan 2001 Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR) with a dual cell setup described previously.[3,4,27,29,31] The magnetic field is produced by a 3.3 T superconducting magnet. The dual cell consists of two adjoining 1-in. cubic cells positioned collinearly in the magnetic field and pumped down to a baseline pressure of 1×10^{-9} Torr. Solid pyridones were introduced to the cell via a solids probe and slightly heated if

dx.doi.org/10.1021/jo201991y | J. Org. Chem. 2012, 77, 1623−1631

necessary. Liquid reference acids or bases were introduced via a heatable batch inlet system. Hydroxide or hydronium ions were produced from water pulsed into the cell, and ionized by an electron beam (typically 8 eV (for OH^-), 20 eV (for H_3O^+), 6 μA, 0.5 s). Ions were generated by deprotonation or protonation of commercially available reference acids or bases with hydroxide or hydronium ions, respectively. Reactive cations and anions of interest were selected and transferred from one cubic cell to another via a 2-mm hole in the middle trapping plate. Transferred ions were cooled with pulsed argon gas that forced the pressure to rise to 10^{-5} Torr. Experiments were conducted at ambient temperature. The typical protocol for bracketing experiments has been described previously.[3,4,27−30,32] Proton transfer reactions were conducted in both directions. For example, for the first set of reactions for proton affinity bracketing of pyridone hydronium ion protonates neutral pyridone (P), resulting in PH^+ formation. PH^+ is transferred into the adjoining cell where it is allowed to react with the neutral reference base with known proton affinity. In the opposite direction, the protonated reference base BH^+ is generated and transferred into the adjoining cell where it is allowed to react with P. The occurrence of proton transfer is regarded as evidence that the reaction is exothermic (denoted as "+" in the tables).

Bracketing experiments were run under pseudo-first-order conditions since the amount of the neutral reactant was always in excess, relative to the reactant ions. Reading the pressure of the neutral compounds from the ion gauges is not always accurate; therefore, we "back out" the neutral substrate pressure from fast control reactions (described previously).[28−30,32,50,51]

We also used the Cooks kinetic method in a Finnigan quadrupole ion trap (LCQ) mass spectrometer[52−56] to measure proton affinity and acidity. The proton-bound complex ions are generated by electrospray (ESI).[57] For each experiment, a solution of the pyridone (250 μM) and reference acid or base (250 μM) is prepared (in 20% methanol/80% water). An electrospray needle voltage of ∼4 kV was used. The flow rate is 25 μL/min. The proton-bound complex ions were isolated and then dissociated by applying collision-induced dissociation (CID); the complexes were activated for about 30 ms. A total of 40 scans was averaged for the product ions.

The Cooks kinetic method involves the formation of a proton bound complex, or dimer, of the conjugate bases of the unknown AH and a reference acid B_iH of known acidity (eq 1). (The same can be done for proton affinity, where a positively charged proton-bound dimer is formed).

$$[AHB_i]^- \xrightarrow{k_1} [B_iH] + A^- \qquad [AHB_i]^- \xrightarrow{k_2} [AH] + B_i^- \qquad \text{eq. 1}$$

The proton-bound dimer $[AHB_i]^-$ is dissociated via collision-induced dissociation (CID). The rate constants k_1 and k_2 are for the two different dissociation pathways. The relationship of these rate constants to ΔH_{acid} is shown in eq 2. R is the gas constant, and T_{eff} is the effective temperature[58] of the activated dimer.[52−56] The ratio of the amounts (intensities) of the two deprotonated products yields the relative acidity of the two compounds of interest, assuming the dissociation has no reverse activation energy barrier and that the dissociation transition structure is late and therefore indicative of the stability of the two deprotonated products. These assumptions are generally true for proton bound systems. In order to obtain the acidity of compound AH, the natural logarithm of the relative intensity ratios is plotted versus the acidities for a series of reference acids, where the slope is $1/RT_{eff}$ and the y-intercept is $(-\Delta H_{AH}/RT_{eff})$. The T_{eff} is obtained from the slope. The acidity of compound AH (ΔH_{AH}) is calculated from either eq 2 or the y-intercept.

$$\ln(k_1/k_2) = (1/RT_{eff})(\Delta H_{BiH} - \Delta H_{AH}) \qquad \text{eq. 2}$$

Calculations. Calculations were conducted at the B3LYP/6-31+G(d)[59−61] and M06-2X/6-311+G(2df,2p)[34,35] levels as implemented in Gaussian09.[62] The geometries were fully optimized, and frequencies were calculated. No scaling factor was applied. All of the values reported are at ΔH at 298 K. The acidity and PA values include the enthalpy of the proton at 298 K (1.5 kcal mol^{-1}). All calculated transition state structures have one negative frequency.

■ ASSOCIATED CONTENT

Supporting Information

Cartesian coordinates for all calculated species (including higher energy tautomers), other additional data as noted in manuscript, and full citations for references with more than 16 authors. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jee.lee@rutgers.edu.

■ ACKNOWLEDGMENTS

A.Z.M., A.P., and J.K.L. gratefully acknowledge the support of the NSF, ACS-PRF, and NCSA. We are extremely grateful to Professor Dean J. Tantillo (University of California, Davis) for the concept and execution of the cover art. We thank Professor Karsten Krogh-Jespersen for helpful discussions, and A.P. thanks Rutgers University for a research fellowship.

■ REFERENCES

(1) Berti, P. J.; McCann, J. A. B. *Chem. Rev.* **2006**, *106*, 506−555.
(2) Stivers, J. T.; Drohat, A. C. *Arch. Biochem. Biophys.* **2001**, *396*, 1−9.
(3) Kurinovich, M. A.; Lee, J. K. *J. Am. Chem. Soc.* **2000**, *122*, 6258−6262.
(4) Kurinovich, M. A.; Lee, J. K. *J. Am. Soc. Mass Spectrom.* **2002**, *13*, 985−995.
(5) Zhachkina, A.; Lee, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 18376−18385.
(6) 3-Methyluracil rather than uracil was studied to avoid complicating deprotonation at the N3-H site; see ref 5 for details.
(7) Walsh, C. *Enzymatic Reaction Mechanisms*; Freeman: San Francisco, 1979.
(8) Pullman, B.; Pullman, A. *Adv. Heterocycl. Chem.* **1971**, *13*, 77−159.
(9) Kwiatkowski, J. S.; Pullman, B. *Adv. Heterocycl. Chem.* **1975**, *18*, 199−335.
(10) Sonnenberg, J. L.; Wong, K. F.; Voth, G. A.; Schlegel, B. *J. Chem. Theory Comput.* **2009**, *5*, 949−961, and references therein.
(11) Beak, P. *Acc. Chem. Res.* **1977**, *10*, 186−192.
(12) Sato, H.; Hirata, F.; Sakaki, S. *J. Phys. Chem. A* **2004**, *108*, 2097−2102.
(13) Hatherley, L. D.; Brown, R. D.; Godfrey, P. D.; Pierlot, A. P.; Caminati, W.; Damiani, D.; Melandri, S.; Favero, L. B. *J. Phys. Chem.* **1993**, *97*, 46−51.
(14) Nowak, M. J.; Lapinski, L.; Fulara, J.; Les, A.; Adamowicz, L. *J. Phys. Chem.* **1992**, *96*, 1562−1569.
(15) De Kowalewski, D. G.; Contreras, R. H.; Diez, E.; Esteban, A. *Mol. Phys.* **2004**, *102*, 2607−2615.
(16) Furlong, J. J. P.; Mercedes Schiavoni, M.; Castro, E. A.; Allegretti, P. E. *Russ. J. Org. Chem.* **2008**, *44*, 1725−1736.
(17) Cook, M. J.; Katritzky, A. R. *Tetrahedron Lett.* **1976**, *31*, 2685−2688.
(18) Beak, P.; Fry, F. S. *J. Am. Chem. Soc.* **1973**, *95*, 1700−1702, and references therein.
(19) Piacenza, M.; Grimme, S. *J. Comput. Chem.* **2004**, *25*, 83−99.
(20) Fu, A.; Li, H.; Du, D.; Zhou, Z. *J. Phys. Chem. A* **2005**, *109*, 1468−1477.
(21) Maris, A.; Ottaviani, P.; Caminati, W. *Chem. Phys. Lett.* **2002**, *360*, 155−160.

(22) Hazra, M. K.; Chakraborty, T. *J. Phys. Chem. A* **2006**, *110*, 9130−9136.
(23) Barone, V.; Adamo, C. *J. Phys. Chem.* **1995**, *99*, 15062−15068.
(24) Dkhissi, A.; Houben, L.; Smets, J.; Adamowicz, L.; Maes, G. *J. Mol. Struct.* **1999**, *484*, 215−227.
(25) Tsuchida, N.; Yamabe, S. *J. Phys. Chem. A* **2005**, *109*, 1974−1980.
(26) Sharma, S.; Lee, J. K. *J. Org. Chem.* **2004**, *69*, 7018−7025.
(27) Sharma, S.; Lee, J. K. *J. Org. Chem.* **2002**, *67*, 8360−8365.
(28) Sun, X.; Lee, J. K. *J. Org. Chem.* **2007**, *72*, 6548−6555.
(29) Liu, M.; Xu, M.; Lee, J. K. *J. Org. Chem.* **2008**, *73*, 5907−5914.
(30) Liu, M.; Li, T.; Amegayibor, S.; Cardoso, D. S.; Fu, Y.; Lee, J. K. *J. Org. Chem.* **2008**, *73*, 9283−9291.
(31) Kurinovich, M. A.; Lee, J. K. *Chem. Commun.* **2002**, 2354−2355.
(32) Zhachkina, A.; Liu, M.; Sun, X.; Amegayibor, S.; Lee, J. K. *J. Org. Chem.* **2009**, *74*, 7429−7440.
(33) Lee, J. K. *Int. J. Mass Spectrom.* **2005**, *240*, 261−272.
(34) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215−241.
(35) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157−167.
(36) Wheeler, S. E.; Moran, A.; Pieniazek, S. N.; Houk, K. N. *J. Phys. Chem. A* **2009**, *113*, 10376−10384.
(37) Guimon, C.; Garrabe, G.; Pfister-Guillouzo, G. *Tetrahedron Lett.* **1979**, *28*, 2585−2588.
(38) Brown, R. S.; Tse, A.; Vederas, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 1174−1176.
(39) NIST Chemistry WebBook, NIST Standard Reference Database Number 69; retrieved in 2011. Linstrom, P. J., Mallard, W. G., Eds.; National Institute of Standards and Technology: Gaithersburg, MD, http://webbook.nist.gov.
(40) If more than one value is listed for an atom, the arrows show the site of protonation (for example, the O2 of 2-pyridone can be protonated on the N1 side or the C3 side).
(41) We also attempted to measure the acidity using the Cooks kinetic method, but the signal corresponding to the protonated dimer of 2-pyridone and a series of reference bases was neither strong nor stable enough to conduct the experiment.
(42) Eyet, N.; Villano, S. M.; Bierbaum, V. M. *Int. J. Mass Spectrom.* **2009**, *283*, 26−29.
(43) On the basis of calculations, enol **1b′** is 5 kcal mol^{-1} less stable than enol **1b** and is thus unlikely to be present in any significant quantity.
(44) Although generally electrospray is believed to be a soft ionization technique that vaporizes solution-phase ions with integrity, there do exist examples whereby some structures when electrosprayed can isomerize in the desolvation process, though this has not been shown for pyridones: Tian, Z.; Kass, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 10842−10843, and references therein.
(45) It is also possible that the protonated dimer is a mixture of structures, although because the PA measured by Cooks is comparable to that obtained by bracketing, the likelihood is that the major, if not exclusive, structure is proton bound on the C3 side of the keto.
(46) Gronert, S.; Feng, W. Y.; Chew, F.; Wu, W. *Int. J. Mass Spectrom.* **2000**, *195/196*, 251−258.
(47) Ritchie, C. D.; Sager, W. F. *Prog. Phys. Org. Chem.* **1964**, *2*, 323−400.
(48) Hansch, C.; Leo, A.; Unger, S.; Kim, K. H.; Nikaitani, D. *J. Med. Chem.* **1973**, *16*, 1207−1216.
(49) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley-Interscience: New York, 1979.
(50) Chesnavich, W. J.; Su, T.; Bowers, M. T. *J. Chem. Phys.* **1980**, *72*, 2641−2655.
(51) Su, T.; Chesnavich, W. J. *J. Chem. Phys.* **1982**, *76*, 5183−5185.
(52) Cooks, R. G.; Kruger, T. L. *J. Am. Chem. Soc.* **1977**, *99*, 1279−1281.
(53) McLuckey, S. A.; Cameron, D.; Cooks, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 1313−1317.
(54) McLuckey, S. A.; Cooks, R. G.; Fulford, J. E. *Int. J. Mass Spectrom. and Ion Physics* **1983**, *52*, 165−174.
(55) Brodbelt-Lustig, J. S.; Cooks, R. G. *Talanta* **1989**, *36*, 255−260.
(56) Green-Church, K. B.; Limbach, P. A. *J. Am. Soc. Mass Spectrom.* **2000**, *11*, 24−32.
(57) Fenn, J. B.; Mann, M.; Meng, C. K.; F., W. S.; Whitehouse, C. M. *Science* **1989**, *246*, 64−71.
(58) Drahos, L.; Vékey, K. *J. Mass Spectrom.* **1999**, *34*, 79−84.
(59) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Chem. Phys.* **1996**, *100*, 12974−12980.
(60) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.
(61) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(62) Frisch, M. J. et al. *Gaussian 09*; Gaussian, Inc.: Wallingford CT, 2009.