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Regioselectivity of Pyridine Deprotonation in the Gas Phase

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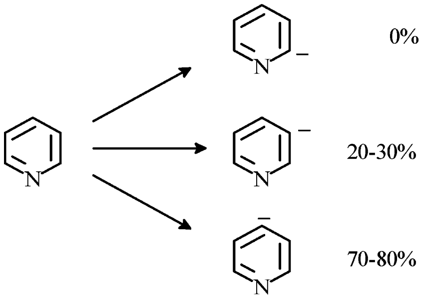
Received October 12, 2006



The regioselective deprotonation of pyridine in the gas phase has been investigated by using chemical reactivity studies. The mixture of regioisomers, trapped as carboxylates, formed in an equilibrium mixture is determined to result from 70−80% deprotonation in the 4-position, and 20−30% deprotonation at the 3-position. The ion formed by deprotonation in the 2-position is not measurably deprotonated at equilibrium because the ion is destabilized by lone-pair repulsion. From the composition of the mixture, the gas-phase acidities (ΔH°_{acid}) at the 4-, 3-, and 2-positions are determined to be 389.9 ± 2.0, 391.2−391.5, and >391.5 kcal/mol, respectively. The relative acidities of the 4- and 3-positions are explained by using Hammett−Taft parameters, derived by using the measured gas-phase acidities of pyridine carboxylic acids. The values of σ_F and σ_R are −0.18 and 0.74, respectively, showing the infused nitrogen in pyridine to have a strong π electron-withdrawing effect, but with little σ-inductive effect.

Introduction

Nitrogen-containing rings are commonly found as components in natural products, and therefore significant effort has been expended in determining the effect that nitrogen infusion has on the properties of benzene-like systems.[1−19] For example, it has been found that nitrogen has little effect on those aspects generally associated with aromaticity, as the stabilization energy[20,21] and magnetic properties[21] of pyridine are very similar to those of benzene. However, the presence of nitrogen does have a significant effect on the reactivity. In addition to having a natural effect on the basicity, the nitrogen in the ring is generally viewed as having an electronic effect similar to that of a nitro group, serving to deactivate the ring toward electrophilic addition.[7,16,17] Unfortunately, the interpretation of pyridine reactivity is often complicated because the reacting species is not necessarily the free base, but may instead be a complex

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10.1021/jo062117x CCC: $37.00

with Lewis acid present in solution thereby changing the electronic properties of the nitrogen center.[22] This aspect affects not only the rates of reaction in electrophilic addition reactions, but also the regioselectivity of acid−base reactions wherein positive charge on the nitrogen complexed to a cation can stabilize the negative charge formed upon deprotonation.[23,24] Therefore, physical studies of intrinsic pyridine properties and its reactions need to be carried out under conditions in which it exists as the free base, which can be achieved by using appropriately substituted systems,[7,25] or by carrying out the studies in the gas phase.[26]

The effect of nitrogen complexation is evident in the observed gas-phase reactivity. While studying the gas-phase hydrogen/deuterium exchange of deprotonated pyridine *n*-oxide, we noted a distinct difference between its chemistry and that of simple deprotonated pyridine. When allowed to react with D_2O, deprotonated pyridine *n*-oxide efficiently exchanged all protons with deuterium, whereas deprotonated pyridine was found to undergo only two very slow H/D exchanges.[26] This result indicates that all of the positions in pyridine *n*-oxide can be accessed in gas-phase acid/base reactions, whereas not all of the positions on pyridine itself are accessible in the reaction with OH^-. The limited H/D exchange reactivity of deprotonated pyridine is consistent with predictions based on AM1 calculations by Meot-ner and Kafafi[27] that predict the 4-position to be slightly more acidic than the 3-position, with deprotonation at the 2-position significantly higher in energy. The instability of the anion formed by deprotonation at the 2-position is readily explained as being due to electron-pair repulsion between the 2-position and the nitrogen,[28] but the origins of the 3- and 4-isomeric differences have not been examined experimentally.

In this work we report a detailed investigation of the regioselectivity of the gas-phase deprotonation of pyridine. We determined the equilibrium composition of the mixture formed upon deprotonation of pyridine, and from the extent of 3- and 4- deprotonation we have measured the gas-phase acidity difference between the 3- and 4-positions. To understand the origins of the observed selectivity, we have used experimental and computational methods to investigate the electronic effects of the infused nitrogen in the aromatic ring. Our results show the nitrogen in the ring to be a strong π-electron-withdrawing group, similar to the effect of a nitro group[7] but, unlike a nitro group, essentially non-inductive.

Experimental Section

All experiments were carried out at room temperature in a flowing afterglow triple-quadrupole apparatus described elsewhere.[29,30] Hydroxide ion was prepared in the 1 m long flow reactor by electron ionization of a 2:1 mixture of methane and nitrous oxide in helium buffer ($P(\mathrm{He}) = 400$ mTorr, $P(\mathrm{CH_4}) = 4$ mTorr). Ions carried down the flow tube by the flowing helium were allowed to undergo reaction with neutral vapors introduced by micrometering valves along the length of the reactor. Ions in the instrument are extracted through a nosecone into a differentially pumped region containing a triple-quadrupole analyzer. Collision-induced dissociation (CID) experiments were carried out by selecting the ion with the desired mass-to-charge ratio using the first quadrupole, and then injecting them into the second quadrupole (radio frequency only), where they undergo collision with an argon gas. The collision energy is controlled by the quadrupole pole offset voltage, which can be scanned for energy-resolved CID measurements. The reactant and product ions are analyzed with the third quadrupole and are detected with an electron multiplier operated in pulse counting mode.

Materials. Gas purities were as follows: He (99.995%), F_2 (5% in He), methane (99.5%), and nitrous oxide (99%). All other reagents were obtained from commercial sources and were used as supplied.

Results and Discussion

Here we describe the results of our study of the regioselectivity of deprotonation of the pyridine. In the first sections, we describe the determination of the selectivity of the deprotonation reaction by using hydrogen/deuterium exchange reactions and the collision-induced dissociation branching ratios of pyridine carboxylates. The next sections describe an investigation of the electronic properties of the nitrogen in a pyridine ring. The results indicate that the nitrogen in the ring acts as a strongly π-electron-withdrawing group but with little inductive effect, consistent with the observed and computed regiospecific properties of the pyridine ring.

H/D Exchange. DePuy and co-workers have reported labeling studies indicating that the 2-position in pyridine is inaccessible upon deprotonation with hydroxide, and that deprotonated pyridine undergoes 2 H/D exchanges with D_2O.[26] We have reproduced their H/D exchange results, but also find that the H/D exchange is very inefficient for deprotonated pyridine formed by proton transfer with hydroxide. Even under very high flows of D_2O, the amount of $C_5H_2D_2N^-$ formed is less than that for $C_5H_4N^-$. Under comparable flows of water, deprotonated pyridine *n*-oxide, $C_5H_4NO^-$, is completely converted to $C_5D_4NO^-$, and deprotonated chlorobenzene, $C_6H_4Cl^-$, is completely converted to $C_6D_4Cl^-$. Given the similarity between the gas-phase acidities of pyridine and chlorobenzene,[27,31] the difference in the H/D exchange can be attributed to the difference in the regioselectivity of the deprotonation. Whereas chlorobenzene is deprotonated almost exclusively in the ortho position,[31,32] the H/D exchange behavior we observed for deprotonated pyridine agrees with previous data indicating that the 2-positions are not accessible upon deprotonation by hydroxide. As shown in Figure 1, if the ion were deprotonated in the 2-position (**1a**), it would be expected to undergo one, three, or four H/D exchange reactions. However, because the 2-position is inaccessible, [26] only two H/D exchanges are observed.

Theoretical calculations performed by using the B3LYP and MP2 computational methods with Gaussian 03[33] agree with our

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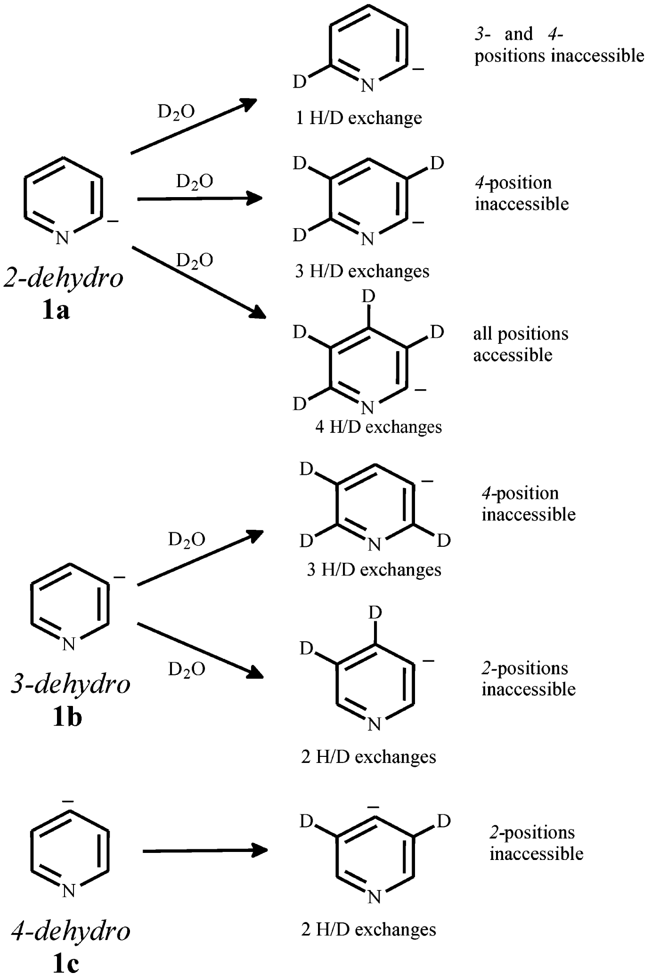


FIGURE 1. H/D exchange results expected for deprotonated pyridine given the position accessibility.

TABLE 1. Calculated Relative Enthalpies of Pyridinide Anions[a]

	geometry[b]	2-dehydro **1a**	3-dehydro **1b**	4-dehydro **1c**
B3LYP/aug-cc-pVDZ	I	9.7	2.1	0.0
B3LYP/aug-cc-pVTZ	I	9.8	2.1	0.0
MP2/aug-cc-pVDZ	I	10.1	0.7	0.0
MP2/aug-cc-pVTZ	I	10.2	0.6	0.0
MP4/aug-cc-pVDZ	I	9.5	1.5	0.0
MP2/aug-cc-pVDZ	II	10.0	0.6	0.0
MP2/aug-cc-pVTZ	II	10.2	0.6	0.0
MP4/aug-cc-pVDZ	II	9.4	1.5	0.0
EHT[c]		5.8	0.0	3.9
HF/4-31*[d]	HF/3-21G*	10.0	3.4	0.0
AM1[e]		5.8	0.9	0.0
exptl[f]			1.3−1.6	0.0

[a] Relative energies converted to 298 K enthalpies by using unscaled frequencies calculated at the B3LYP/aug-cc-pVDZ level of theory. [b] Geometry I: B3LYP/aug-cc-pVDZ. Geometry II: MP2/aug-cc-pVDZ. [c] Reference 36. [d] Reference 35. [e] Reference 27. [f] Determined from the composition of the equilibrium mixture.

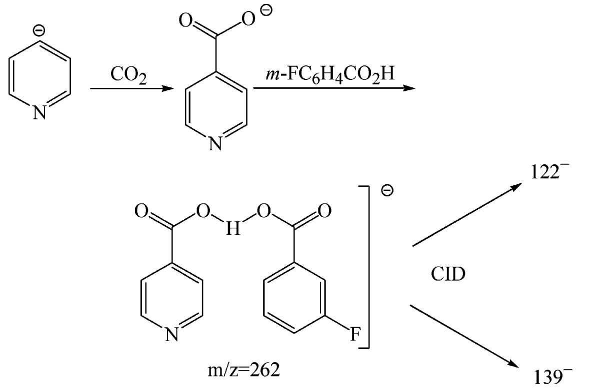
experimental results (Table 1). The lowest energy anion is predicted to be the 4-isomer, with a calculated enthalpy that is 0.6−2.1 kcal/mol lower than that for the 3-isomer. The acidity at the 2-position is calculated to be ca. 10 kcal/mol higher than that of the 4-position. Assuming that the experimentally measured gas-phase acidity of pyridine (389.9 ± 2.0 kcal/mol, vide infra) applies to deprotonation at the 4-position, the gas-phase acidity at the 2-position is predicted to be ca. 400 kcal/mol, much higher than the gas-phase acidity of water (390.3 kcal/mol).[34] Thus, the 2-position is predicted to be inaccessible to deprotonation by hydroxide, consistent with the conclusions from the H/D exchange experiments. Predicted relative acidities calculated at the AM1 and HF/4-31G*//HF/3-21G* levels of theory,[27,35] also included in Table 1, are in good agreement with the B3LYP and MP2 calculations. Extended Hückel Theory (EHT) reported by Hoffman and co-workers[36] predicts too high of an energy for the 2-anion.

TABLE 2. Measured Branching Ratios for CID of Proton Dimers between Pyridine Carboxylates and *m*-Fluorobenzoic Acid

	$R = I(m/z\ 122)/I(m/z\ 139)$	
pyridine carboxylate isomer	20 eV	30 eV
2-isomer (picolinic acid)[a]	0.067	0.031
3-isomer (nicotinic acid)[a]	1.31	1.77
4-isomer (isonicotinic acid)[a]	4.17	5.16
mixture[b]	3.58	4.16

[a] Authentic structures obtained by deprotonation of the corresponding carboxylic acid. [b] Obtained by carboxylation of ions formed by deprotonation.

3- vs 4-Selectivity. The 3-position vs 4-position selectivity of deprotonation was investigated by using pyridine carboxylate anions. The reaction of carbanions and CO_2 to form carboxylates in the gas phase occurs at or near the collision rate.[37] Therefore, upon reaction with CO_2, the $C_5H_4N^-$ ion mixture formed by deprotonation of pyridine is completely converted to carboxylate ions, $C_5H_4NCO_2^-$. Reaction of the pyridine carboxylate with reference *m*-fluorobenzoic acid forms a proton-bound dimer that undergoes CID to either regenerate the pyridine carboxylate or form the *m*-fluorobenzoate ion (eq 1). The measured ratios [$R_{mix} = I(C_5H_4NCO_2^-)/I(C_6H_5CO_2^-)$] for the mixture of carboxylates, measured at two collision energies (20 and 30 eV, laboratory frame of reference), were compared with those for authentic 2-, 3-, and 4-pyridine carboxylate ions, formed by deprotonation of picolinic, nicotinic, and isonicotinic acids, respectively. The average branching ratios are shown in Table 2. Qualitatively, it is observed that the branching ratio for the mixture is most similar to that for the authentic 4-isomer, indicating that the mixture predominantly consists of the 4-dehydro-isomer, with



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minor contributions from the 2- or 3-dehydro-isomers. Assuming that the 2-dehydro-isomer is not accessed in the deprotonation, the composition of the mixture can be calculated by using eq 2, where R_m and R_p are the branching ratios for the authentic carboxylate ions, and x_m and x_p are their mole fractions in the mixture ($x_m + x_p = 1$).

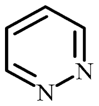
$$R_{mix} = x_p R_p + x_m R_m \tag{2}$$

From the measured results in Table 2, we obtain $x_p = 0.71$ at 20 eV and $x_p = 0.79$ at 30 eV. Therefore, we conclude that the mixture consists of about 70−80% 4-dehydro-isomer, whereas the 3-dehydro-isomer constitutes 20−30%.[38]

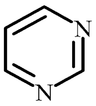
To ensure that the system was an equilibrium mixture, and not merely a kinetic mixture, of 3-dehydro- and 4-dehydropyridine, the $C_5H_4N^-$ ions were allowed to react with water before reaction with CO_2. Water (D_2O) is known to undergo reversible proton exchange with deprotonated pyridine,[27]and will therefore produce an equilibrium mixture reflecting the thermal conditions of the flow reactor. The observed branching ratios were the same as those measured without water added, confirming that the system was at equilibrium. Moreover, the branching ratios do not change when adding the carbon dioxide further upstream in the flow reactor, indicating that equilibrium is established very quickly, presumably with excess pyridine as the acid catalyst. Therefore, we are able to estimate thermochemical properties using the relationship $\Delta G° = -RT \ln K_{eq}$, with $T = 300$ K. From our measured isomer fractions, we estimate the free energy difference between the 3- and the 4-positions to be 0.9−1.2 kcal/mol. Calculations at the B3LYP/aug-cc-pVDZ level of theory predict that the entropy difference for deprotonation between the two positions is 1.5 cal/(mol K), so that $\Delta H°_{3-4} = \Delta G°_{3-4} + T\Delta S°_{3-4} = 1.3-1.6$ kcal/mol, in excellent agreement with the computed difference of 0.6−2.1 kcal/mol (Table 1).

The experimental results in this work can be combined with those from previous studies to obtain the regiospecific thermochemical properties for pyridine deprotonation in the gas phase. The gas-phase acidity of pyridine has been measured by Meot-ner and Kafafi, who used temperature-dependent equilibrium studies of the proton-transfer reactions of pyridine with hydroxide and methoxide.[27] From the measured equilibrium constants, the quantity ΔH_{acid} for pyridine was determined to be 1.1 kcal/mol higher than that for water, and 9.5 kcal/mol higher than that for methanol, with corresponding $\delta\Delta S°_{acid}$ values of 9.8 and 1.6 cal/(mol K), respectively. However, the present results indicate that the products formed upon deprotonation of pyridine constitute a mixture of isomers. By using our measured energy difference for the 3- and 4-isomers to account for the composition of the mixture and using Meot-ner and Kafafi's experimental result for pyridine, [27] we obtain $\Delta G°_{acid} = 382.1$ kcal/mol for the 4-position of pyridine (see the Supporting Information). From the equilibrium mixture, the acidity at the 3-position is found to be 0.9−1.2 kcal/mol higher, giving $\Delta G°_{acid} = 383.0-383.3$ kcal/mol. Last, our results indicate that the isomer resulting from deprotonation in the 2-position is not formed in detectable amounts, indicating that the 2-position is at least less acidic than the 3-position, with $\Delta G°_{acid} > 383$ kcal/mol. The absolute uncertainties in these values are likely ±2.0 kcal/mol. The entropies for deprotonation at the 4-, 3-, and 2-positions of pyridine are calculated at the B3LYP/aug-cc-pVDZ level of theory to be 26.0, 27.5, and 27.9 cal/(mol K), respectively. The difference between the deprotonation entropies is close to the value of $R \ln 2$ that is expected[39] given the loss in rotational symmetry upon deprotonation at the 2- and 3-positions that does not occur upon deprotonation at the 4-position (or, conversely, the twofold degeneracy for deprotonation at the 2- and 3-positions that is not present for the 4-position), whereas the absolute values are slightly lower than those (30−32 cal/(mol K)) estimated from the temperature-dependent studies of Meot-ner and Kafafi.[27] Combination of the $\Delta S°_{acid}$ values with the $\Delta G°_{acid}$ results described above gives 298 K values of $\Delta H°_{acid}$(4-position) = 389.9 ± 2.0 kcal/mol, $\Delta H°_{acid}$(3-position) = 391.2−391.5 kcal/mol (1.3−1.6 kcal/mol higher than that for the 4-position), and $\Delta H°_{acid}$(2-position) > 391.5 kcal/mol. By comparison, the relative acidities in solution appear to be a function of the experimental conditions,[40−42] but in general, the 2-positions are kinetically favored, and the 4-position is thermodynamically favored.[40,41]

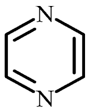
The inaccessibility of the 2-position in the deprotonation of pyridine is not surprising because the anion that would be formed would suffer from extensive electron-pair repulsion. For example, the enthalpy of formation of pyridazine[27,43] (**2a**), which has adjacent nitrogen atoms, is ca. 20 kcal/mol greater than those for either pyrimidine[27,44,45] (**2b**) or pyrazine[27,44,45] (**2c**), where the nitrogen atoms are separated. In deprotonated pyridine, the energy difference between the 2- and 4-isomers is calculated to be 10 kcal/mol. However, comparison to the diazines does not account for the energy difference between the 3- and 4-anions, as the enthalpies of formation of **2b** and **2c** are within 0.3 kcal/mol.[44,45]



2a



2b



2c

Hammett−Taft Parameters for an Infused Nitrogen in an Aromatic Ring. To elucidate the origins of the trend in the positional acidities in the pyridine ring, we have carried out an investigation of the electronic effects of a nitrogen in an aromatic system. We have used the approach outlined by Taft and Topsom[46] to obtain the *effective* Hammett parameters, σ_F and σ_R, for a nitrogen infused in an aromatic ring, where σ_F and σ_R are the inductive and resonance parameters for a substituent, respectively. By using a linear free energy analysis, Taft and

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[38] The reported composition values assume a mixture of 3- and 4-isomers only. The fraction of 4-isomer would be higher if there is any *2*-anion component. In the limit where the minor isomer fraction is purely the 2-isomer, the fraction of 4-isomer is 80−85%.

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Topsom have shown that the acidities of meta- and para-substituted benzoic acids follow the relationship shown in eqs 3a and 3b, where $\delta\Delta G^\circ_{\text{acid}}$ is the difference in the gas-phase acidities of the substituted and unsubstituted benzoic acid.[47]

$$-\delta\Delta G^\circ_{\text{acid}}(\text{meta}) = 11.5\sigma_{\text{R}} + 14.7\sigma_{\text{F}} - 0.1 \tag{3a}$$

$$-\delta\Delta G^\circ_{\text{acid}}(\text{para}) = 14.6\sigma_{\text{R}} + 15.0\sigma_{\text{F}} - 0.2 \tag{3b}$$

$$\Delta G^\circ_{\text{acid}}(\text{meta}) - \Delta G^\circ_{\text{acid}}(\text{para}) = 3.1\sigma_{\text{R}} + 0.3\sigma_{\text{F}} - 0.1 \tag{3c}$$

Whereas the acidity of the 3-carboxylic acid (nicotinic acid) has been measured previously by using the bracketing approach ($\Delta G^\circ_{\text{acid}} = 326.4 \pm 2.7$ kcal/mol),[48] the gas-phase acidity of the 4-carboxylic acid (isonicotinic acid) has not been determined. Both have been measured in this work. Because the pyridine carboxylates readily form proton-bound dimers with reference acids, the acidities of the 2-, 3-, and 4-pyridinecarboxylic acids were determined by using the kinetic method.[49,50] In this mass spectrometric measurement, the acidity difference between a substrate, AH, and a reference, BH, is related to the branching ratios for CID of proton-bound dimers [$R = I(\text{B}^-)/I(\text{A}^-)$] by eq 4, where T_{eff} is the effective temperature of the dissociation,[51,52] $\Delta\Delta S$ is the difference in activation entropies for the formation of B^- and A^- from the proton-bound dimer,[53−56] and the E subscript indicates the terms that are dependent on the collision energy of the dissociation.

$$-\ln R_{\text{E}} = \frac{\Delta H_{\text{acid}}(\text{B}_i\text{H}) - \Delta H_{\text{acid}}(\text{AH}) - T_{\text{eff,E}}\Delta\Delta S}{RT_{\text{eff,E}}} \tag{4}$$

In the simple kinetic method,[57] the entropy difference is assumed to be negligible, such that the acidity can be determined from a plot of ln$R$ measured at a single energy versus $\Delta H^\circ_{\text{acid}}$ for a series of reference acids, B_iH. In this work, we utilize the extended kinetic method,[56,58] which explicitly includes the entropy component to the branching ratio. According to eq 4, a plot of ln$R$ versus $\Delta H^\circ_{\text{acid}}(\text{B}_i\text{H})$ at a given energy has a slope $m_{\text{E}} = -1/RT_{\text{eff,E}}$ and an intercept $y_{\text{E}} = \Delta H_{\text{acid}}(\text{AH})/RT_{\text{eff,E}} + \Delta\Delta S/R$. If the dissociation is carried out at a series of energies, a second regression plot of y_{E} versus $-m_{\text{E}}$ can be constructed, which has a slope $\Delta H^\circ_{\text{acid}}(\text{AH})$ and the intercept is $\Delta\Delta S/R$. Because the slope and intercept obtained in the first regression are not independent, using the approach described above leads to an artificially high correlation for the second regression. Armentrout[50] has shown that the artificial correlation can be removed by plotting ln$R$ versus $\Delta H^\circ_{\text{acid}}(\text{B}_i\text{H}) - \Delta H_{\text{acid}}(\text{avg})$, where $\Delta H_{\text{acid}}(\text{avg})$ is the average of the gas-phase acidities of the references. When using this approach, the slope of the second regression is $\Delta H^\circ_{\text{acid}}(\text{AH}) - \Delta H_{\text{acid}}(\text{avg})$.

TABLE 3. Gas-Phase Acidities of Pyridine Carboxylic Acids[a]

acid	$\Delta H^\circ_{\text{acid}}$[b]	$\Delta S^\circ_{\text{acid}}$[c]	$\Delta G^\circ_{\text{acid}}$[d]
picolinic acid (2-isomer)	343.9 ± 1.8		
nicotinic acid (3-isomer)	334.4 ± 2.0	25.7	326.7 ± 2.0 326.4 ± 2.7[e]
isonicotinic acid (4-isomer)	332.6 ± 1.7	24.3	325.3 ± 1.7
benzoic acid			333.1 ± 2.0[f]

[a] Values in kcal/mol. [b] Obtained by using the kinetic method; see the Supporting Information. [c] Calculated by using frequencies for the neutral acid and conjugate base anion obtained at the B3LYP/6-31+G* level of theory. [d] 300 K value obtained by using $\Delta G = \Delta H - T\Delta S$. [e] Reference 59. [f] Reference 60.

TABLE 4. Substituent Parameters for Common Substituents[a]

substituent	σ_{F}	σ_{R}
"infused nitrogen"	−0.18	0.76
COCN	0.66	0.28
CHO	0.31	0.19
NO_2	0.65	0.18
CN	0.60	0.10
CF_3	0.44	0.07
CH_3	0.00	−0.08
Cl	0.45	−0.17
F	0.44	−0.25
HO	0.30	−0.38
$\text{C}_2\text{H}_5\text{O}$	0.25	−0.45
σ radical[b]	0.57	−0.47
NH_2	0.14	−0.52

[a] All values except those for radical site and infused nitrogen were taken from Taft and Topsom (ref 46). [b] Reference 62

Branching ratios and regression plots required for determination of the gas-phase acidities of picolinic, nicotinic, and isonicotinic acids are provided as Supporting Information. The measured acidities are listed in Table 3. Isonicotinic acid (the 4-isomer) is the most acidic of the three isomers, and the picolinic acid (*2*-isomer) is the least acidic. By using the acidities of the 3- and 4-isomers along with eq 3, the σ_{F} and σ_{R} values for the nitrogen in the ring are determined to be −0.18 and 0.76, respectively. These values are interpreted to mean that the nitrogen in the aromatic ring is a weakly inductively donating group, but that it is an exceedingly strong π-electron-withdrawing group. As shown in Table 4,[61] the infused nitrogen has by far the largest σ_{R} value of any substituent, including strongly π-withdrawing groups CHO ($\sigma_{\text{R}} = +0.16$) or even COCN ($\sigma_{\text{R}} = 0.28$). Although the values of σ_{F} and σ_{R} are somewhat surprising, especially the weakly donating inductive effect, they are consistent with qualitative assessments of the experimental data. In particular, the fact that the 4-position in pyridine is more acidic than the 3-position and that isonicotinic acid is more acidic than nicotinic acid clearly indicates that the nitrogen is a strong π-withdrawing group because π-withdrawing groups in the 4-position are better able to stabilize negative charge in the anion. As eq 3 shows, the difference in the acidity at the 3- and 4-positions is mostly a reflection of the value of σ_{R}.

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(47) Technically, σ_{F} and σ_{R} are defined for substituents connected to the carbon in the meta and para positions of benzoic acids. Hence, the values of σ_{F} and σ_{R} measured in this work are the effective Hammett parameters, and correspond to what the Hammett parameters would be for a substituent that has the same effects on benzoic acid acidities as do the nitrogens in the 3- and 4-pyridine carboxylic acids.

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(59) Breuker, K.; Knochenmuss, R.; Zenobi, R. *Int. J. Mass Spectrom.* **1999**, 25−38.

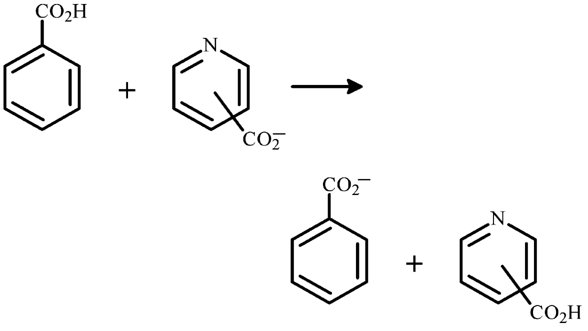
(60) Fujio, M.; McIver, R. T., Jr.; Taft, R. W. *J. Am. Chem. Soc.* **1981**, *103*, 417.

(61) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

A positive value of σ_R, which is characteristic of π-electron-withdrawing groups (Table 4), would indicate that the value of $\Delta G°_{acid}$ for 3-pyridine carboxylic acid is higher than that for 4-pyridine carboxylic acid, such that the 4-isomer is more acidic. An illustrative comparison can be made with *m*- and *p*-nitrobenzoic acids, which have gas-phase acidities ($\Delta G°_{acid}$) of 322.0 and 321.1 kcal/mol, respectively. Despite the fact that the nitro-substituent is a good π electron-withdrawing group ($\sigma_R = 0.18$), the difference between the acidity of the 3- and 4-position is only 0.9 kcal/mol, compared to the difference of 1.4 kcal/mol between the pyridine carboxylic acids. According to eq 3c, a larger difference between the acidities of the meta- and para-substituted carboxylic acids would indicate a larger value of σ_R. Hence, the nitrogens in 3- and 4-pyridine carboxylic acids affect the gas-phase acidities of the aryl carboxylic acid as would a benzoic acid substituent that is a stronger π electron-withdrawing substituent than NO_2. However, the absolute gas-phase acidity values of the pyridine acids (332−334 kcal/mol) are much higher than those of the nitro-substituted benzoic acids (321−322 kcal/mol), which indicates a smaller inductive effect. Indeed, the σ_R estimated by using eq 3c, when used in eqs 3a and 3b, essentially accounts for all of the increase in the acidities of the pyridine carboxylic acids compared to benzoic acid, and little inductive effect needs to be invoked. Ultimately, the effect of the infused nitrogen is the inverse of that of a CF_3 group. Trifluoromethyl is an example of a substituent that is strongly inductively withdrawing, but weakly π-withdrawing. Conversely, the infused nitrogen is strongly π-withdrawing, but weakly inductive.

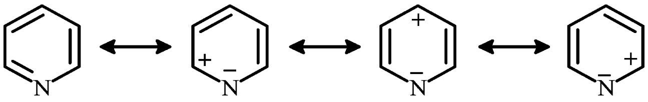
The accuracies of the measured σ parameters for the nitrogen are dependent on the accuracy of the acidity measurements. Considering the uncertainties in the measured acidities and the uncertainty in the acidity of benzoic acid, the uncertainties in the σ values are calculated to be approximately ±0.30. Although these uncertainties are large, they do not affect the conclusions regarding the electronic effects of the nitrogen. Even in the limit where the actual σ_F value is 0.3 higher and σ_R is 0.3 lower than that determined in this work, the nitrogen would still be an exceedingly strong π acceptor but weakly inductive (Table 4). However, given the relatively large uncertainties, it is not possible to rule out the possibility that the σ_F value is positive but small. Preliminary measurements of the σ values utilizing the acidities of hydroxypyridines[63] are consistent with the conclusions obtained in this work that the apparent inductive effect is small.

Theoretical calculations are in agreement with the assessment of the electronic properties of the nitrogen in pyridine. At the B3LYP/aug-cc-pVDZ level of theory,[64] the free energy changes of the isodesmic reaction in eq 5 are calculated to be 5.2 and 6.8 kcal/mol for nicotinic and isonicotinic acids, respectively. These acidity differences correspond to σ_F and σ_R values of −0.07 and +0.55, respectively, which are similar to the experimentally determined values.



(5)

SCHEME 1



The π-withdrawing effects of the nitrogen in pyridine are consistent with the results of previous studies. Katritzky and others have reported measurements of the σ and σ^+ parameters for aza-substitution in the ortho, meta, and para positions. [14] The measured values of σ range from 0.75 to 1.0 for the nitrogen in the ortho position, 0.65 to 0.74 for nitrogen in the meta position, and 0.8 to 1.1 for nitrogen in the para position.[65] Although the measured values of σ_o, σ_m, and σ_p vary depending on the reaction investigated, they generally indicate that the infused nitrogen is a good electron-withdrawing group.[3,5,6,8,11,12,15] Moreover, the fact that σ_p is significantly larger than σ_m highlights the nitrogen as a π-electron-withdrawing group. However, the present results reveal that the electron-withdrawing effect is almost solely through a resonance effect, unlike what is found for a nitro group, or other common electron-withdrawing groups, which have large inductive components in addition to the resonance effects.

Conclusion

The π-electron-withdrawing capabilities of the nitrogen in pyridine account for the difference in the acidities of the 3- and 4-positions, as a simple resonance picture (Scheme 1) illustrates the advantage of forming the ion in the 4-position. Although the ion formed by deprotonation at the 2-position also likely benefits from resonance stabilization, the electron-pair repulsion makes it inaccessible under equilibrium conditions. The resonance stabilization of the 4-ion accounts for the observation that pyridine is ca. 10 kcal/mol more acidic than benzene, and also explains why the ion formed by deprotonation at the 2-position is only 10 kcal/mol less stable than the ions formed by deprotonation in the 4-position while **2a** is 20 kcal/mol higher in energy than **2b** and **2c**. Thus, resonance stabilizes ion **1a**, but not as much as it is destabilized by lone-pair repulsion.

The lack of a strong inductive effect from the nitrogen is surprising, but the fact that it is consistent with what is obtained when using computed acidities suggests it is not just experimental error. However, it is important to recognize that the interpretation of the electronic properties in this case is carried out *within the construct of the Hammett−Taft model*, and therefore is subject to the inherent assumptions of that empirical approach. For example, the characterization of the infused nitrogen as σ electron donating indicates that it is electron donating with respect to the other substituents, and does not require that it actually donates electron density. This is reflected in the σ charges (Scheme 2), calculated by using the Natural Population Analysis (NPA)[66] approach. In an absolute sense,

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[62] Wenthold, P. G.; Squires, R. R. *Int. J. Mass Spectrom. Ion Processes* **1998**, *175*, 215−224.

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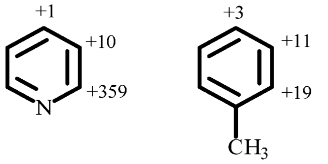
[64] Frisch, M. J.; et al. *Gaussian 98*, Revision A.09; Gaussian, Inc.: Pittsburgh, PA, 1998.

[65] σ^+ values are approximately 0.2 higher than the σ value for similiar processes.

[66] Reed, A. E.; Weinstock, F.; Weihhold, J. *J. Chem Phys.* **1985**, *83*, 735.

SCHEME 2



Calculated σ charges, millielectrons

the nitrogen acts like a σ-electron-withdrawing group, and creates a very large σ-charge density at the 2-position. However, the effect drops off rapidly, with very little charge calculated at the 4-position. For comparison, the calculated σ charges for toluene are also included in Scheme 2. Whereas the charge at the 2-position is larger in pyridine, toluene is calculated to have larger σ charge at the 3- and 4-positions! Thus, although the infused nitrogen in pyridine is σ-electron donating, it is *less* donating to the 3- and 4-positions than is a methyl group. Given that the nitrogen acts less donating than the methyl group ($\sigma_F = 0.00$, Table 4), it would be expected to have an effective Hammett−Taft parameter that is negative.

Acknowledgment. This work was supported by the National Science Foundation (CHE04-54874). We also thank the donors to the Petroleum Research Foundation, administered by the American Chemical Society, for partial support of this work.

Supporting Information Available: A description of the determination of the gas-phase acidity of pyridine taking into account the formation of a mixture of isomers, the branching ratios, representative plots, and second regression plots for the determination of the acidity of pyridine carboxylic acids by using the kinetic method, and *Z*-matrices, energies, and frequencies for all species calculated. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062117X