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The Stability of Aryl Carbanions Derived from Pyridine *N*-Oxide: The Role of Resonance in Stabilizing Aryl Anions

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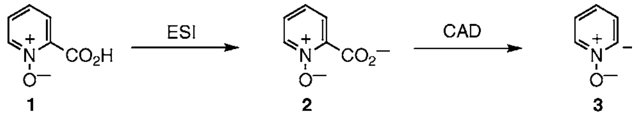
Abstract: The gas phase stability of carbanions centered at various positions on pyridine *N*-oxide were investigated by computational and experimental methods. In addition, G3MP2 computations were completed on ring-deprotonated pyridine and *N*-methylpyridinium. With these species, the effect of a nitrogen-centered positive charge on carbanion stability was assessed. Introduction of the nitrogen-oxide group into the benzene ring decreases the ΔH_{acid} by ~20 kcal/mol, but surprisingly, the effect is nearly independent of the position of the group (*ortho*, *meta*, or *para*). The results indicate that the *N*-oxide offers a balance of field, resonance, and local effects that cancels out any positional preferences. G3MP2 calculations indicate that a similar lack of positional selectivity is seen in nitrobenzene and benzonitrile. Overall, the data suggest that π-effects are limited in phenyl anions, and as a result, ylide-like, rather than carbene-like, resonance structures are most important in the anions derived from ring deprotonation of arenes and heterocycles of these general types.

Introduction

In model studies on the mechanism of orotidine 5′-monophosphate decarboxylase, the stability of carbanions resulting from the decarboxylation of orotate analogues as well as their relevance to the rate of the enzymatic decarboxylation have been examined.[1−7] The presence of zwitterionic or carbene resonance structures has been proposed as an important factor in the stabilization of these carbanion intermediates.[8,9] Kass and coworkers[10] have completed extensive photoelectron spectroscopy and computational studies on zwitterionic species derived from pyridinium dicarboxylates. Their results suggest that the ionic environment created in the substrate binding pocket of orotidine 5′-monophosphate decarboxylase could limit the stabilization provided to zwitterionic intermediates. Finally, Schafman and Wenthold recently have provided a detailed analysis of the effect of ring nitrogens on the stability of aryl carbanions.[11]

Scheme 1



In this report, we examine the energetic contribution of zwitterionic (ylide) and carbene resonance forms to the stability of pyridine *N*-oxide carbanions. These carbanions can be generated readily and selectively in the gas phase by electrospray ionization (ESI) of the corresponding carboxylates followed by collision-activated dissociation (CAD) (Scheme 1). The net negative charge on these compounds allows us to examine their reactivity and stability in the gas phase by mass spectrometry. Surprisingly, the position of the carbanion, relative to the *N*-oxide, has almost no effect on its proton affinity. The inserted *N*-oxide provides an unexpected example of a powerful anion-stabilizing group that has almost no positional effects (*ortho*, *meta*, or *para*) in the benzene system. We also explore the generality of this result by examining the positional ΔH_{acid} of *N*-methylpyridinium, halobenzenes, nitrobenzene, and benzonitrile.

Results

Methanolic solutions of acid **1** lead to the formation of anion **2** during electrospray ionization. This anion can be selectively isolated, and when subjected to collision-activated dissociation (CAD), it produces carbanion **3** via decarboxylation. To determine its proton affinity (PA), **3** was allowed to react with a series of organic acids of known ΔH_{acid}. It readily removes a proton from 1,4-difluorobenzene ($\Delta H_{acid} = 380 \pm 2$ kcal/mol).[12] In reactions with benzonitrile ($\Delta H_{acid} = 383 \pm 3$ kcal/mol),

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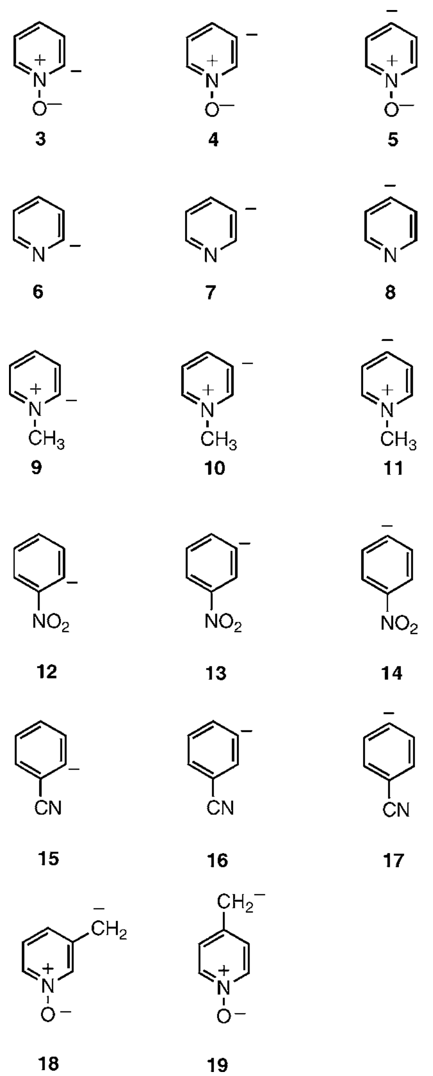
10.1021/ja906473v

Scheme 2



proton transfer occurs to a minor extent (∼15%) with the major channel being adduct formation. With CH_3OD ($\Delta H_{acid} = 382 \pm 1$ kcal/mol for CH_3OH[13]), H/D exchange dominates (see below), but some CH_3O^- formation is observed. Finally with bromobenzene ($\Delta H_{acid} = 383 \pm 2$ kcal/mol), we did not see a proton transfer reaction. These data point to **3** having an effective proton affinity (PA) of 381 ± 3 kcal/mol. The fact that H/D exchange competes with proton transfer in the reaction with CH_3OD is solid evidence for a proton affinity near that of CH_3OH. However, this behavior also suggests that **3** potentially could be rearranging during the reaction with the probe reagent, producing ions **4** or **5** (Scheme 2). It is well-known that gas-phase acid/base complexes often undergo multiple proton transfers before separating and that, in the absence of significant barriers, the experimentally determined PA corresponds to the most stable anion that can be formed by proton transfer.[14] Given that we are observing H/D exchange with **3**, it is likely that rearrangements would occur if **4** or **5** were as stable as or more stable than **3**. To explore this issue with the decarboxylation product from **2**, we profiled the exchange process using increasing amounts of CH_3OD and extended reaction times. When treated with CH_3OD, the carbanion exchanges up to four hydrogens for deuteriums, indicating that rearrangements (i.e., proton transfers) occur in the reaction complex and all the sites have relatively similar PAs (Figure 1). However, the fourth exchange is difficult to see because the proton transfer reaction with CH_3OD is competing with the exchange and almost completely depletes the signal for **3** before the fourth exchange can occur. For comparison, the isomeric *meta* and *para* carbanions, **4** and **5** (Scheme 2), were formed by decarboxylation of the appropriate carboxylates and were subjected to the same set of reactions. With the probe reagents, similar proton transfer behavior was observed and the PAs were bracketed to the same value as **3**. In addition, very similar profiles were seen in the H/D exchange reaction with CH_3OD (Figure 1). There are subtle differences in the profiles shown in Figure 1, but because signal intensities are relatively low at this point in the exchange process, it is difficult to make a definitive statement. Exchange experiments were also completed with D_2O. In this case, four exchanges were readily observed as well as some adduct formation.[15] One concern is that during CAD, the pyridine oxide anions might rearrange to either a single pyridine oxide isomer or a ring-opened isomer. Two pieces of evidence suggest that the pyridine oxide anions are formed regioselectively and intact. First, under harsh source and CAD conditions, the *meta* isomer gives a partial yield of an anion that does not exchange with D_2O. This species is likely ring-opened and a logical mechanism is available (Scheme 3). The resulting anion has a computed PA of only 356 kcal/mol and should not exchange with D_2O. The *ortho* and *para* systems do not offer analogous mechanisms for ring-opening, and the CAD products fully exchange with D_2O when subjected to the same conditions. Second, in addition to the presence of an unreactive species in the *meta* system, there are subtle differences in the D_2O exchange profiles of the *ortho*, *meta*, and *para* systems that suggest that the exchange processes start from initially different species.[16,17]

Taken together, these data confirm our conclusion that the pyridine *N*-oxide carbanions have an effective PA of 381 ± 3 kcal/mol, but they do not allow us to assess the ΔH_{acid} of the individual sites (*ortho*, *meta*, and *para*) in pyridine oxide. To gain more insight into this issue, we undertook a computational modeling study at the G3MP2 level on carbanions **3**, **4**, and **5** (Scheme 2, Table 1). At this level, the *ortho*, *meta*, and *para* carbanions are predicted to have PAs between 382 and 384 kcal/mol. These values are in good accord with our experimental results and suggest that all the sites have similar PAs. This is consistent with the observation of multiple H/D exchanges and the fact that all the carbanions give similar H/D exchange profiles. Based on the calculations, the *meta* carbanion is the most stable, but only by a small amount.

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(13) The ΔH_{acid} of CH_3OD may be nearly 2 kcal/mol higher than that of CH_3OH. However the deuteron affinities of the pyridine oxide carbanions are also larger for similar reasons. The net effect is expected to be small (tenths of a kcal/mol): Barlow, S. E.; Dang, T. T.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1990**, *112*, 6832.

(14) Grabowski, J. J.; Depuy, C. H.; Van Doren, J. M.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 7384.

(15) It should be noted that the presence of two exchangeable deuteriums in D_2O allows for H/D exchange at sites with a wider range of acidities than CH_3OD.

(16) For example, under a standard set of conditions with D_2O, the species give deuterium incorporations (1:2:3:4 incorporations) of 9%, 34%, 41%, and 16% for *ortho*; 5%, 32%, 45%, and 18% for *meta*; and 7%, 33%, 42%, and 18% for *para*. Given the relative acidities, a subtle variation is expected.

(17) Additional evidence that the CAD products formed under typical conditions are truly carbanions comes from the fact that they undergo addition reactions with CO_2, a classic gas-phase carbanion reaction.

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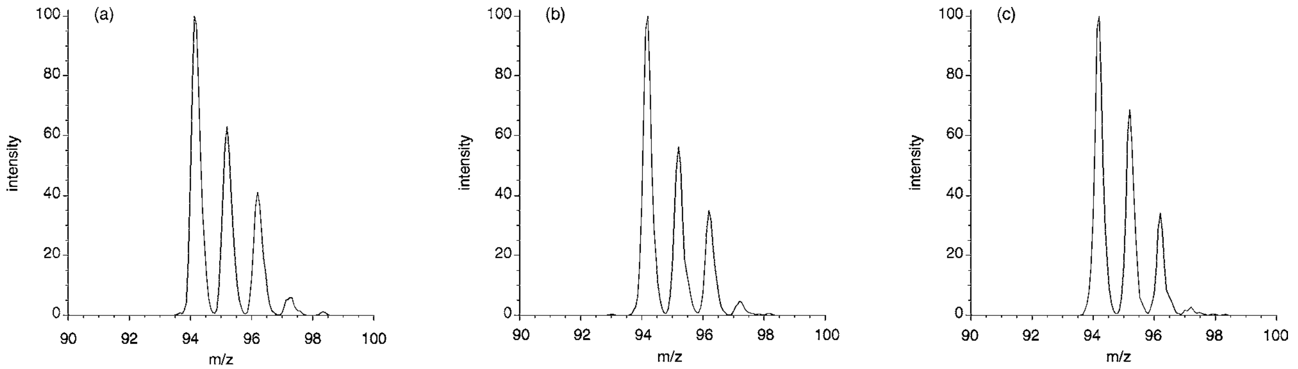


Figure 1. Spectra from the reaction of CH_3OD with **3** (a), **4** (b), and **5** (c). Reaction time is 500 ms. CH_3OD pressure is $\sim 10^{-6}$ Torr.

Scheme 3

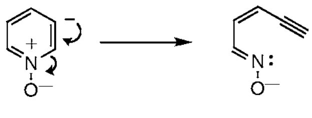
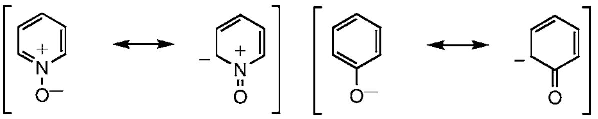


Table 1. Proton Affinity (PA) of Carbanions in Scheme 2

Carbanions	Experimental (kcal/mol)	Calculated[a] (kcal/mol)
3	381[c]	382.5
4	381[c]	381.8
5	381[c]	383.5
6		400.8
7		393.1
8	389.9[b]	391.1
9		270.7
10		285.2
11		287.0
12	354[c,d]	380.8
13	354[c,d]	384.7
14	354[c,d]	383.5
15	383[c,d]	382.8
16	383[c,d]	385.3
17	383[c,d]	385.0
18		368.6
19		365.4

[a] Calculated at the G3MP2 level. [b] Reference 11. [c] Experimentally, the location of the carbanion center could not be determined unambiguously. [d] Reference 18.

Scheme 4



Discussion

The introduction of the *N*-oxide group into benzene decreases its ΔH_{acid} by $\sim$20 kcal/mol but does so nearly equally at each of the positions on the ring. This is a remarkable result. For comparison, the ΔH_{acid} of fluorobenzene varies over 12 kcal/mol from *ortho* to *para*.[19] Large variations are also seen in other pyridine derivatives (see below). This implies that the three key interactions associated with this group, resonance, inductive, and charge/dipole, must balance each other despite the fact that each is expected to have significant positional effects. Resonance will be most important in *ortho* and *para*. The inductive effect should drop with the distance to the carbanion, though possibly not much between *meta* and *para* (see Taft correlation below). The interaction of the carbanion with the large N−O bond moment is a more complicated effect based on both distance and orientation, but simple point-charge models clearly indicate that it should also drop with distance from the *N*-oxide. Therefore, aside from resonance, the expected impact of the *N*-oxide in stabilizing anions should drop along the series: *ortho* > *meta* > *para*. How can a balance be achieved in this system? There are two options: (1) resonance is *destabilizing* and counteracts all of the expected inductive stabilization at the *ortho* position or (2) the *ortho* position suffers from direct interactions with the *N*-oxide and cannot fairly be compared with the *meta* and *para* positions. The fact that the *para* position is only slightly less acidic than *meta*, despite being disfavored in terms of inductive effects, argues against a strong destabilizing resonance effect on top of the inductive effect; however, this does not rule out a mildly destabilizing resonance effect. In the *ortho*-deprotonated pyridine oxide, the carbanion and oxo group have a 1,3-relationship and lone pair/lone pair repulsion could be significant. This would lead to destabilization that could counter the expected inductive advantage of the *ortho* position.

To further explore the substituent effect of the *N*-oxide in the ring, we have turned to an analysis developed by Schafman and Wenthold.[11] Using the established relationship between resonance and field effects determined by Taft for benzoic acids in the gas phase (eqs 1 and 2), it is possible to extract pseudo-Hammett parameters for the ring *N*-oxide.[20] For this analysis, one needs the gas-phase acidities of the *N*-oxides of nicotinic and isonicotinic acids. We have calculated them at the G3MP2 level and obtained ΔH_{acid} values of 329.5 and 330.4 kcal/mol, respectively. At this level, benzoic acid is calculated to have a ΔH_{acid} of 340.3, suggesting that the *N*-oxide increases the ΔH_{acid} of the benzoic acid by $\sim$10 kcal/mol. Assuming that entropy effects are equivalent for the each of the deprotonations and solving for σ_R and σ_F, one obtains values of −0.35 and 1.01, respectively. This indicates that the dominant effect of the ring *N*-oxide is a stabilization of the carboxylate by field effects. It also suggests that it is a moderate π-donor, destabilizing the carboxylate. The π-donation is no surprise given that pyridine *N*-oxide is isoelectronic phenoxide, a system where the O^- is a strong π-donor (Scheme 4). Interestingly, the σ_R value for the ring *N*-oxide is close to that of an OCH_3 substituent ($\sigma_R = -0.42$). Finally, one notes that, in this pair of equations, the field effects coefficient is similar for *meta* and *para* (actually slightly greater for *para*) so it is the resonance coefficient that is critical in distinguishing the impact of a substituent on the *meta* and *para* positions.

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(19) Wenthold, P. G.; Squires, R. R. *J. Mass Spectrom.* **1995**, *30*, 17.

(20) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1.

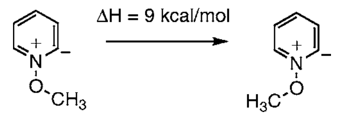
$$-\delta\Delta G\circ_{\mathrm{acid}}(meta) = 11.5\sigma_{\mathrm{R}} + 14.7\sigma_{\mathrm{F}} - 0.1 \qquad (1)$$

$$-\delta\Delta G\circ_{\mathrm{acid}}(para) = 14.6\sigma_{\mathrm{R}} + 15.0\sigma_{\mathrm{F}} - 0.2 \qquad (2)$$

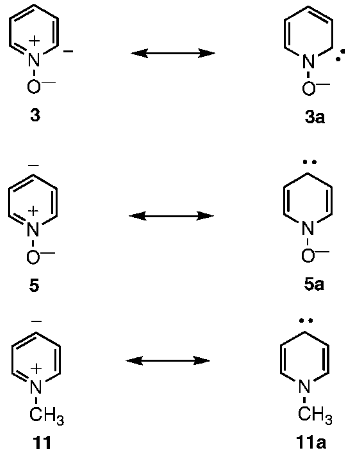
The second issue is the effect of the 1,3-interaction between the lone pairs on the *ortho* carbanion and the oxygen of the *N*-oxide. One simple way to model the interaction is to compare the stabilities of two conformations of deprotonated *N*-methoxypyridinium (Scheme 5). Here, the methyl group can block the lone pair/lone pair interaction in one of the conformations (syn carbanion/methyl), but not the other. The syn conformation also may benefit from a weak hydrogen-bonding interaction between the methyl hydrogens and the carbanion. At the G3MP2 level, the syn conformation is 9 kcal/mol more stable than the anti, which is a rotational transition state for the system (see Supporting Information). This indicates that significant destabilization can be generated by this type of lone pair/lone pair interaction.[21]

This analysis provides the following rationalization for the positional acidities of *N*-pyridine oxide. The ring *N*-oxide provides powerful stabilization of the carbanions by an inductive effect. This is negated to a small extent at the *para* position due to an unfavorable resonance interaction, but the effect is rather small. The *ortho* position suffers from this small resonance effect and from a significantly destabilizing 1,3-interaction with the O$^-$ group that cancels much of the added inductive effect expected for a group directly attached to the acidifying *N*-oxide. The net outcome is a slight preference for deprotonation at the *meta* position. In any case, there is no evidence for the *N*-oxide group being a π-acceptor and favoring resonance forms such as **3a** or **5a** where the carbanion is viewed as a carbene-like center (Scheme 6).

Scheme 5



Scheme 6



To put the present results in context, comparisons can be made to the carbanions derived from pyridine and *N*-methylpyridinium. Deprotonated pyridine has an experimental PA of 389.9 kcal/mol,[11] and therefore oxidation decreases the ΔH_{acid} of pyridine by ~10 kcal/mol. Schafman and Wenthold have analyzed positional acidities in pyridine in detail and has found that the *para* position is slightly more acidic than the *meta* position, and both are much more acidic than the *ortho* position.[11] To allow for a fair comparison, we have recomputed the positional acidities of pyridine at the G3MP2 level (Table 1, Scheme 2), and the values are consistent with Wenthold's work. The most striking difference between these two systems is that the positional acidities in pyridine vary by over 9 kcal/mol compared to the 2 kcal/mol variation in the *N*-oxide, despite the fact that it is a much more acidifying group. In Wenthold's analysis, they concluded that the *ortho* carbanion is strongly disfavored by the presence of adjacent, coplanar lone pairs on the nitrogen and carbon. The slight preference for *para* over *meta* is driven by the ring nitrogen being a π-acceptor and providing some resonance stabilization to the carbanion. Using eqs 1 and 2, Wenthold assigned a σ_{R} value of 0.76 to the ring nitrogen. A comparison to the analogous analysis for the *N*-oxide (see above) suggests that oxidation dramatically reverses the effect of the nitrogen and converts it into a π-donor rather than acceptor ($\sigma_{\mathrm{R}} = -0.35$). In Table 1 (Scheme 2) are also positional data for the ΔH_{acid} of *N*-methylpyridinium (methyl deprotonation is not included in the table, but it is calculated to be the most acidic site with $\Delta H_{\mathrm{acid}} = 263.9$ kcal/mol). This compound produces a neutral species upon deprotonation and is naturally much more acidic than the other compounds in the study. In *N*-methylpyridinium, the pattern is the reverse of pyridine. The *ortho* position is significantly more acidic than the others, and there is a slight preference for the *meta* over the *para* position. Here, one expects a massive inductive effect from the cationic nitrogen, which stabilizes the *ortho* position without any of the lone pair/lone pair interactions that are problematic in pyridine and the *N*-oxide. The preference of *meta* over *para* can be ascribed to diminishing inductive effects or a mild, destabilizing resonance effect. The latter explanation is less likely because the nitrogen in pyridine acts as a π-acceptor (see above), and methylation seemingly should enhance that. Nonetheless, if the nitrogen in *N*-methylpyridinium is not a strong enough π-acceptor to make the *para* position more stable than the *meta* position, then resonance form **11a** (Scheme 5) must be a relatively minor contributor to the stability of the *para* carbanion.

The next question is whether the pyridine *N*-oxide system is unique in its lack of positional preference. Wenthold and Squires[19] have shown that in halobenzenes, there is a strong positional preference in the order *ortho* > *meta* > *para*, suggesting a distance-dependent inductive effect. The magnitude varies from 12 kcal/mol for fluorobenzene to 5 kcal/mol for bromobenzene. Each of the halogens reduces the ΔH_{acid} of the *ortho* position by ~14 kcal/mol relative to benzene. Kass has investigated anisole and found the same order but a much smaller effect with ΔH_{acid} reductions ranging from 3.5 (*ortho*) to ~0 (*para*) kcal/mol.[22] Positional data are less available for benzenes with powerful electron-withdrawing groups like cyano and nitro. Meot-Ner has provided experimental data for the acidities of these substituted benzenes as well as low-level calculations (AM1) for the positional selectivity.[18] G3MP2 calculations on these systems are provided in Table 1 (Scheme 2). The new computational data for cyanobenzene are consistent with the experiments, but there is a large discrepancy with

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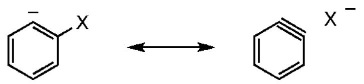
(21) The ortho position in fluorobenzene is much more acidic than the other positions and therefore must not suffer greatly from this effect. However, in the fluorobenzene system, the ortho anion can take advantage of an important benzyne/fluoride resonance form that is not available for the *N*-pyridine oxide ortho carbanion and could provide significant stabilization.

(22) Dahlke, G. D.; Kass, S. R. *Int. J. Mass Spectrom.* **1992**, *117*, 633.

nitrobenzene (over 25 kcal/mol). The experimental value appears to be anomalously low (about the same as the benzylic site in 4-nitrotoluene[23]) and is likely in error given that multiple computational approaches give values near the G3MP2 value in Table 1. In the calculations on nitrobenzene, the most acidic site is the *ortho* position, but it is only 4 kcal/mol more acidic than the least acidic position, *meta*, which is only 1 kcal/mol less acidic than *para*. An identical pattern is seen with cyanobenzene (benzonitrile). The *ortho* position is the most acidic and *meta* the least, but the variation is only ~2 kcal/mol. Therefore both of these substituents provide nearly 20 kcal/mol of acidification, but the positional effects are relatively minor. In fact, the cyano and nitro substituents have much the same effect on the ΔH_{acid} of benzene as the in-ring *N*-oxide group. However, there is one subtle difference. In the pyridine *N*-oxide, the preferred site is *meta*, whereas this is the least acidic site in cyanobenzene and nitrobenzene. This is perfectly consistent with the view that the *N*-oxide is a π-donor and the cyano and nitro groups are π-acceptors, but the impact of the π-effects in these systems is a remarkably small component of the overall substituent effect. If we take the difference in ΔH_{acid} of the *meta* and *para* positions as a measure of the π-effect on acidity, it represents −9%, 7%, and 2% of the acidifying effect of the *N*-oxide, nitro, and cyano groups, respectively. This is not a completely fair comparison for the nitro and cyano groups because the *para* position is slightly disfavored by inductive effects (reducing the apparent π-effect), but this should be a minor factor (the opposite is the case in the *N*-oxide). To put these data in context, one can make a comparison to the impact of these groups on the experimental ΔH_{acid} values of the toluenes. Using the same approach and values from the NIST database, the π-effect accounts for 34% of the ΔH_{acid} reduction at the benzylic site in nitrotoluene ($\Delta H_{acid} = 363$ kcal/mol *meta* and 353 kcal/mol *para*) and 41% in cyanotoluene ($\Delta H_{acid} = 369$ kcal/mol *meta* and 360 kcal/mol *para*), relative to toluene ($\Delta H_{acid} = 382$ kcal/mol). Experimental data are not available for the corresponding 3- and 4-methylpyridine *N*-oxides, but G3MP2 calculations indicate that 19% of the stabilization is derived from the π-effect (**18** and **19** in Table 1). Unlike the parent, deprotonated pyridine *N*-oxide, the π-effect is stabilizing in the benzylic anions and 4-methylpyridine oxide is more acidic than 3-methylpyridine oxide. The contrast is striking, and it is clear that, in the phenyl anions, π-effects are minimal and resonance is not the key factor in determining the acidifying effect of a substituent, even for the most powerful π-acceptors. In the phenyl anions, the carbon lone pair is orthogonal to the π-system so resonance effects are indirect and involve depleting the electron density in the π-orbital of the carbanion to offset the excess density associated with the lone pair. In the extreme, this leads to the carbene resonance form where the carbanion has no electron density in the π -orbital and no formal charge (e.g., **3a** and **5a** in Scheme 6). As the results above suggest, this resonance form is a minor contributor and powerful inductive effects in the σ-framework are the most important factors in decreasing the ΔH_{acid} of the phenyl anions. The situation with the benzylic anions is quite different because direct resonance is possible and the charge is delocalized. In contrast, resonance forms like **3a** and **5a** involve the development of charge separation in the π-system with the depletion of electron density at the carbanion site (to neutralize it) and accumulation of electron density at the substituent. Finally, the strong preference for the *ortho* position in the halobenzenes is undoubtedly related to the influence of a benzyne/halide resonance form (Scheme 7). For example, the 2-chlorophenyl anion has significant lengthening of the C−Cl bond (0.1 Å) and distortion of the benzene framework that is consistent with this type of resonance form (see Supporting Information). Analogous resonance forms are not expected to be as important in the other substituted phenyl anions, and little or no bond lengthening is seen in their *ortho* anions.

Scheme 7



One can also probe the electron distributions in these systems with Natural Population Analysis.[24] Looking only at the charges on the carbanion center, it is clear that substituent effects are minor. As a reference point, the carbanion is assigned a net charge of −0.45 in the phenyl anion. In nitrobenzene, the *meta* and *para* carbanions both have calculated charges of −0.41 at the deprotonation site. In carbanions derived from pyridine *N*-oxide, the charges are −0.43 and −0.45 at the *meta* and *para* deprotonation sites, respectively. Further insight can be gained by examining the occupancy of the p-orbitals in the π-system. This is fairly straightforward because, with the exception of the *ortho* anion of nitrobenzene, the compounds are all roughly planar. The data are shown in Figure 2 for pyridine *N*-oxide, nitrobenzene, and benzene. Comparisons to the neutral parent compounds indicate that there is a consistent pattern in the electronic reorganization after deprotonation. There is a significant depletion of density at the deprotonation site (~0.25 electron) that is made up by increases on the other carbons, particularly the *meta* and *para* carbons (relative to the carbanion center). This is most easily seen in the benzene itself because the distribution is not distorted by substituents. Notably, the *meta* and *para* positions have identical occupancies. The striking feature of the data in Figure 2 is the insensitivity of the data to substituent and positional effects despite the presence of a powerful electron-withdrawing group in the case of nitrobenzene. To put this result in perspective, similar calculations indicate that a nitro group reduces the p-orbital occupancy

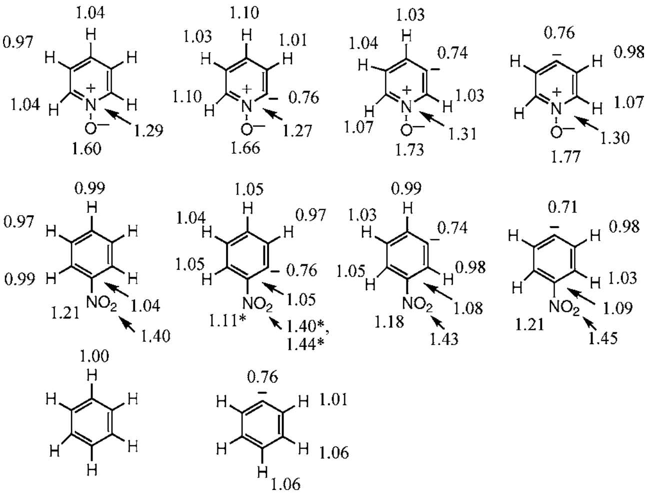


Figure 2. Natural population analysis of p-orbitals involved in the π-system. Values are placed near hydrogens but refer to the associated carbons. In the *ortho* anion of nitrobenzene, the nitro group is significantly twisted out of the benzene plane. Values for some of the nitrogen and oxygen atoms are marked with an * to indicate that they are contaminated by contributions from the σ-framework.

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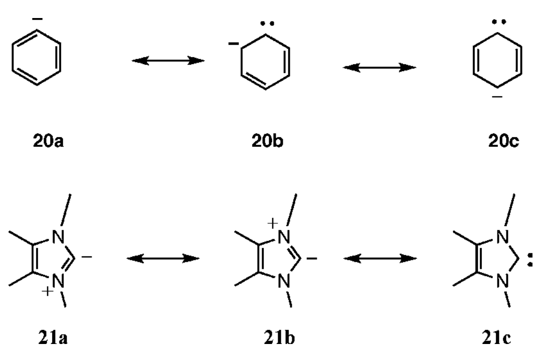
[23] Typically benzylic sites are much more acidic. For example, 4-methylbenzonitrile is over 20 kcal/mol more acidic than benzonitrile.

Scheme 8



of the benzylic carbon of deprotonated 4-nitrotoluene from 1.41 to 1.21 electrons compared to toluene. In addition, the nitro group reduces the calculated charge on the carbanion center from −0.78 to −0.57 in the benzylic system. In each case, the magnitude of the substituent effect on the electron density is several-fold greater in the benzylic anion relative to the aryl anion. Although it might be tempting to assign a carbene resonance form based on the depleted π-occupancy at the carbanion centers of the aryl anions, the patterns in Figure 2 are more consistent with a general polarization of the π-cloud in response to the formation of the carbanion rather than direct contributions from specific resonance forms such **20b** and **20c** (Scheme 8).

These results also provide insight into the role of resonance effects in the deprotonation of other nitrogen heterocycles such as *N*,*N*-dimethylimidazolium. Although its deprotonation product has often been shown in the carbene-like resonance form, **21c** (Scheme 8), the limited resonance effects seen in the deprotonation products of pyridine, pyridine *N*-oxide, and *N*-methylpyridinium suggest that charge-separated resonance forms such as **3**, **5**, **11**, **21a**, and **21b** are the best descriptors of these species. This is consistent with the conclusions of early computational work on these systems by Boehme and Frenking,[25] and Heinemann.[26] The greater contribution from charge-separated, ylide resonance forms is not surprising in that the carbene resonance form requires creating a hole in a potentially aromatic π-system and forcing a carbon to lose its octet, two situations that are typically highly destabilizing. However, as noted in the previous work and here, these systems are characterized by significant polarization in both the σ and π frameworks and, therefore, are not easily characterized by conventional Lewis structures.

Conclusions

The introduction of an *N*-oxide group into the benzene ring greatly, and nearly equally, decreases the ΔH_{acid} of the *ortho*, *meta*, and *para* positions. This result is quite different from what is seen when a nitrogen (i.e., pyridine) or methylated nitrogen (i.e., *N*-methylpyridinium) is introduced into the ring. In those cases, strong positional effects are observed with the *ortho* position being much less (pyridine) or more (*N*-methylpyridinium) acidic than the other positions. In the deprotonated pyridine *N*-oxide species, it appears that there is a balance between strong inductive effects (stabilizing all positions, but most significantly *ortho*), mild resonance effects (destabilizing *ortho* and *para*), and lone pair/lone pair interactions (destabilizing *ortho*). Similar effects are seen in nitrophenyl and cyanophenyl anions. The overall conclusion is that inductive effects are the key factor in the acidity of benzene derivatives with resonance effects playing a minor role. As a result, carbene-like resonance forms are expected to have limited importance even when powerful π electron-withdrawing groups are added to the ring.

Methods

All experiments were completed in a modified Finnigan-LCQ quadrupole ion trap mass spectrometer. Ions were generated by electrospray from 10^{-4}−10^{-5} M solutions of the precursors in methanol using a flow rate of 3−5 μL/min. Typically, an electrospray needle voltage of approximately 4000 V was used. The electrospray ionization source was optimized for the carboxylates derived from the precursor acids for carbanions **3**, **4**, and **5**. These carboxylate ions were isolated in the ion trap and then subjected to collision activated dissociation by a resonant excitation pulse (0.5−1.5 V for ∼30 ms). This process led to large signals for **3**, **4**, and 5, and subsequently all other ions were ejected from the trap. We observed that some decarboxylation occurred during electrospray ionization, but this could be suppressed by reducing the temperature of the heated desolvation capillary. Once a stable signal for the carbanion was established, the neutral reagent was added to the helium buffer gas of the ion trap using a gas handling system that has been described previously.[27,28] In short, the neural reagent is delivered by a syringe pump (30−300 μL/h) to a fast flow of helium (0.5−2 L/min). The great majority of the gas is diverted, and ∼0.25 mL/min is drawn into the ion trap. Using the mixing ratio (reagent/He), the He pressure in the trap (1.75×10^{-3} Torr), and a correction for differential effusion, the partial pressure of the reagent in the trap can be determined. The neutral reagent is added continuously throughout the experiment. To test for proton transfer, the ions (**3**, **4**, and **5**) were allowed to react with the neutral reagent ($\sim 5 \times 10^{-7}$ Torr) for 100−300 ms (time between the isolation of the carbanion and the ejection of all ions to obtain a mass spectrum). Rapid proton transfer (i.e., near the collision rate) was taken as evidence that the reaction was exothermic. In most cases, adducts between the anions and neutrals reagents were also observed. In the H/D exchange experiments, CH_3OD was used as the reagent gas and allowed to react for up to 1 s. Due to mass cutoffs that are inherent to ion trap mass spectrometry, we were not able to obtain good quantitative data on the signals of CH_3O^- product ions.

Calculations. Calculations were completed with the GAUSSIAN03 quantum mechanical package using the composite G3MP2 method.[29] Values are estimated enthalpies at 298 K, employed a frequency scaling factor of 0.9135,[30] and include the enthalpy of a proton in the PA determinations.

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Supporting Information Available: Complete ref 29 and the G3MP2 energies and geometries for species in the study. This material is available free of charge via the Internet at http://pubs.acs.org.

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