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Kinetic and Thermodynamic Acidities of Substituted 1-Benzyl-1-methoxy-2-nitroethylenes. Strong Reduction of the Transition State Imbalance Compared to Other Nitroalkanes

Claude F. Bernasconi,* Mahammad Ali,[†] and Janette C. Gunter

Contribution from the Department of Chemistry and Biochemistry of the University of California, Santa Cruz, California 95064

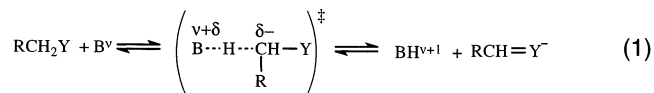***Abstract:*** Acidity constants of six substituted 1-benzyl-1-methoxy-2-nitroethylenes (**2-Z** with Z = m-NO$_2$, m-CF$_3$, m-Cl, H, p-Me, p-MeO) and their respective nitronic acids were determined in 50% DMSO−50% water (v/v) at 20 °C. Kinetic data were obtained on the reversible deprotonation of all six **2-Z** by OH$^-$ and piperidine and on the reversible deprotonation of **2-NO$_2$** by piperazine, 1-(2-hydroxyethyl)piperazine, and morpholine in the same solvent. These data allowed a determination of the Brønsted coefficients α (dependence on acidity of **2-Z**) and β (dependence on amine basicity). The fact that $\alpha > \beta$ indicates the presence of a transition state imbalance which, however, is much smaller than that for the deprotonation of arylnitromethanes. The reasons for this reduction in the imbalance and their relevance to a recent study of the deprotonation of Fischer carbene complexes are discussed.

Introduction

Proton transfers involving nitroalkanes have generated an unusual amount of interest over many years.[1−16] A major reason is that these reactions show some extreme features regarding reactivity and transition state structure. One such feature is that they have the highest intrinsic barriers[17] or lowest intrinsic rate constants[17] for proton transfers in solution.[8a,18] Another feature, directly related to the first, is that the transition state imbalance which is characteristic of proton transfers from carbon acids activated by π acceptors[18] manifests itself more strongly than for any other type of carbon acids.[2,8d,18]

The term "imbalance" refers to the observation that the de-localization of the incipient negative charge into the π acceptor

lags behind the progress of proton transfer at the transition state. This is shown, in exaggerated form, in eq 1 for a generalized carbon acid with the π acceptor Y. The lag in the charge

$$RCH_2Y + B^\nu \rightleftharpoons \left(\begin{array}{c} \nu+\delta \quad \delta- \\ B\cdots H\cdots CH - Y \\ | \\ R \end{array} \right)^{\ddagger} \rightleftharpoons BH^{\nu+1} + RCH = Y^- \quad (1)$$

delocalization is responsible for the high intrinsic barriers of these reactions.[18] The increased barriers arise because the transition state cannot take advantage of the resonance stabiliza-

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* Address correspondence to this author. E-mail: bernasconi@chemistry.ucsc.edu.

† Current address: Department of Chemistry, Jadavpur University, Kolkata 700 032, India.

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(17) The intrinsic barrier, $\Delta G_o^{\ddagger}$ (intrinsic rate constant, k_o), of a reaction with a forward rate constant k_1 and a reverse rate constant k_{-1} is defined as $\Delta G_o^{\ddagger} = \Delta G_1^{\ddagger} = \Delta G_{-1}^{\ddagger}$ ($k_o = k_1 = k_{-1}$) when $\Delta G° = 0$ ($K_1 = 1$). For proton transfers, statistical factors are usually included; see below.

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tion of the carbanion, since this stabilization is barely developed at the transition state.[19]

The transition state imbalances reveal themselves when comparing the Brønsted α values obtained by varying a remote substituent on the carbon acid with the Brønsted β value determined by varying the basicity of the proton acceptor. Depending on the location of the substituent with respect to the site of charge development on the carbon acid, one observes either α > β or α < β.[22] The best known example is the

(2)
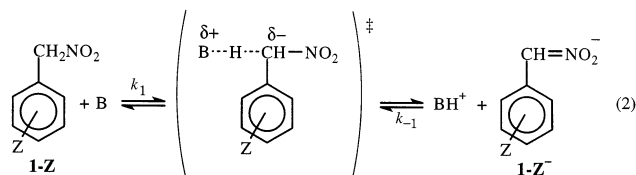
deprotonation of arylnitromethanes by secondary alicyclic amines, eq 2, where $\alpha = d\log k_1/d\log K_a^{CH} = 1.29$ and $\beta = d\log k_1/dpK_a^{BH} = 0.56$.[2a] In fact, in this case, the difference between α and β is so large that α is outside the "normal" range of 0−1 and hence the α value alone reveals the imbalance.

In this paper, we report results relating to the deprotonation of 1-benzyl-1-methoxy-2-nitroethylenes, **2-Z**, by amines. **2-Z** include structural features that are not present in the nitroalkanes studied so far: the nitro group is in a vinylogous position with respect to the acidic proton, and the presence of the methoxy group attached to the C=C double bond leads to a strong push−pull effect, shown in the canonical structure **2-Z**±.
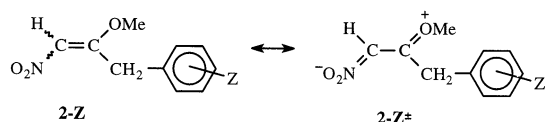
The specific question we wish to address is whether these special structural features may affect the actual size of the transition state imbalance and/or its manifestation in terms of α and β values. This question is not only of interest within the context of nitroalkane deprotonation but also bears directly on some puzzling observations in the deprotonation of Fischer carbene complexes of the type **3-Z**.[24] These carbene complexes
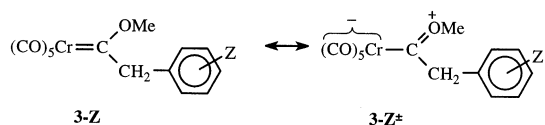
are quite acidic because the anionic charge can be delocalized into the $(CO)_5Cr$-moiety (**3-Z**−).[25] Hence, it is not surprising that their proton transfer reactions have high intrinsic barriers, and it is logical to assume that the high barriers are the result

of the same kind of transition state imbalance (**4**) that is observed with the nitroalkanes and other organic carbon acids.[18] However,
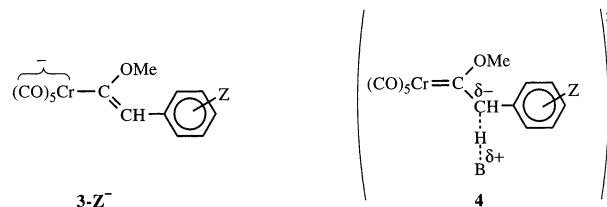
according to a recent report,[24] the Brønsted α values for the deprotonation of **3-Z** by *n*-butylamine or piperidine are indistinguishable from the β values obtained from the reactions of **3-H** or **3-F** with a series of primary aliphatic or secondary alicyclic amines.

The notion that Fischer carbene complexes would behave in a fundamentally different way from purely organic carbon acids in that the high intrinsic barriers for proton transfer are *not* related to transition state imbalances was deemed implausible.[24] Rather, the lower than expected α values were attributed to an effect of the push−pull resonance symbolized by **3-Z**± which lowers α and hence masks the imbalance.

Since **2-Z** and **3-Z** are structurally very similar, one may expect that the push−pull resonance of the nitro compound (**2-Z**±) may also lower α and bring it closer to β than in the reaction of eq 2. A major objective of the present study is to test this hypothesis. The results will show that the difference between α and β for the deprotonation of **2-Z** by amines is indeed considerably smaller than that for eq 2 but α is still greater than β.

Results

General Features. Rate and equilibrium constants for the reactions of **2-Z** (Z = $NO_2(m)$, $CF_3(m)$, $Cl(m)$, H, Me(*p*), and OMe(*p*)) with piperidine and for the reactions of **2-NO₂**(*m*) with piperidine, 1-(2-hydroxyethyl)piperazine, and morpholine were determined. All experiments were performed in 50% DMSO− 50% water (v/v) at 20 °C and a constant ionic strength of 0.5 M maintained by KCl. Pseudo-first-order conditions, with the substrate as the minor components, were used throughout. The reactions were monitored spectrophotometrically, mostly in a stopped-flow spectrophotometer.

The pK_a^{CH} values of **2-Z** range from 10.9 to 12.3. Since most amines have pK_a^{BH} values well below this range, the majority of the kinetic experiments had to be performed by first generating the anion in an ∼0.01 M KOH solution and then mixing it with the appropriate amine buffer. A complicating feature was that the pK_a^{NOH} values of the *aci* form (nitronic acid) of **2-Z** are fairly high. This means that reaction of the anion with the more acidic amine buffers led to rapid equilibrium protonation of the nitro group prior to carbon protonation. This is shown in Scheme 1.[26] The observed pseudo-first-order rate constants for Scheme 1 are given by eq 3.

$$k_{obsd} = k_1^{OH}[OH^-] + k_1^{B}[B] + (k_{-1}^{H_2O} + k_{-1}^{BH}[BH]) \times$$

$$\frac{K_a^{NOH}}{K_a^{NOH} + a_{H^+}} \quad (3)$$

(19) For discussions relating to the origins of the imbalance, see, for example, refs 3, 12, 16, 18, 20, and 21.

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(22) When the substituent is closer to the negative charge at the transition state than in the fully formed carbanion, as in the example of eq 2, α > β. When the substituent is closer to the negative charge in the anion than at the transition state, α < β. An example for this situation is provided by the reaction of 2-nitro-4-*Z*-phenylacetonitriles with bases.[23]

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(25) For a recent review, see: Bernasconi, C. F. *Chem. Soc. Rev.* **1997**, *26*, 299.

Table 1. Reaction of **2-Z** with OH⁻ and Piperidine in 50% DMSO−50% Water (v/v) at 20 °C.[a] Rate Constants and pK_a Values

Z	σ	k_1^{OH} (M⁻¹ s⁻¹)	$k_{-1}^{H_2O\,b}$ (s⁻¹)	$k_1^{B\,c}$ (M⁻¹ s⁻¹)	$k_{-1}^{BH\,d}$ (M⁻¹ s⁻¹)	p$K_a^{CH\,e}$ (spectro)	p$K_a^{CH\,f}$ (kinet)	pK_a^{NOH}
m-NO₂	0.71	621 ± 22	6.51 × 10⁻³	113 ± 3 (118 ± 3)	86.9 ± 4.3	10.91 ± 0.03	10.69 ± 0.03	9.55 ± 0.11
m-CF₃	0.43	357 ± 12	7.64 × 10⁻³	58.6 ± 2.2 (64.9 ± 2.5)	93.9 ± 4.7	11.22 ± 0.05	11.11 ± 0.04	9.62 ± 0.10
m-Cl	0.23	230 ± 7	6.20 × 10⁻³	46.5 ± 0.5 (52.8 ± 0.6)	92.9 ± 13.4	11.32 ± 0.06	11.25 ± 0.07	9.68 ± 0.20
H	0.00	86.7 ± 0.67	9.09 × 10⁻³	13.9 ± 0.1 (14.6 ± 0.1)	108 ± 8	11.91 ± 0.03	11.99 ± 0.05	10.27 ± 0.09
p-Me	−0.17	58.8 ± 0.31	1.07 × 10⁻²	9.89 ± 0.10 (10.8 ± 0.1)	134 ± 7	12.15 ± 0.07	12.04 ± 0.03	10.50 ± 0.06
p-MeO	−0.27	57.9 ± 0.67	1.49 × 10⁻²	7.87 ± 0.07 (8.89 ± 0.07)	151 ± 9	12.30 ± 0.05	12.16 ± 0.04	10.77 ± 0.07

[a] $\mu = 0.5$ M (KCl). [b] $k_{-1}^{H_2O} = k_1^{OH} K_w / K_a^{CH}$ with $K_w = 1.29 \times 10^{-16}$ M² (ref 29) and K_a^{CH} determined spectrophotometrically. [c] $k_1^B = (k_{-1}^{BH} K_a^{CH} / K_a^{BH}$ with k_{-1}^{BH} and K_a^{CH} determined by curve fit to eq 6; numbers in parentheses obtained from experiments at pH > pK_a^{CH}. [d] k_{-1}^{BH} determined from curve fit to eq 6. [e] Determined spectrophotometrically. [f] Determined kinetically by curve fit to eq 6.

Scheme 1

2-Z ≡ CH   **2⁻-Z ≡ C⁻**

HC
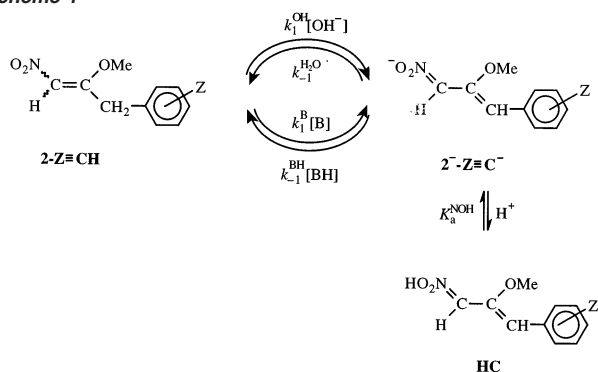
Spectrophotometric pK_a^{CH} Determinations. The anions (**2-Z⁻ ≡ C⁻**) absorb strongly in the 360−380 nm range, which allowed the spectrophotometric determination of the pK_a^{CH} values of **CH**. The absorbance, *A*, at a given pH is given by eq 4, where A_{CH} refers to the

$$A = \frac{A_{CH} a_{H^+} + A_{C^-} K_a^{CH}}{K_a^{CH} + a_{H^+}} \quad (4)$$

absorbance of **CH** at pH ≪ pK_a^{CH} and A_{C^-} is the absorbance of **C⁻** at pH ≫ pK_a^{CH}. Representative plots of *A* versus a_{H^+} are shown in Figure S1 (Supporting Information).[27] Nonlinear least-squares fit of the data to eq 3 yielded the pK_a^{CH} values reported in Table 1.

Kinetics in KOH Solutions. Kinetic runs were performed at 9−12 KOH concentrations ranging from 0.005 to 0.25 M. Plots of k_{obsd} versus [OH⁻] were linear with negligible intercepts; that is, under these conditions, the deprotonation is virtually irreversible and eq 3 reduces to eq 5.

$$k_{obsd} = k_1^{OH}[OH^-] \quad (5)$$

The k_1^{OH} values are summarized in Table 1 along with $k_{-1}^{H_2O}$ obtained as $k_{-1}^{H_2O} = k_1^{OH} K_w / K_a^{CH}$ with K_w being the ionic product of the solvent.[28]

Kinetics in Piperidine Buffers. Most experiments were conducted by mixing **C⁻** with the buffer at a pH which was generally lower than pK_a^{CH}. Rates were measured as a function of buffer concentration and of pH. At any given pH, k_{obsd} was determined at 6−7 different buffer concentrations ranging from

0.02 to 0.2 M *total* buffer concentration. Plots of k_{obsd} versus piperidinium ion concentration ([BH⁺]) were linear with intercepts indistinguishable from zero, indicating that the $k_1^{OH}[OH^-]$ and $k_{-1}^{H_2O}$ terms in eq 3 are negligible. Figure S2[27] shows a representative set of data. The slope of these plots is given by eq 6.

$$\text{slope} = k_{-1}^{BH}\left(\frac{K_a^{CH}}{a_{H^+}} + \frac{K_a^{NOH}}{K_a^{NOH} + a_{H^+}}\right) \quad (6)$$

Similar data were obtained at 10−18 different pH values. Some representative plots of the slopes versus a_{H^+} are shown in Figure S3.[27] The three parameters, k_{-1}^{BH}, K_a^{CH}, and K_a^{NOH} were evaluated by a nonlinear least-squares fit of the slopes to eq 6. From k_{-1}^{BH}, k_1^B was then calculated as $k_1^B = k_{-1}^{BH} K_a^{CH} / K_a^{BH}$. For most compounds, there is good agreement between K_a^{CH} obtained from this curve fit and the spectrophotometrically determined value; the largest discrepancy between the two values is for **2-NO₂** (0.13 log units).

A few experiments were conducted by mixing **CH** with the piperidine buffer at pH > pK_a^{CH}. Specifically, for the reactions of **2-NO₂**, **2-CF₃**, and **2-Cl**, the pH was 12.19, while the reactions of **2-H**, **2-Me**, and **2-OMe** were run in a 0.01 M KOH solution at pH 13.89. Under these conditions, the protonation of **C⁻** on the nitro group is negligible ($K_a^{NOH} \gg a_{H^+}$) but the deprotonation of **CH** by OH⁻/reprotonation of **C⁻** by water are not negligible. Hence, eq 3 becomes eq 7. Plots of k_{obsd} versus free amine concentration ([B]) have slopes given by eq 8 and intercepts given by eq 9.

$$k_{obsd} = k_1^{OH}[OH^-] + k_1^B[B] + k_{-1}^{H_2O} + k_{-1}^{BH}[BH] \quad (7)$$

$$\text{slope} = k_1^B\left(1 + \frac{a_{H^+}}{K_a^{CH}}\right) \quad (8)$$

$$\text{intercept} = k_1^{OH}[OH^-] + k_{-1}^{H_2O} \quad (9)$$

In most cases, the forward reaction is dominant so that the slope ≈ k_1^B.

The k_1^B values obtained from these experiments are also reported in Table 1. They agree very well with the k_1^B values determined from the first series of experiments. This close agreement indicates good internal consistency of the data.

Kinetics of the Reactions of 2-NO₂ with Piperidine, 1-(2-Hydroxyethyl)piperazine, and Morpholine. These experiments were conducted at pH values between 11.4 and 11.5 held constant by a dilute triethylamine buffer (total buffer concentration 0.03 M). Under these conditions, eq 3 becomes eq 10; that

(26) In principle, Scheme 1 should include a $k_1^{H_2O}$ term for deprotonation of **CH** by water and a $k_{-1}^H a_{H^+}$ for protonation of **C⁻** by H₃O⁺. However, all experiments were conducted in a pH range where these terms are negligible.
(27) See paragraph concerning Supporting Information at the end of this paper.
(28) p$K_w = 15.89$.[29]

Table 2. Rate Constants for the Reaction of **2-NO$_2$** with Piperazine, 1-(2-Hydroxyethyl)piperazine, and Morpholine in 50% DMSO−50% Water (v/v) at 20 °C[a]

B	pK_a^{BH}	k_1^B (M^{-1} s^{-1})	k_{-1}^{BH} (M^{-1} s^{-1})
morpholine	8.72	9.73 ± 0.34	(1.51 ± 0.16) × 10^3
HEPA[b]	9.51	23.9 ± 0.5	(5.78 ± 0.53) × 10^2
piperazine	9.90	55.3 ± 1.1	(5.66 ± 0.58) × 10^2
piperidine[c]	11.02	113 ± 3	86.9 ± 4.3

[a] μ = 0.5 M. [b] HEPA = 1-(2-hydroxyethyl)piperazine. [c] Results from Table 1.

is, again $K_a^{NOH} \gg a_{H^+}$, while the $k_1^{OH}[OH^-]$ and $k_{-1}^{H_2O}$ terms are negligible.

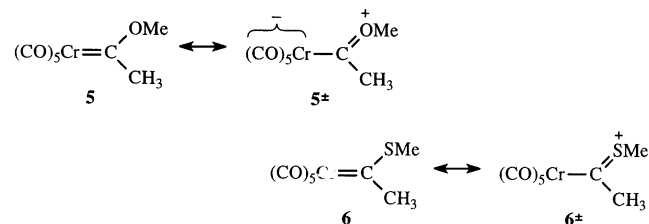$$k_{obsd} = k_1^B[B] + k_1^{Et_3N}[Et_3N] + k_{-1}^{BH}[BH^+] + k_{-1}^{Et_3NH}[Et_3NH^+] \tag{10}$$

The slope of the plots of k_{obsd} versus [B] are again given by eq 8. The k_1^B value obtained from these experiments, along with k_{-1}^{BH} calculated as $k_1^B K_a^{BH}/K_a^{CH}$, are reported in Table 2.

Discussion

Thermodynamic Acidities. The pK_a^{CH} values range from 10.9 to 12.3, while the pK_a^{NOH} values range from 9.55 to 10.77; for example, for **2-H**, pK_a^{CH} = 11.91 and pK_a^{NOH} = 10.27. This compares with pK_a^{CH} = 7.93 and pK_a^{NOH} = 4.75 for phenylnitromethane (**1-H**) in the same solvent (50% DMSO−50% water).[8a]

The main reasons for the high acidity of phenylnitromethane is the strong stabilization of the anion (**1-Z$^-$**) by delocalization of the negative charge into the nitro group. The anion of the 1-benzyl-1-methoxy-2-nitroethylenes (**2-Z$^-$**, Scheme 1) is similarly stabilized and, because of the conjugation between the C=C and the C=N double bonds, may potentially enjoy an even greater resonance stabilization than **1-Z$^-$**. Nevertheless, **2-H** is significantly less acidic than **1-H**.

The main factor responsible for the reduced acidity of **2-H** appears to be the resonance stabilization of the *acid* form (**2-H** ↔ **2-H$^\pm$**) by the push−pull effect. That this kind of resonance effect can lead to a very substantial stabilization is revealed when comparing the acidities of the two Fischer carbene complexes **5** and **6**. The pK_a^{CH} values of **5** and **6** are 12.50[30] and 9.05,[31] respectively. The higher pK_a^{CH} of **5** is

$$(CO)_5Cr=C\begin{smallmatrix}OMe\\CH_3\end{smallmatrix} \leftrightarrow (CO)_5Cr-C\begin{smallmatrix}\overset{-}{OMe}\\CH_3\end{smallmatrix}$$

5 **5$^\pm$**

$$(CO)_5Cr=C\begin{smallmatrix}SMe\\CH_3\end{smallmatrix} \leftrightarrow (CO)_5Cr-C\begin{smallmatrix}\overset{+}{SMe}\\CH_3\end{smallmatrix}$$

6 **6$^\pm$**

mainly the result of the strong resonance stabilization of **5** due to the importance of **5$^\pm$**; the corresponding resonance structure of **6** (**6$^\pm$**) is much less important because the MeS group is a weaker π donor than the MeO group. Since the nitro group appears to be an ever stronger π acceptor than the (CO)$_5$Cr group,[25] the stabilizing effect of **2-H$^\pm$** can indeed be expected to be quite substantial.
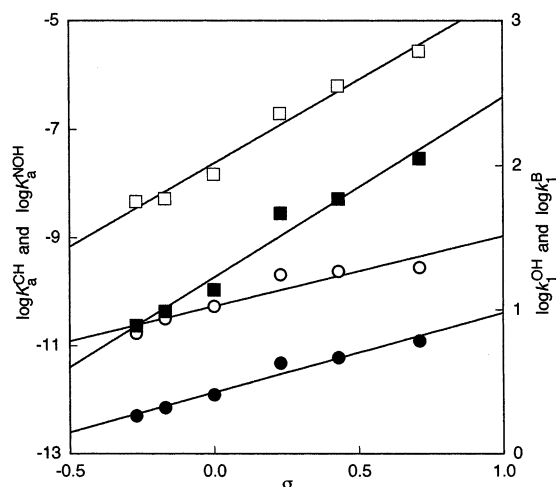
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(31) Bernasconi, C. F.; Ali, M. *J. Am. Chem. Soc.* **1999**, *121*, 3039.

Figure 1. Hammett plots. Left axis: ●, log K_a^{CH}; ○, log K_a^{NOH}. Right axis: ■, log k_1^{Pip}; □, log k_1^{OH}.

Table 3. Hammett ρ Values

parameter	ρ	parameter	ρ
K_a^{CH}	1.47 ± 0.14	$k_{-1}^{H_2O}$	−0.32[a]
K_a^{NOH}	1.32 ± 0.24	$k_1^{B\ b}$	1.24 ± 0.11
k_1^{OH}	1.15 ± 0.09	$k_{-1}^{BH\ b}$	−0.23[c]

[a] Calculated as $\rho(k_{-1}^{H_2O}) = \rho(k_1^{OH}) - \rho(K_a^{CH})$. [b] B = piperidine. [c] Calculated as $\rho(k_{-1}^{BH}) = \rho(k_1^B) - \rho(K_a^{CH})$.

The acidity of the nitronic acid (**HC** in Scheme 1) is even more strongly reduced relative to the *aci* form of phenylnitromethane, decreasing the K_a^{NOH}/K_a^{CH} ratio of 1.51 × 10^3 for phenylnitromethane to 43.6 for **2-H**. This situation is reminiscent of the decrease in the K_a^{NOH}/K_a^{CH} ratio from 1.07 × 10^7 for CH$_3$NO$_2$ to 1.51 × 10^3 for PhCH$_2$NO$_2$.[8a] This decrease was attributed to a stabilization of the neutral *aci* form by the resonance effect shown in **7a** ↔ **7b**.[8a] A similar resonance stabilization is likely for **2-H**, that is, **8a** ↔ **8b**. The fact that
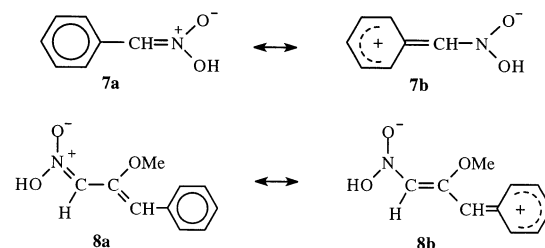
the K_a^{NOH}/K_a^{CH} ratio for **2-H** is smaller than that for **1-H** suggests that the resonance stabilization provided by **8b** is even more effective than that provided by **7b**.

Hammett Plots. Figure 1 shows Hammett plots for K_a^{CH}, K_a^{NOH}, k_1^{OH}, and k_1^{Pip}. The respective ρ values are reported in Table 3. The $\rho(K_a^{CH})$ value 1.47 is somewhat larger than $\rho(K_a^{NOH})$ = 1.32. This indicates that anion stabilization by electron withdrawing substituents is not the only factor responsible for the positive ρ values but effects on the stability of the respective acids (**CH** and **HC**) also play a role. Specifically, the higher $\rho(K_a^{CH})$ suggests that a destabilization of the **CH** acid by electron withdrawing substituents contributes to the increased acidity. A likely reason for this destabilization is the push−pull interaction between the methoxy and the nitro groups

(**2-Z$^\pm$**). Because the positive charge in **2-Z$^\pm$** is closer to the substituent than the negative charge, an electron withdrawing substituent is overall destabilizing.[32]

It may appear surprising that the difference between $\rho(K_a^{CH})$ and $\rho(K_a^{NOH})$ is not larger than it is because the nitronic acid does not have a resonance form with a positive charge on the methoxy group. However, it has a resonance form with a positive charge on the phenyl group (**8b**), and hence, there should also be a destabilizing effect by electron withdrawing substituents which enhances $\rho(K_a^{NOH})$ and brings it closer to $\rho(K_a^{CH})$.

The absolute magnitude of $\rho(K_a^{CH})$ and $\rho(K_a^{NOH})$ is quite large, considering the distance between the substituent and the site of negative charge in the anion. In comparison, the $\rho(K_a^{CH})$ for the phenylnitromethanes (**1-Z**) is 0.83.[2a] One factor that is responsible for the enhanced ρ-value is the lower polarity of 50% DMSO−50% water (**2-Z**) compared to that of water (**1-Z**). The two types of compounds are also not directly comparable, since in the case of **2-Z$^-$** the electronic effect is transmitted through a conjugated π system.

The $\rho(k_1^{OH})$ value for the rate constant of deprotonation of **2-Z** by OH$^-$ (1.15) is slightly lower than that for the reaction with piperidine (1.24). On the basis of electrostatic effects, one might have expected that $\rho(k_1^{OH}) > \rho(k_1^{Pip})$ instead, because the transition state for the OH$^-$ reaction (**9**) derives additional stabilization from the interaction of electron withdrawing substituents with the partial negative on OH, while the transition state for the piperidine reaction (**10**) is electrostatically destabilized by the interaction of Z with B$^{\delta+}$. Hence, the fact that
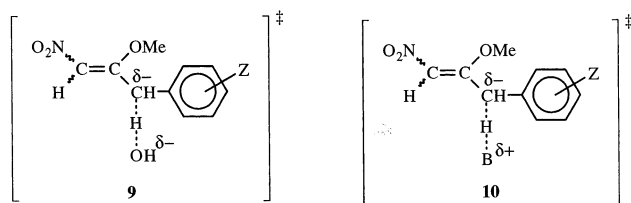
$\rho(k_1^{OH}) < \rho(k_1^{Pip})$ suggests that at the transition state the proton transfer is more advanced for the piperidine reaction and that this feature more than offsets the electrostatic effects. This is consistent with the Hammond−Leffler[35,36] postulate that calls for an earlier transition state for the thermodynamically more favorable reaction with OH$^-$.

Brønsted Plots. Plots of log k_1^{OH} and log k_1^{Pip} versus log K_a^{CH} are shown in Figure 2, while plots log(k_1^{B}/q) and log(k_{-1}^{B}) versus pK_a^{BH} − pK_a^{CH} + log(p/q) for the dependence of the reaction of **2-NO₂** on amine basicity are shown in Figure 3; q and p are statistical factors.[37] The various α and β values are summarized in Table 4, along with log k_o for the intrinsic rate constant of the reaction of **2-NO₂** with amines; the latter was
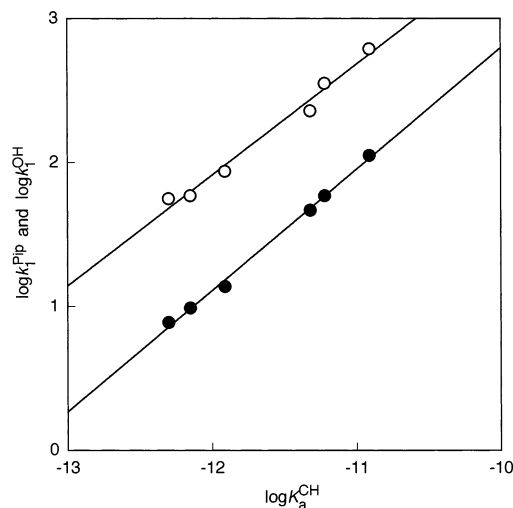
(32) This type of ρ-enhancing effect through destabilization of the push−pull reactants has been observed in several reactions involving Fischer carbene complexes;[33,34] in fact, the destabilizing effect of electron withdrawing substituents on the carbene complex appears to be more important than the stabilizing effect on its anionic product,[34] and the same may very well be the case with **2-Z**.
(33) Bernasconi, C. F.; Ali, M. *J. Am. Chem. Soc.* **1999**, *121*, 11384.
(34) Bernasconi, C. F.; Whitesell, C.; Johnson, R. A. *Tetrahedron* **2000**, *56*, 4917.
(35) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.
(36) Leffler, J. E.; Grunwald, E. *Rates and Equilibria in Organic Reactions*; Wiley: New York, 1963; p 156.
(37) Footnote d in Table 4.

Figure 2. Brønsted plots for dependence on nitroalkene acidity. ●, log k_1^{Pip}; ○, log k_1^{OH}.

Figure 3. Brønsted plot for dependence on amine basicity.

Table 4. Brønsted Coefficients and Intrinsic Rate Constant

parameter	value
$\alpha = d\log k_1^{B}/d\log K_a^{CH}$ ^{a}	0.84 ± 0.03^b
$\beta = d\log k_1^{B}/dpK_a^{BH}$ ^{c}	0.47 ± 0.05
$\log k_o^{B}$ ^{d,e}	1.87 ± 0.02
$\alpha = d\log k_1^{OH}/d\log K_a^{CH}$	0.77 ± 0.05^e

^{a} B = piperidine. ^{b} α calculated as $\rho(k_1^{B})/\rho(K_a^{CH}) = 0.84 \pm 0.14$. ^{c} On the basis of **2-NO₂**. ^{d} $\log k_o^{B} = \log(k_1^{B}/q)$ when pK_a^{BH} − pK_a^{CH} + log(p/q) = 0, where q is the number of equivalent basic sites on B and p is the number of equivalent protons on BH$^+$. ^{e} α calculated as $\rho(k_1^{OH})/\rho(K_a^{CH}) = 0.78 \pm 0.12$.

obtained by extrapolation of log(k_1^{B}/q) to pK_a^{BH} − pK_a^{CH} + log(p/q) = 0 and will be discussed below.

The α value of 0.84 for the deprotonation of **2-Z** by piperidine exceeds the β value of 0.47 obtained from the dependence on amine basicity. This indicates the presence of a significant transition state imbalance whereby charge delocalization into the nitro group lags behind proton transfer, just as is the case for the deprotonation of arylnitromethanes (**1-Z**, eq 2). However, the difference between α and β for the reaction of **2-Z** (0.84 − 0.47 = 0.37) is much smaller than that for the reaction of **1-Z** (1.29 − 0.56 = 0.72). This result could either mean that the

actual imbalance for the reaction of **2-Z** is smaller than that for the reaction of **1-Z** or that the true size of the imbalance is masked by some factor that reduces α below what it might be on the basis of the actual imbalance.[38] A definite answer cannot be given, but the recent results obtained for the deprotonation of **3-Z**[24] are suggestive. As mentioned in the Introduction, there is every reason to believe that the reactions of **3-Z** also have an imbalanced transition state, yet the experimental α and β values were found to be approximately equal. Hence, it was concluded that the imbalance is masked because α is reduced by the push–pull resonance effect (**3-Z**[±]) to bring it to the level of β. Since the same push–pull resonance effect operates in **2-Z**, one expects it to lower α as well, which provides at least part of the reason α − β is much smaller for the deprotonation of **2-Z** than for the deprotonation of **1-Z**.

A number of explanations as to how the push–pull resonance effect may reduce α have been discussed in great detail in ref 24. Perhaps the simplest view[39] is to assume that the partial positive charge on the MeO group of **2-Z**$^{\delta+\delta-}$ (resonance hybrid of **2-Z** and **2-Z**[±]) is largely maintained at the transition state (**11**), implying that **11** is a more accurate representation of the transition state than **10**. This means that the stabilizing effect

2-Z $^{\delta+\,\delta-}$ **11**
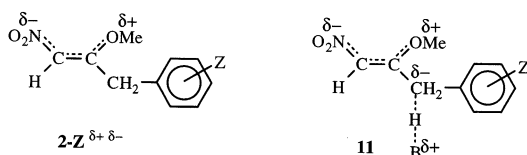
of an electron withdrawing substituent on the negatively charged carbon is partially offset by its destabilizing effect on the positively charged MeO group and hence α is reduced. This notion is complementary to one which views the contribution of **2-Z**[±] to the structure of the carbon acid as tantamount to preorganizing the NO_2 group toward its structure in the anion. This implies that the difference in the distribution of the negative charge between transition state (**11**) and anion is less dramatic than that in the reaction of phenylnitromethane, leading to a reduction in α.[24]

Intrinsic Rate Constant. The log k_o^B value 1.87 for the intrinsic rate constant[17] is considerably higher than log k_o^B = −0.25 for the deprotonation of phenylnitromethane by secondary alicyclic amines in the same solvent.[8a] To understand the possible reasons for this large difference in log k_o^B values which is equivalent to a 2.9 kcal/mol difference in $\Delta G_o^\ddagger$, it is useful to briefly review the relevant factors that affect intrinsic barriers ($\Delta G_o^\ddagger$) in such proton transfers. As discussed in detail elsewhere,[18] the change in the intrinsic barrier, $\delta\Delta G_o^\ddagger$, that results from the introduction of a π acceptor (Y in RCH_2Y, eq 1) is given by eq 11;

$$\delta\Delta G_o^\ddagger = (\lambda_{\mathrm{res}} - \beta)\,\delta\Delta G_{\mathrm{res}}^o \qquad (11)$$

$\delta\Delta G_{\mathrm{res}}^o$ is the change in the free energy of the reaction attributed to the resonance stabilization of the carbanion, λ_{res} is a measure of the progress in resonance development at the transition state, and β is the Brønsted coefficient obtained from

the buffer base dependence; β is assumed to be an approximate measure of proton transfer at the transition state.[40] For a transition state in which resonance development lags behind proton transfers, we have $\lambda_{\mathrm{res}} < \beta$, and $\lambda_{\mathrm{res}} - \beta$ may be considered a measure of the imbalance.[45] Hence, eq 11 predicts $\delta\Delta G_o^\ddagger > 0$ (increase in the intrinsic barrier or decrease in k_o), since resonance stabilization of the anion implies $\delta\Delta G_{\mathrm{res}}^o < 0$.

According to eq 11, the change in the intrinsic barrier that arises from *changing* the π acceptor may then be the result of a change in the resonance stabilization of the anion (change in $\delta\Delta G_{\mathrm{res}}^o$), of a change in the imbalance ($\lambda_{\mathrm{res}} - \beta$), or a combination of both. With respect to the case at hand, we offer the following analysis. In the section discussing the pK_a^{CH} values, it was concluded that there is probably no significant reduction in the resonance stabilization of **2-H**[−] relative to that of **1-H**[−], despite the lower acidity of **2-H**. Hence, there is no significant change in $\delta\Delta G_{\mathrm{res}}^o$. This would imply that the greater log k_o^B value for **2-H** is the result of a smaller imbalance, a notion seemingly supported by the fact that α − β for the reaction of **2-H** (0.84 − 0.47 = 0.37) is much smaller than that for the reaction of **1-H** (1.29 − 0.56 = 0.73). However, as argued earlier, the reduction in the α value for **2-H** is, at least in part, due to the push–pull effect rather than due to a true reduction in the imbalance, and hence, this factor cannot explain the entire increase in log k_o^B. Instead we propose that a significant portion of the increase in log k_o^B is the consequence of the same preorganization effect mentioned as the reason for the low α value; that is, the nitro group is being preorganized toward its electronic configuration in the anion. Since this results in more charge being delocalized into the nitro group at the transition state (**11**), its energy is lowered.

The importance of this preorganization effect in lowering intrinsic barriers has been demonstrated in the reaction of nucleophiles with p-Me_2N and p-MeO-substituted β-nitrostyrenes, where a similar push–pull resonance effect prevails (**12** ↔ **12**[±]).[46]

12   **12**[±]
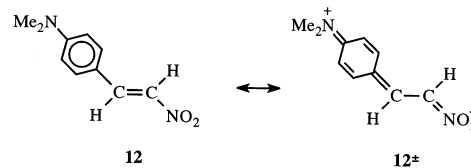
Conclusions

(1) The title compounds are significantly less acidic than phenylnitromethane. This is probably not the result of reduced

(38) A small fraction of the reduction of α may be attributed to the slightly less protic/polar solvent (50% DMSO−50% water versus water); in pure DMSO, α for the reaction of **1-Z** with benzoate ion is 0.92.[4b]

(39) Bernasconi, C. F.; Ruddat, V. *J. Am. Chem. Soc.* **2002**, *124*, 14968.

(40) This is the traditional view,[35,36,41,42] although this view has been challenged.[43,44] The fact that one finds α > β in cases where the charge in the carbanion presumably shifts away from the Z substituent whereas one observes α < β in cases where the charge in the carbanion is presumably closer to the Z substituent than it is in the transition state[22] may itself be taken as strong evidence in support of the traditional view.

(41) Kresge, A. J. *Acc. Chem. Res.* **1975**, *8*, 354.

(42) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511.

(43) (a) Pross, A. *J. Org. Chem.* **1984**, *49*, 1811. (b) Pross, A.; Shaik, S. S. *New J. Chem.* **1989**, *13*, 427.

(44) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 4737.

(45) Note that λ_{res} should not be confused with α. λ_{res} is not directly accessible experimentally, although it can be estimated;[8i,18b] it is independent of the location of the Z substituent relative to the site of negative charge development which contrasts with α which, for a given imbalance, can either be larger or smaller than β.[22] Note also that for $\lambda_{\mathrm{res}} = \beta$ (no imbalance) there is no change in the intrinsic barrier ($\delta\Delta G_o^\ddagger = 0$).

(46) Bernasconi, C. F.; Renfrow, R. A.; Tia, P. R. *J. Am. Chem. Soc.* **1986**, *108*, 4541.

Scheme 2
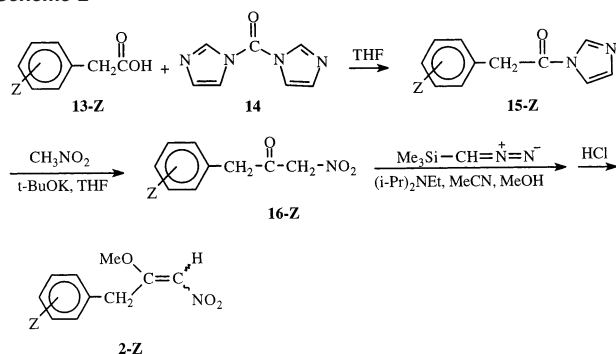
resonance stabilization of the anions (**2-Z$^-$**) but a consequence of push–pull resonance in the acid (**2-Z**). The rather low acidity of the *aci* form of **2-Z** may be attributed to resonance stabilization of the nitronic acid (**8a ↔ 8b**).

(2) The $\rho(K_a^{CH})$ value for **2-Z** is higher than that for the arylnitromethanes (**1-Z**). A destabilizing effect of **2-Z** by electron withdrawing substituents due to the partial positive charge on the MeO group (**2-Z$^\pm$**) is the most likely reason for the larger than expected ρ-value. A similar explanation holds for the high $\rho(K_a^{NOH})$, due to the partial positive charge on the phenyl group (**8b**).

(3) The $\rho(k_1^{Pip})$ value is larger than the $\rho(k_1^{OH})$, implying that, at the transition state, proton transfer is more advanced for the piperidine reaction, as called for by the Hammond–Leffler postulate.

(4) The Brønsted α value (0.84) exceeds the Brønsted β value (0.47) but less so than for the deprotonation of arylnitromethanes ($\alpha = 1.29$, $\beta = 0.56$). The smaller α value for the reaction of **2-Z** appears to result from the push–pull resonance effect (**2-Z$^\pm$**) which leads to a transition state (**11**) in which the stabilizing effect of electron withdrawing substituents is partially offset by their destabilizing effect on the positively charged MeO group.

(5) The log k_o^B value for the deprotonation **2-H** is substantially higher than that for the deprotonation of **1-H**. This result is attributed to the preorganization of the nitro group toward its electronic configuration in the anion which leads to a more delocalized and hence more stabilized transition state (**11**).

Experimental Section

Synthesis of Substituted 1-Benzyl-1-methoxy-2-nitroethylenes. The synthetic pathways are outlined in Scheme 2.

A. Synthesis of 16-Z. The synthesis of the α-nitroketones, **16-Z**, was based on a method described by Baker and Putt.[47] In a typical procedure, a 100 mL three-necked round-bottom flask fitted with a water jacketed condenser and an Ar gas bubbler and a rubber septum fitted with a needle to equalize the Ar pressure was charged with the appropriate carboxylic acid, **13-Z** (10 mmol), and 1,1′-carbonyldiimidazole (Aldrich) (**14**) (12 mmol, 1.94 g) in 50 mL of dry tetrahydrofuran (freshly distilled from calcium hydride in argon atmosphere). The suspension was then heated to reflux for about 1 h to yield the crude imidazolide **15-Z**, which was directly used in the condensation with nitromethane. For the latter reaction, a similarly

(47) Baker, D. C.; Putt, S. R. *Synthesis* **1978**, 478.

equipped round-bottom flask was charged with 20 mL of THF saturated with Ar, *tert*-butyl alcohol (0.89 g, 12 mmol), and clean KH (0.52 g, 13 mmol). Nitromethane (2.84 g, 47 mmol) was added, and the mixture was stirred for 15 min whereupon **15-Z** was added and the mixture was refluxed for 17 h. After the mixture was cooled to room temperature, the suspension was filtered and the crude enolate was washed with dichloromethane (2 × 50 mL). Approximately 100 mL of distilled water was then poured onto the solid which immediately dissolved, and the aqueous solution was adjusted to pH ∼3 by addition of HCl; the product was extracted with ethyl acetate (3 × 100 mL), maintaining the pH ∼3. The organic layers were collected and dried over anhydrous MgSO$_4$, and the solvent was removed under high vacuum to give crude **16-Z**. In the case of **16-CF$_3$**, no solid product was obtained, even on cooling the refluxed solution to −35 °C. To get the solid, the crude solution was dried under high vacuum and the solid thereby obtained was dissolved in 100 mL water which was then filtered over silica gel layer in a sintered glass crucible. All compounds were recrystallized from EtOH/H$_2$O (yields 60–70%). ^{1}H and ^{13}C NMR data are reported in Tables S1 and S2,[27] respectively.

B. Synthesis of 2-Z. The synthesis of **2-Z** was based on procedures reported by Aoyama et al.[48] In a 100 mL round-bottom flask, 5 mmol of **16-Z** was dissolved in 20 mL of acetonitrile–methanol (9:1) and saturated with Ar. A 0.9 g (7 mmol) amount of *N,N*-diisopropylethylamine was added and stirred for 2 min. To this stirred solution, 4.15 mL (7.0 mmol) of trimethylsilyldiazomethane was added dropwise. The reaction mixture was then diluted with 100 mL of dilute HCl, and the products were extracted with ethyl acetate. The organic phases were then collected, washed successively with saturated bicarbonate and sodium chloride solutions, then dried over anhydrous MgSO$_4$, and finally concentrated under high vacuum at room temperature. The crude products were purified by column chromatography using silica gel. The silica gel column was packed by making a slurry of 90% pentane, 5% methylene chloride, and 5% diethyl ether. The elution was carried out by increasing the percentage of ether and methylene chloride (30–40% yield). ^{1}H and ^{13}C NMR data are reported in Tables S3 and S4,[27] respectively.

For **2-NO$_2$**, two isomers were isolated. The tentative stereochemical assignments in Table S3[27] are based on models that predict the vinylic proton of the E isomers to be at lower field than for the Z isomers.[48] The Z:E ratio was approximately 4:1.

Other Materials. DMSO was refluxed over CaH$_2$ and distilled under vacuum. KOH and HCl were prepared from J. T. Baker's "dilute it" analytical concentrates. Water was obtained from a Milli-Q purification system. Piperidine, 1-(2-hydroxyethyl)piperazine, and morpholine were refluxed over Na/CaH$_2$ and freshly distilled. Piperazine was recrystallized twice from water.

Kinetic and pK_a Measurements. The procedures, including pH-meter calibration in 50% DMSO–50% water, were the same as described earlier[8a] except that the stopped-flow measurements were performed in an Applied Photophysics DX.17MV apparatus.

Supporting Information Available: Figures S1–S3 (kinetic and absorbance data) and Tables S1–S4 (NMR data) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

(48) Aoyama, T.; Terasawa, S.; Sudo, K.; Shioiri, T. *Chem. Pharm. Bull.* **1984**, *32*, 3759.
(49) Crews, P.; Rodríguez, J.; Jaspars, M. *Organic Structure Analysis*; Oxford University Press: New York, 1998; p 83.