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Kinetics of the Deprotonation of Methylnitroacetate by Amines: Unusually High Intrinsic Rate Constants for a Nitroalkane

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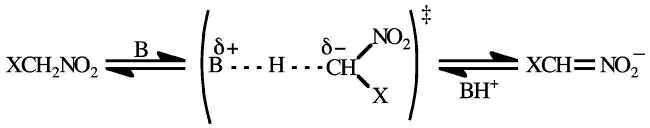
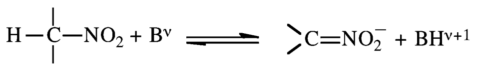


$\Delta G_o^{\ddagger}\ (X = CO_2Me) << \Delta G_o^{\ddagger}\ (X = H)$

A kinetic study of the reversible deprotonation of methylnitroacetate (**4H**) by primary aliphatic amines, secondary alicyclic amines, hydroxide ion, and water in water at 25 °C and in 50% DMSO/50% water (v/v) at 20 °C is reported. Intrinsic rate constants, k_0, determined by extrapolation or interpolation of Brønsted plots have been determined. In comparison to proton transfers involving other nitroalkanes, the intrinsic rate constants for **4H** are exceptionally high; for example, log k_0 for the reaction of **4H** with secondary alicyclic amines in water (1.22) is 1.81 log units higher than log k_0 for nitromethane (−0.59), while in 50% DMSO/50% water, log k_0 for **4H** (2.44) is 1.71 log units higher than that for nitromethane (0.73). A general discussion of the factors affecting intrinsic rate constants of proton transfer from nitroalkanes is presented; it provides the context for an understanding as to why k_0 is so high for the proton transfers from **4H**. The correlation between intrinsic rate constants for the addition of nucleophiles to alkenes of the type R′R″C═CXY and the intrinsic rate constants of proton transfers from carbon acids of the type H_2CXY is also discussed as a general proposition as well as with specific reference to the $Ph(SMe)C{=}C(NO_2)CO_2Me/H_2C(NO_2)CO_2Me$ pair.

Introduction

Proton transfers involving nitroalkanes have generated a great deal of interest over many years.[1−16] A major reason for this interest is that they represent textbook cases of what makes proton transfers from carbon acids activated by π-acceptors very much slower than proton transfers from “normal” acids.[17] In fact, the intrinsic rate constants (k_0)[18] of reactions of the type of eq 1 are typically more than 10 orders of magnitude lower than those for the diffusion-controlled deprotonation of normal acids.



$$H-\overset{|}{\underset{|}{C}}-NO_2 + B^{\nu} \rightleftharpoons \rangle C{=}NO_2^- + BH^{\nu+1} \qquad (1)$$

The main factor responsible for the slowness of reactions such as eq 1 as well as proton transfers from carbon acids with π-acceptors other than nitro groups is the transition state which is imbalanced in the sense that the degree of charge delocal-

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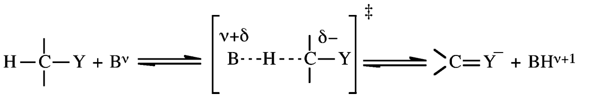
ization into the π-acceptor group lags behind proton transfer.[21] This is shown, in exaggerated form, in eq 2 for a generalized carbon acid with the π-acceptor Y. Because of the imbalance, the transition state cannot take advantage of the resonance stabilization of the carbanion since this stabilization is barely developed at the transition state. As a result, the intrinsic barrier ($\Delta G_0^‡$) of the reaction is very high[22] or the intrinsic rate constant (k_0) is very low. In hydroxylic solvents, the lag in the solvation of the negative charge adds to the overall imbalance and contributes substantially to the enhanced intrinsic barrier.[21]

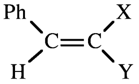


(2)

The deprotonation of nitroalkanes is characterized by stronger imbalances than the deprotonation of any other carbon acids, and hence, these reactions have the highest intrinsic barriers or lowest intrinsic rate constants.

Apart from solvent effects, there are significant variations in the intrinsic rate constants of eq 1 which depend on what other groups are attached to the central carbon. For example, in water with secondary alicyclic amines as the proton acceptors, log k_0 values of −1.22 ($PhCH_2NO_2$),[8a] −0.59 (CH_3NO_2),[8a] 1.02 ($PhSCH_2NO_2$),[8h] and 1.57 ($PhCOCH_2NO_2$)[8g] have been reported. A broad understanding of these variations should contribute new insights into the factors that affect intrinsic barriers of proton transfers and of other reactions, as well.

In this paper, we report a kinetic study of the deprotonation of methylnitroacetate by a series of primary aliphatic and secondary alicyclic amines as well as by OH^- and water. The motivation for this study was twofold. The first one is to further explore the effect of substituents attached to the central carbon of nitroalkanes on the intrinsic barriers of proton transfers. The second is related to previous observations according to which the equilibrium constants and intrinsic rate constants of nucleophilic additions to activated alkenes of the types **1**−**3** often correlate with the pK_a values and intrinsic rate constants, respectively, for the deprotonation of the corresponding carbon acids H_2CXY.[21b,23,24]



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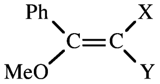

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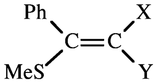
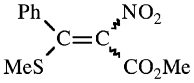


3

Methylnitroacetate (**4H**) is the carbon acid that corresponds to **5**, whose reactions with thiolate ion and amine nucleophiles have recently been investigated. Our study was performed in water at 25 °C and in 50% DMSO/50% water at 20 °C; the latter is the same solvent used for the reactions of **5** and other alkenes with nucleophiles.[23,24]

$MeO_2CCH_2NO_2$

4H



5

Results

General Features. All rate and pK_a determinations were carried out at an ionic strength of 0.5 M maintained with KCl. The rates were measured under pseudo-first-order conditions with **4H** as the minor component. The reactions were monitored spectrophotometrically at 295 nm (water) or at 304 nm (50% DMSO/50% water), which corresponds to λ_{max} of the methylnitroacetate ion in the respective solvents.

Acidity Constant. The pK_a^{CH} of **4H** in water was determined by classic spectrophotometric methodology applying eq 3 where A is the absorbance at pH ∼ pK_a^{CH}

$$\mathrm{pH} = \mathrm{p}K_a^{CH} + \log \frac{A - A_{C^-}}{A_{CH} - A} \qquad (3)$$

measured in aminoacetonitrile buffers, A_{C^-} is the absorbance of the anion measured in KOH solution, and A_{CH} is the absorbance of the carbon acid measured in HCl solution. A plot of $\log(A - A_{C^-})/(A_{CH} - A)$ versus pH is shown in Figure S1 of the Supporting Information;[25] it yields p$K_a^{CH} = 5.58 \pm 0.02$. As discussed below, this pK_a^{CH} value was confirmed kinetically. The pK_a^{CH} of **4H** in 50% DMSO/50% water (5.95 ± 0.05) has been determined before.[26]

Kinetics. A complete reaction scheme which includes the fast equilibrium between the nitronate ion (**4**$^-$) and the nitronic acid (**H4**) is shown in eq 4; K_a^{NOH} is the acidity constant of the nitronic acid, while B and BH^+ refer to the amine and protonated amine, respectively. The observed pseudo-first-order rate constant for

$$\underset{\mathbf{4H}}{MeO_2CCH_2NO_2} \xrightleftharpoons[k_{-1}^{H}a_{H^+} + k_{-1}^{H_2O} + k_{-1}^{BH}[BH^+]]{k_1^{H_2O} + k_1^{OH}[OH^-] + k_1^{B}[B]}$$
$$\underset{\mathbf{4}^-}{MeO_2CCH{=}NO_2^-} \xrightleftharpoons[K_a^{NOH}]{H^+} \underset{\mathbf{H4}}{MeO_2CCH{=}NO_2H} \qquad (4)$$

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[18] The intrinsic barrier, $\Delta G_0^‡$ (intrinsic rate constant, k_0), of a reaction with a forward rate constant k_1 and a reverse rate constant k_{-1} is defined as $\Delta G_0^‡ = \Delta G_1^‡ = \Delta G_{-1}^‡$ ($k_0 = k_1 = k_{-1}$) when $\Delta G° = 0$ ($K_1 = 1$).[19,20] For proton transfers, statistical factors are usually included.[20]

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[22] For the reaction in the reverse direction, it is the early loss of anionic resonance stabilization that is the cause of the high intrinsic barrier.

eq 4 is given by eq 5; the $K_a^{NOH}/(K_a^{NOH} + a_{H^+})$ term only becomes important in highly acidic solutions.

$$k_{obsd} = k_1^{H_2O} + k_1^{OH}[OH^-] + k_1^B[B] + (k_{-1}^H a_{H^+} + k_{-1}^{H_2O} + k_{-1}^{BH}[BH^+]) \frac{K_a^{NOH}}{K_a^{NOH} + a_{H^+}} \quad (5)$$

A. Reactions of 4H with Amines. The reaction with the following amines were examined: piperidine, piperazine, *N*-(2-hydroxyethyl)piperazine, morpholine, *n*-butylamine, 2-methoxyethylamine, glycinamide, and aminoacetonitrile. The rates were measured in 1:1 buffers, that is, at a pH that corresponds to the pK_a^{BH} of the protonated amines. For all amines except for aminoacetonitrile, the relationship $pK_a^{BH} \gg pK_a^{CH}$ holds, and hence eq 5 reduces to eq 6.

$$k_{obsd} = k_1^{H_2O} + k_1^{OH}[OH^-] + k_1^B[B] \quad (6)$$

Figure S2[25] shows some representative plots of k_{obsd} versus amine concentration which yield k_1^B values from the slopes; k_{-1}^{BH} can be calculated as $k_{-1}^{BH} = k_1^B K_a^{BH}/K_a^{CH}$. The intercepts are too small to provide meaningful data on $k_1^{H_2O}$ and/or k_1^{OH}.

For aminoacetonitrile ($pK_a^{BH} = 5.61$ in water and $pK_a^{BH} = 5.39$ in 50% DMSO/50% water), the relationship $pK_a^{BH} \leq pK_a^{CH}$ holds, and hence eq 5 takes on the form of eq 7:

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

in this pH range, $k_1^{OH}[OH^-]$ and $k_{-1}^{H_2O}$ are negligible and K_a^{NOH} still greatly exceeds a_{H^+}. The slopes of plots of k_{obsd} versus [B] are given by eq 8.

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

For the reactions in water, such slopes were determined at eight different pH values ranging from pH 4.40 to 6.30. By plotting these slopes versus a_{H^+} (Figure S3[25]), $k_1^B = 21.7 \pm 1.2$ M^{-1} s^{-1} and $pK_a^{CH} = 5.54 \pm 0.03$ were obtained; the pK_a^{CH} value is in excellent agreement with the spectrophotometric value of 5.58, and the average, 5.56, will be adopted as the actual pK_a^{CH}. In 50% DMSO/50% water, the slope according to eq 8 was determined only at one pH (5.39); in this case, k_1^B was obtained using the known pK_a^{CH}.

B. Reaction of 4H with OH⁻. In water, the rate of deprotonation of **4H** by OH^- was measured in KOH solutions, ranging in concentrations from 2.5×10^{-4} to 3.66×10^{-3} M. Under these conditions, eq 5 reduces to $k_{obsd} = k_1^{OH}[OH^-]$. In 50% DMSO/50% water, the deprotonation was too fast for measurements in KOH solutions. However, k_1^{OH} could be obtained by determining the intercepts of plots of k_{obsd} versus *n*-butylamine concentration obtained at various buffer ratios in the pH range from pH 10.61 to 12.12. These intercepts correspond to $k_1^{H_2O} + k_1^{OH}[OH^-]$. A plot of these intercepts versus $[OH^-]$ is shown in Figure S4.[25] It yields $k_1^{OH} = (4.39 \pm 0.28) \times 10^5$ M^{-1} s^{-1}; in principle, the intercept corresponds to $k_1^{H_2O}$, but its experimental uncertainty is much too large to provide a reliable $k_1^{H_2O}$ value. A more reliable $k_1^{H_2O}$ was obtained based on experiments in HCl solutions described below.

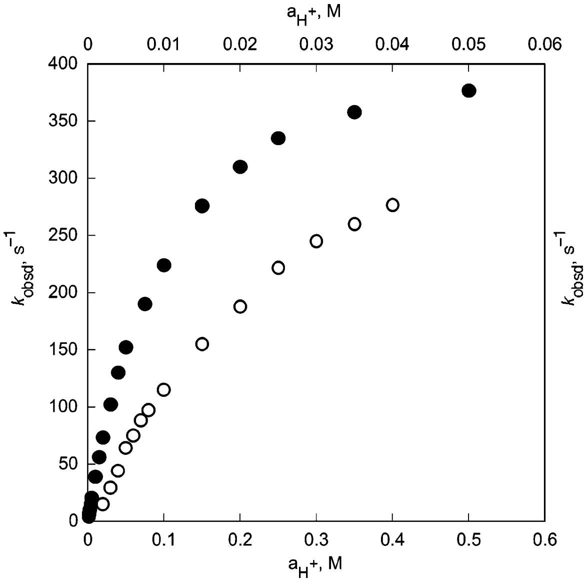

FIGURE 1. Reaction of 4^- with H_3O^+. Plots of k_{obsd} versus a_{H^+} according to eq 9. ●, Reaction in water (bottom *x*-axis); ○, reaction in 50% DMSO/50% water (top *x*-axis).

TABLE 1. Rate Constants for Proton Transfer in Water at 25 °C and in 50% DMSO/50% Water (v/v) at 20 °C, $\mu = 0.5$ M (KCl)

base	pK_a^{BH}	k_1^B (M^{-1} s^{-1})[b]	k_{-1}^{BH} (M^{-1} s^{-1})[c]
water (25 °C), $pK_a^{CH} = 5.56 \pm 0.02$			
piperidine	11.39	1.53×10^5	2.16×10^{-1}
piperazine	10.15	2.71×10^4	6.65×10^{-1}
HEPA[a]	9.43	9.71×10^3	1.25×10^0
morpholine	8.97	3.98×10^3	1.48×10^0
n-$BuNH_2$	10.78	5.87×10^4	3.38×10^{-1}
$MeOCH_2CH_2NH_2$	9.60	4.60×10^3	4.01×10^{-1}
$H_2NCOCH_2NH_2$	8.23	5.68×10^2	1.16×10^0
$NCCH_2NH_2$	5.61	2.81×10^1	2.40×10^1
OH^-	15.10[d]	2.65×10^5 [e]	2.26×10^{-3} [f]
H_2O	1.74	1.22×10^{-2} [g]	4.46×10^3 [h]
50% DMSO/50% H_2O (20 °C), $pK_a^{CH} = 5.95 \pm 0.05$			
piperidine	11.02	7.00×10^4	5.96×10^{-1}
piperazine	9.90	3.10×10^4	3.40×10^0
HEPA[a]	9.51	1.93×10^4	5.32×10^0
morpholine	8.72	6.06×10^4	1.03×10^1
n-$BuNH_2$	10.61	1.90×10^4	4.16×10^{-1}
$MeOCH_2CH_2NH_2$	9.63	5.16×10^3	1.08×10^0
$H_2NCOCH_2NH_2$	8.28	9.12×10^2	4.27×10^0
$NCCH_2NH_2$	5.39	2.63×10^1	9.54×10^1
OH^-	17.33[i]	4.39×10^5 [j]	5.04×10^{-5} [k]
H_2O	−1.44	1.63×10^{-2} [l]	1.45×10^4 [m]

[a] *N*-(2-Hydroxyethyl)piperazine. [b] Error limits better than 6%. [c] Error limits better than 15%. [d] $pK_w = 15.89$ (ref 35). [e] $k_1^{OH} = (2.65 \pm 0.10) \times 10^5$ M^{-1} s^{-1}. [f] $k_{-1}^{H_2O} = (2.26 \pm 0.12) \times 10^{-3}$ s^{-1}. [g] $k_1^{H_2O} = (1.22 \pm 0.04) \times 10^{-2}$ s^{-1}. [h] $k_{-1}^H = (4.46 \pm 0.11) \times 10^3$ M^{-1} s^{-1}. [i] $pK_w = 13.63$ (Brandariz, I.; Fiol, S.; Sastre Vicente, M. *Ber. Bunsen-Ges Phys. Chem.* **1995**, *99*, 749). [j] $k_1^{OH} = (4.39 \pm 0.28) \times 10^5$ M^{-1} s^{-1}. [k] $k_{-1}^{H_2O} = (5.04 \pm 0.60) \times 10^{-5}$ s^{-1}. [l] $k_1^{H_2O} = (1.63 \pm 0.28) \times 10^{-2}$ s^{-1}. [m] $k_{-1}^H = (1.45 \pm 0.15) \times 10^4$ M^{-1} s^{-1}.

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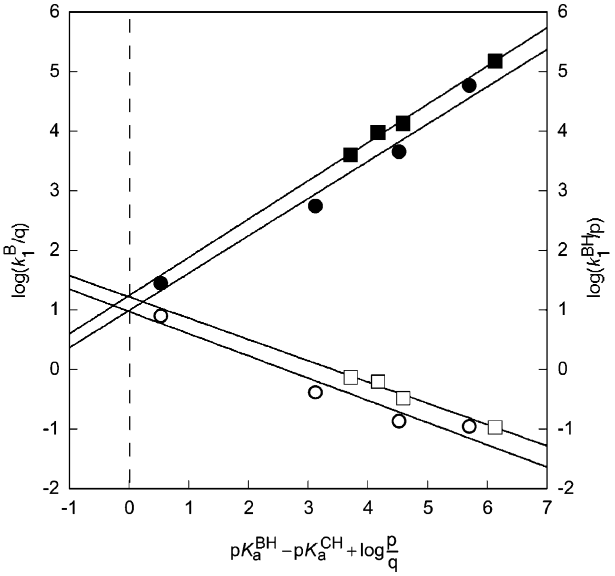

FIGURE 2. Statistically corrected Brønsted plots for the reaction of **4H** with amines in water. Filled symbols, k_1^B; open symbols, k_{-1}^{BH}. ● and ○, primary aliphatic amines; ■ and □, secondary alicyclic amines. The dashed line goes through the points where $\log(k_1^B/q)$ and $\log(k_{-1}^{BH}/p)$ lines intersect, which corresponds to log k_0.

C. Reaction of 4^- with H_3O^+. Rates of protonation of 4^- by the hydronium ion were measured in HCl solutions after converting **4H** into its anion in a dilute KOH solution. Plots of k_{obsd} versus a_{H^+} for the reaction in water are shown in Figure 1. They are given by eq 9.

$$k_{obsd} = \frac{k_{-1}^{H} K_a^{NOH} a_{H^+}}{K_a^{NOH} + a_{H^+}} \tag{9}$$

A nonlinear least-squares fit of the data to eq 9 provided $K_a^{NOH} = (1.05 \pm 0.05) \times 10^{-1}$ M^{-1} ($pK_a^{NOH} = 0.98 \pm 0.02$) and $k_{-1}^{H} = (4.46 \pm 0.11) \times 10^{3}$ M^{-1} s^{-1} in water, and $K_a^{NOH} = (3.72 \pm 0.39) \times 10^{-2}$ M^{-1} ($pK_a^{NOH} = 1.43 \pm 0.04$) and $k_{-1}^{H} = (1.45 \pm 0.15) \times 10^{4}$ M^{-1} s^{-1} in 50% DMSO/50% water.

Discussion

All rate constants determined in this study are reported in Table 1. Figures 2 and 3 show Brønsted plots for the reactions of **4H** with the primary aliphatic and secondary alicyclic amines. The Brønsted coefficients and log k_0 values for the intrinsic rate constants are summarized in Table 2. The α and β values are in the range normally observed in proton transfers involving nitroalkanes and thus require no further comment. The fact that log k_0 for the primary amines is about 1 log unit lower than that for the secondary amines is also typical[27] and indicates that steric crowding at the transition state is not important.[29]

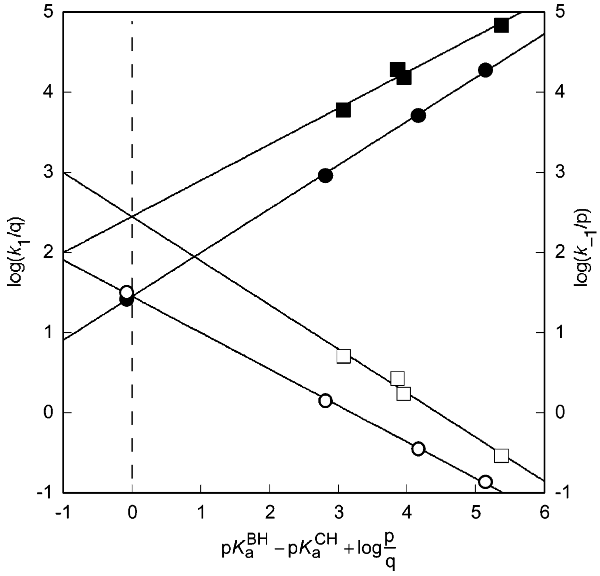

FIGURE 3. Statistically corrected Brønsted plots for the reaction of **4H** with amines in 50% DMSO/50% water. Filled symbols, k_1^B; open symbols, k_{-1}^{BH}. ● and ○, primary aliphatic amines; ■ and □, secondary alicyclic amines. The dashed line goes through the points where $\log(k_1^B/q)$ and $\log(k_{-1}^{BH}/p)$ lines intersect, which corresponds to log k_0.

TABLE 2. Brønsted Coefficients and Log k_0 Values for the Reactions of 4H with Primary Aliphatic and Secondary Alicyclic Amines

	β	α	log k_0[a]
	water (25 °C)		
primary amines	0.63 ± 0.07	0.37 ± 0.07	0.97 ± 0.26
secondary amines	0.64 ± 0.04	0.34 ± 0.04	1.22 ± 0.17
	50% DMSO/50% H_2O		
primary amines	0.55 ± 0.01	0.45 ± 0.01	1.45 ± 0.02
secondary amines	0.45 ± 0.05	0.55 ± 0.05	2.44 ± 0.06

[a] Log $k_0 = \log(k_1^B/q) = \log(k_{-1}^{BH}/p)$ for $pK_a^{BH} - pK_a^{CH} + \log(p/q) = 0$; q and p are statistical factors; see ref 20.

The focus of our discussion will be on how the intrinsic rate constants for **4H** compare with the log k_0 values for the other nitroalkanes. Table 3 lists such log k_0 values for the deprotonation of a variety of nitroalkanes by amines and carboxylate ions in water and 50% DMSO/50% water (v/v). The nitroalkanes are arranged in an order of increasing acidity spanning a pK_a^{CH} range of 5.61 units in water and 6.45 units in 50% DMSO/50% water.

It is noteworthy that **4H** stands out by having the highest log $k_0(R_2NH)$ and log $k_0(RNH_2)$ values of any of the nitroalkanes in 50% DMSO/50% water and the second highest log $k_0(R_2NH)$ in water. Since its pK_a^{CH} is quite low, this suggests some correlation between intrinsic rate constants and acidity. However, as Figures 4 and 5 show, the correlation between log k_0 and pK_a^{CH} is rather poor. This is because the various factors that typically affect acidities, such as resonance, inductive, steric, polarizability, solvation effects, and hyperconjugation, exert either enhanced, diminished, or even opposite effects on intrinsic rate constants. The underlying reason for this state of affairs is

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(27) The lower intrinsic reactivity of primary amines is the result of the stronger solvation of their protonated form compared to that of the protonated secondary amines, coupled with the fact that at the transition state solvation of the incipient ammonium ions lags behind proton transfer.[21,28]

(28) (a) Bell, R. P. *The Proton in Chemistry*, 2nd ed.; Cornell University: Ithaca, NY, 1973; Chapter 10. (b) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1968; p 178.

(29) When there is substantial steric crowding, the difference between log $k_0(R_2NH)$ and log $k_0(RNH_2)$ becomes smaller.[9c,30]

(30) (a) Bernasconi, C. F.; Bunnell, R. D.; Terrier, F. *J. Am. Chem. Soc.* **1988**, *110*, 6514. (b) Bernasconi, C. F.; Fairchild, D. E. *J. Phys. Org. Chem.* **1992**, *5*, 409. (c) Bernasconi, C. F.; Sun, W. *J. Am. Chem. Soc.* **1993**, *115*, 12526.

TABLE 3. Intrinsic Rate Constants for Proton Transfers Involving Nitroalkanes[a]

		water (25 °C)				50% DMSO/50% H_2O (20 °C)			
	nitroalkane	pK_a^{CH}	log $k_0(R_2NH)$	log $k_0(RNH_2)$	log $k_0(RCO_2^-)$	pK_a^{CH}	log $k_0(R_2NH)$	log $k_0(RNH_2)$	log $k_0(RCO_2^-)$
1	CH_3NO_2[b]	10.28	−0.59			11.32	0.73		
2	$HOCH_2CH_2NO_2$[c]	9.40	−0.59	−1.30	−0.90				
3	$(HOCH_2)_2CHNO_2$[c]	9.07	−1.14	−1.84	−1.09				
4	$PhCH_2CH_2NO_2$[d]	8.55	−1.16	−2.06					
5	$PhCH_2NO_2$[b]	6.77	−1.22		−2.10	7.93	−0.25		−0.57
6	$PhSCH_2NO_2$[d]	6.67	1.02	−0.13					
7	*$MeO_2CCH_2NO_2$* (**4H**)[e]	*5.56*	*1.22*	*0.97*		*5.95*	*2.44*	*1.45*	
8	$CH_3CH(NO_2)_2$[f]	5.24			1.00	5.13			1.70
9	$PhCOCH_2NO_2$[g]	4.67	1.57			4.87	1.87		

[a] R_2NH refers to secondary alicyclic amines, RNH_2 to primary aliphatic amines. [b] From ref 8a. [c] From ref 8f. [d] From ref 8h. [e] This work. [f] Bernasconi, C. F.; Kanavarioti, A. *J. Org. Chem.* **1979**, *44*, 4829. [g] From ref 8g.

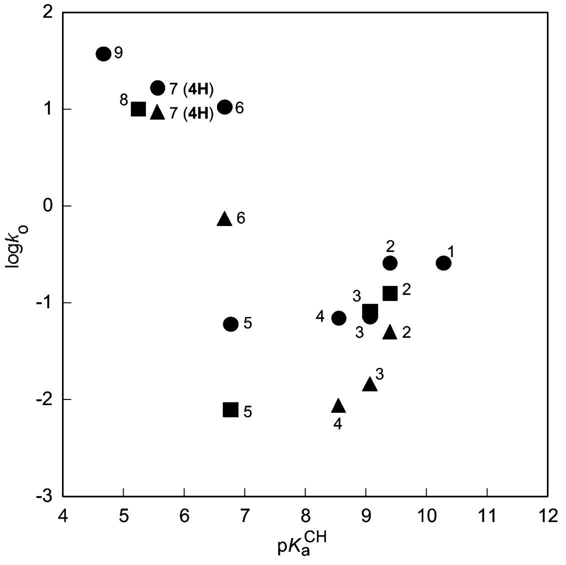


FIGURE 4. Correlation of intrinsic rate constants for the deprotonation of nitroalkanes with their pK_a^{CH} values in water. ●, Secondary alicyclic amines (R_2NH); ▲, primary aliphatic amines (RNH_2); ■, carboxylate ions (RCO_2^-). The numbering of the compounds corresponds to that in Table 3.

the imbalanced nature of the transition state of these reactions (eq 2). We now present a brief general description of the factors that affect the intrinsic rate constants; for more details, see ref 21. This will be followed by a discussion of which of these factors play a major role in determining the intrinsic rate constants of each individual nitroalkane.

Resonance Effects. π-Acceptor substituents that contribute to the stabilization of the nitronate ion by a resonance effect lower the intrinsic rate constant because they add their own imbalance at the transition state.

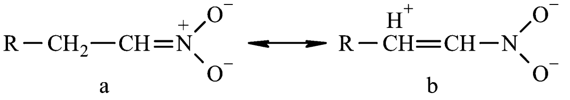
Inductive Effects. Electron-withdrawing (EW) substituents increase the intrinsic rate constant. This is the result of a disproportionately strong stabilization of the transition state relative to that of the anion because the developing negative charge is closer to the substituent at the transition state than in the nitronate ion. Electron-donating (ED) substituents have the opposite effect.

Steric Effects. Steric crowding at the transition state lowers the intrinsic rate constant since there is no corresponding effect on either reactant or product. However, internal steric crowding that prevents the nitro group from achieving coplanarity in the anion enhances the intrinsic rate constant by reducing the resonance effect.

Polarizability Effects. Polarizable substituents increase the intrinsic rate constant in a similar way as inductively stabilizing substituents. Their effect may be potentially greater because the polarizability drops off with the fourth power of distance while inductive effects drop off with the square of distance,[31] although the degree of transition state imbalance may play a role, as well.[8h,21]

Solvation Effects. Solvents that help stabilize the nitronate ion lower the intrinsic rate constant. This effect is particularly strong for hydrogen bonding solvation of the anionic nitro group in hydroxylic solvents. Substituents that help stabilize the nitronate ion reduce the demand for solvation which results in an increase in the intrinsic constant.

Hyperconjugation. The nitronate ions derived from nitroalkanes of the type $RCH_2CH_2NO_2$ receive substantial stabilization from hyperconjugation (structure b in eq 10).[3]



(10)

Since hyperconjugation is akin to a resonance effect, its development at the transition state lags behind proton transfer and depresses the intrinsic rate constant.

The effects of the various factors described above are schematically summarized in Table 4. On the basis of the foregoing discussion, we can now analyze how the intrinsic rate constants for each individual nitroalkane are affected by these factors. This will provide the context for an understanding of why the intrinsic rate constants for the deprotonation of **4H** are so high. We shall use nitromethane as our reference nitroalkane for this purpose.

CH_3NO_2. Changing the solvent from water to 50% DMSO/50% water enhances log $k_0(R_2NH)$ by 1.32 log units. The true solvent effect is actually somewhat larger because of the lower temperature (20 °C) in 50% DMSO/50% water compared to 25 °C in water. The increase in the intrinsic rate constant mainly reflects the reduced solvation of the nitronate ion in the less aqueous solvent. Similar increases are seen in all cases where such comparisons are available ($PhCH_2NO_2$, $\Delta\log k_0(R_2NH) = 0.97$, $\Delta\log k_0(RCO_2^-) = 1.53$; $MeO_2CCH_2NO_2$, $\Delta\log k_0(R_2NH) = 1.22$, $\Delta\log k_0(RNH_2) = 0.48$; $CH_3CH(NO_2)_2$, $\Delta\log k_0(RCO_2^-) = 0.70$; $PhCOCH_2NO_2$, $\Delta\log k_0(R_2NH) = 0.30$).

$HOCH_2CH_2NO_2$. The log $k_0(R_2NH)$ value is the same as that for nitromethane. The $HOCH_2$ group is inductively electron

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(31) (a) Taft, R. W. *Prog. Phys. Org. Chem.* **1983**, *14*, 247. (b) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1.

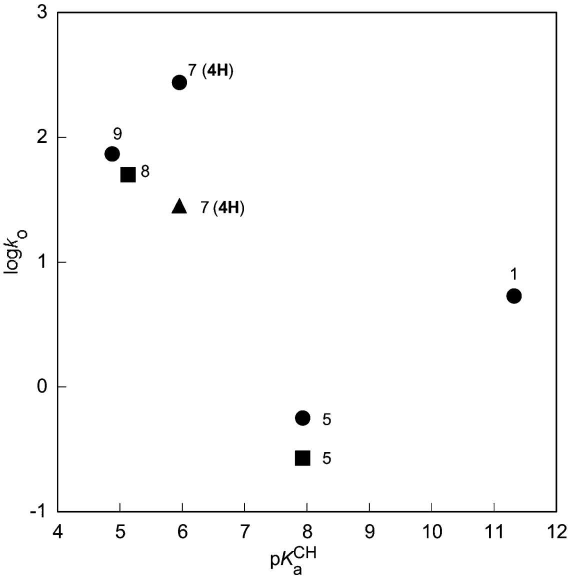

FIGURE 5. Correlation of intrinsic rate constants for the deprotonation of nitroalkanes with their pK_a^{CH} values in 50% DMSO/50% water. ●, Secondary alicyclic amines (R_2NH); ▲, primary aliphatic amines (RNH_2); ■, carboxylate ions (RCO_2^-). The numbering of the compounds corresponds to that in Table 3.

TABLE 4. Summary of Factors that Affect Intrinsic Rate Constants

factor	effect on k_0	factor	effect on k_0
EW inductive	↑	ED inductive	↓
π-acceptor	↓	polarizability	↑
enhanced solvation	↓	reduced solvation	↑
steric crowding at TS	↓	hyperconjugation	↓
internal steric crowding	↑		

withdrawing as manifested in the lower pK_a^{CH}. However, this inductive effect is too small to account for the entire 0.9 pK_a unit difference between this compound and CH_3NO_2; as discussed elsewhere,[8f,h] hyperconjugative stabilization of the nitronate ion contributes to the acidifying effect. It appears then that the intrinsic rate enhancing inductive effect is essentially offset by the intrinsic rate reducing hyperconjugation; there is also a small contribution to the reduction due to a less favorable statistical factor (i.e., 2 protons in $HOCH_2CH_2NO_2$ versus 3 protons in CH_3NO_2).

$(HOCH_2)CHNO_2$. The log $k_0(R_2NH)$ value is 0.55 log units lower than that for CH_3NO_2 or $HOCH_2CH_2NO_2$, and log $k_0(RNH_2)$ is 0.54 log units lower than that for $HOCH_2CH_2NO_2$. In this case, besides the inductive and hyperconjugative factors, a steric effect comes into play; in combination with a still less favorable statistical factor, this tips the balance between the various effects toward a reduction in the intrinsic rate constants.

$PhCH_2CH_2NO_2$. The log $k_0(R_2NH)$ value is 0.57 log units lower than that for CH_3NO_2 or $HOCH_2CH_2NO_2$, and the log $k_0(RNH_2)$ is 0.76 log units lower than that for $HOCH_2CH_2NO_2$. As discussed in detail elsewhere,[8h] strong hyperconjugative stabilization of the nitronate ion appears to be the main factor here. This stabilization accounts for the pK_a^{CH} (8.55) which is lower than that of the $HOCH_2CH_2NO_2$ (9.40),[32] and it explains the reduced intrinsic rate constants.

TABLE 5. pK_a^{NOH} and pK_N Values of Nitroalkanes

	water (25 °C)			50% DMSO/50% H_2O (20 °C)		
nitroalkane	pK_a^{NOH}	pK_a^{CH}	$pK_N{}^a$	pK_a^{NOH}	pK_a^{CH}	$pK_N{}^a$
$CH_3NO_2{}^b$	3.25^c	10.28	7.03			
$HOCH_2CH_2NO_2{}^d$	3.44	8.40	5.96			
$(HOCH_2)CHNO_2{}^d$	3.60	9.07	5.47			
$PhCH_2NO_2{}^b$	3.64	6.79	3.13	4.75	7.93	3.18
$MeO_2CCH_2NO_2$ **(4H)**^{e}	0.98	5.56	4.58	1.43	5.95	4.52

^{a} $pK_N = pK_a^{CH} - pK_a^{NOH}$. ^{b} From ref 8a. ^{c} From ref 34. ^{d} From ref 8f. ^{e} This work.

$PhCH_2NO_2$. The log $k_0(R_2NH)$ value is 0.63 log units lower than log $k_0(R_2NH)$ for CH_3NO_2 in water, while in 50% DMSO/50% water, the difference is 0.98 log units. The main factor in this case is the additional resonance stabilization of the nitronate ion by the phenyl group which greatly increases the acidity ($pK_a^{CH} = 6.77$) and lowers the intrinsic rate constant. The electron-withdrawing inductive effect of the phenyl group adds to the acidity enhancing effect but is insufficient to offset the resonance effect on k_0. Steric hindrance in these reactions with secondary amines may possibly contribute somewhat to the lowering of the intrinsic rate constants.

$PhSCH_2NO_2$. The log $k_0(R_2NH)$ value is 1.61 log units higher than log $k_0(R_2NH)$ for CH_3NO_2, and log $k_0(RNH_2)$ is 1.17 log units higher than log $k_0(RNH_2)$ for $HOCH_2CH_2NO_2$. The low pK_a^{CH} (6.67) reflects the strong stabilization by the PhS group which is the combined result of its electron-withdrawing inductive effect and the high polarizability of the sulfur atom. Both of these effects contribute to the enhanced intrinsic rate constants, with the polarizability factor probably being dominant.

$CH_3CH(NO_2)_2$. The intrinsic rate constants are quite high as can be seen by comparing log $k_0(RCO_2^-)$ in water (1.00) with log $k_0(RCO_2^-)$ for $HOCH_2CH_2NO_2$ (−1.30), or log $k_0(RCO_2^-)$ in 50% DMSO/50% water (1.70) with log $k_0(RCO_2^-)$ for $PhCH_2NO_2$ (−0.57). The main factor here is that steric crowding prevents coplanarity of the two nitro groups in the anion; that is, the resonance effect is reduced and the strong nitronate ion stabilization is largely the result of the inductive effect. Both factors lead to an increase in the intrinsic rate constant. There is probably less hydrogen bonding solvation due to the smaller charge on the nitro group which contributes to the increased k_0 values.

$PhCOCH_2NO_2$. Both the NO_2 and PhCO groups are π-acceptors, but steric hindrance prevents the full development of their resonance effects while their inductive effects gain in relative importance. The result is that log $k_0(R_2NH)$ in water is 2.16 log units greater than log $k_0(R_2NH)$ for CH_3NO_2, while in 50% DMSO/50% water, this difference is 1.14 log units. That reduced solvation also plays a significant role in enhancing the intrinsic rate constants is seen in the larger difference between the log $k_0(R_2NH)$ of $PhCOCH_2NO_2$ and CH_3NO_2 in water than in 50% DMSO/50% water or the rather small solvent effect on log $k_0(R_2NH)$ for $PhCOCH_2NO_2$ when changing from water (1.57) to 50% DMSO/50% water (1.87). Additional support for this conclusion comes from measurements of solvent transfer activity coefficients of the respective nitronate ions.[8g]

$MeO_2CCH_2NO_2$ (4H). This is the nitroalkane with the highest intrinsic rate constants in 50% DMSO/50% water and the second highest in water. Relative to CH_3NO_2, log

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[32] The hyperconjugative stabilization provided by the $PhCH_2$ group is significantly stronger than that provided by the $HOCH_2$ group.[8h]

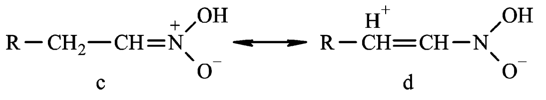
$k_0(R_2NH)$ for **4H** is 1.81 log units higher in water and 1.71 log units higher in 50% DMSO/50% water. The reasons for the high intrinsic rate constants are similar to those for $PhCOCH_2NO_2$. The fact that the CO_2Me group is a weaker π-acceptor[33] than the PhCO group is reflected in the higher pK_a^{CH} values (5.54 and 5.95) compared to those for $PhCOCH_2NO_2$ (4.67 and 4.87). This reduced resonance effect results in a log $k_0(R_2NH)$ value in 50% DMSO/50% water (2.44) that is even higher than that for $PhCOCH_2NO_2$ (1.87), although in water, log $k_0(R_2NH)$ for $PhCOCH_2NO_2$ (1.57) is slightly higher than that for **4H** (1.22).

Acidity of the Nitronic Acid (H4). Table 5 provides a summary of pK_a^{NOH} values for **4H** and those nitroalkanes listed in Table 3 for which these values are known. The table also includes pK_N values defined as $pK_a^{CH} - pK_a^{NOH}$, which is a measure of [nitronic acid]/[nitroalkane] equilibrium ratios, that is, K_N = [nitronic acid]/[nitroalkane].

There are two features that are noteworthy. (1) For the first four nitroalkanes, the pK_a^{NOH} values are essentially the same, while the pK_a^{CH} values decrease. As a result, the pK_N values follow the pattern of the pK_a^{CH} values, which implies an increase in the [nitronic acid]/[nitroalkane] ratio with increasing acidity of the nitroalkane. (2) The pK_a^{NOH} of **4H** is substantially lower than the pK_a^{NOH} values of the other nitroalkanes. Hence, despite the fact that **4H** has the lowest pK_a^{CH} value, pK_N is not as low as it would be if it followed the pattern of the other nitroalkanes.

Since the loss of a proton from the nitroalkane or from the nitronic acid yields the same anion, an explanation of the observed patterns cannot rely on factors that were invoked to explain the stabilization or destabilization of the anion but needs to focus on stabilizing/destabilizing features of the nitroalkane itself or, probably more importantly, of the nitronic acid.

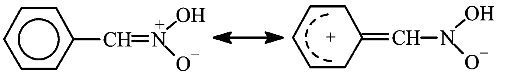
Assuming that most of the stabilization/destabilization occurs in the nitronic acid, the constant pK_a^{CH} values for the first four entries in Table 5 imply that the nitronic acids derived from $HOCH_2CH_2NO_2$, $(HOCH_2)_2CHNO_2$, and $PhCH_2NO_2$ enjoy a similar degree of stabilization relative to $CH_2{=}NO_2H$ as the respective anions do relative to $CH_2{=}NO_2^-$. For $HOCH_2CH_2NO_2$ and $(HOCH_2)_2CHNO_2$, the most important factor appears to be hyperconjugation (structure d in eq 11), which is analogous to structure b in eq 10.



$$R-CH_2-CH{=}\overset{+}{N}(OH)O^- \longleftrightarrow R-\overset{H^+}{CH}{=}CH-N(OH)O^- \quad (11)$$

In fact, a case can be made that hyperconjugation is more effective for the nitronic acids than for the nitronate ions because structure d (eq 11) does not suffer from the destabilizing effect of two negative charges in close proximity as is the case for structure b (eq 10).

For $PhCH_2NO_2$, the strong stabilization of the nitronic acid is the result of a resonance effect (eq 12), as discussed previously.[8a]



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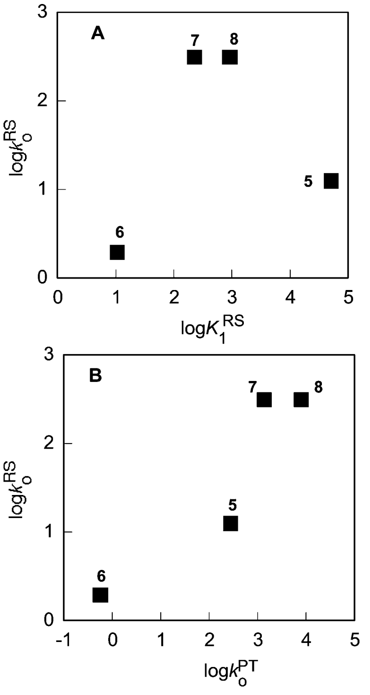
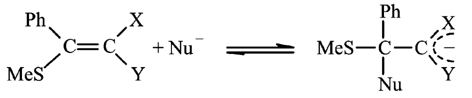


FIGURE 6. Correlation of the intrinsic rate constants for thiolate ion addition to **5**−**8** with the equilibrium constants of thiolate addition (A) and with the intrinsic rate constants for deprotonation of the corresponding carbon acids (B).

In contrast to the other nitronic acids, for the nitronic acid of **4H** (i.e., **H4**), there is no possibility for hyperconjugation or resonance, and this appears to be the main reason why its pK_a^{NOH} is so much lower than that for the other nitronic acids.

Correlation between Nucleophilic Addition to Alkenes and Proton Transfer. The reaction of nucleophiles with alkenes of the types **1**−**3** leads to adducts whose structures resemble carbanions generated by deprotonation of carbon acids of the type H_2CXY. An example is shown in eq 13.



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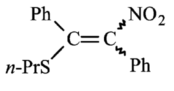

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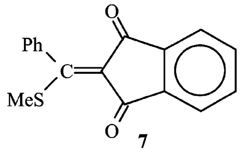

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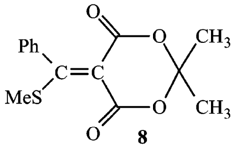

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A logarithmic plot of the intrinsic rate constants for thiolate ion addition to **5**−**8** versus the corresponding equilibrium constants is shown in Figure 6A. The correlation is very poor just as is the case for the proton transfers (Figures 4 and 5). The reasons for the scatter diagram of Figure 6A are essentially the same as for the proton transfers; that is, the factors that determine the equilibrium constants affect the intrinsic rate constants in a different way. However, as Figure 6B shows,

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[33] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

there is a reasonably good correlation between the intrinsic rate constants for nucleophilic addition and those for the deprotonation of the corresponding carbon acids, such as phenylnitromethane, methylnitroacetate, 1,3-indandione, and Meldrum's acid. This means that the intrinsic rate constants in both reaction series are affected by the same factors in a similar way.

Conclusions

Intrinsic rate constants of proton transfers involving nitroalkanes are lower than those for any other class of carbon acids. However, there are large variations in these intrinsic rate constants among the nitroalkanes which are due to the influence exerted by substituents attached to the central carbon. In general, resonance, hyperconjugative, and steric effects exerted by these substituents lower the intrinsic rate constants. On the other hand, inductive and polarizability effects enhance k_0 and so does internal steric crowding because it reduces the resonance effect of the nitro group. Another factor that increases k_0 is reduced hydrogen bonding solvation that arises either from a change to a less hydroxylic solvent or from enhanced internal stabilization of the nitronate ion which lessens the demand for solvation.

The pK_a^{NOH} values of the nitronic acid **H4** are unusually low and do not follow the pattern observed for the other nitronic acids because **H4** does not derive any stabilization from hyperconjugation or resonance effect.

Experimental Section

Materials. Methylnitroacetate was purchased from Aldrich; its purity was shown to be >99% by ^{1}H NMR. Amines were obtained from Aldrich and Acros as analytical grade and purified as follows. Piperidine, morpholine, *n*-butylamine, methoxyethylamine, and 1-(2-hydroxyethyl)piperazine were refluxed over CaH_2 for 1 h and distilled under nitrogen. Aminoacetonitrile hydrochloride and glycinamide hydrochloride were recrystallized twice from 1:2 2-propanol/ethanol; piperazine was used without further purification. KOH and HCl solutions were made from DILUT-IT analytical concentrates (J.T. Baker). Ultrapure water was obtained from a Millipore-Q Plus water system. DMSO was distilled under vacuum over CaH_2.

pH Measurements. pH measurements were made using an Orion 611 digital pH meter equipped with a glass electrode and a Sure-Flow (Corning) reference electrode. In 50% DMSO/50% water, the pH meters were calibrated using Hallé buffers,[34] in water using standard buffers.

UV Spectra and Kinetic Experiments. UV spectra were recorded using an 8452A Agilent diode array spectrophotometer. All kinetic experiments were conducted in an Applied Photophysics DX.17MV stopped-flow spectrophotometer. The reactions were monitored at 295 nm (water) and 304 nm (50% DMSO/50% water), respectively. The reactions with KOH and most amine buffers were conducted by mixing a solution of **4H** with the appropriate buffer solution. For the reactions with HCl and with the most acidic aminoacetonitrile buffers, **4**$^-$ was first generated by incubation with a dilute KOH solution and then mixed with the buffer. The general methodology has been described elsewhere.[8a]

Acknowledgment. This research was supported by Grants CHE-9734822 and CHE-0446622 from the National Science Foundation.

Supporting Information Available: Figures S1−S4 showing data for the pK_a^{CH} determination and kinetic results. This material is available free of charge via the Internet at http://pubs.acs.org.

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[35] Hallé, J. C.; Gaboriaud, R.; Schaal, R. *Bull. Soc. Chim Fr.* **1970**, 2047.