directly in subsequent reactions: ^{1}H NMR (CDCl$_3$) δ 1.33–1.45 (2 s, 9 H), 2.18 (m, 1 H), 2.48 (m, 1 H), 3.48 (m, 1 H), 3.71 (m, 1 H), 4.14 (m, 1 H), 4.35–4.49 (2 dd, J = 8.7, 3.0 Hz, 1 H), 5.16 (m, 2 H), 7.34 (s, 5 H); FAB MS MH$^+$ calcd for $C_{17}H_{23}N_4O_4$ 347.1719, found 347.1726.

(4*R*)-1-(*tert*-Butoxycarbonyl)-4-amino-D-proline (40). The azido benzyl ester (2.65 g, 7.65 mmol) was hydrogenated as for the preparation of **6**. This gave 1.47 g (83% yield) of **40**, mp 263–264 °C (dec, darkening starting at 222 °C), after crystallization form water/EtOH: ^{1}H NMR (D$_2$O) δ 1.42–1.46 (m, 9 H), 2.12 (m, 1 H), 2.66 (m, 1 H), 3.72 (m, 2 H), 4.00 (m, 1 H), 4.18 (dd, J = 9.0, 3.9 Hz, 1 H); $[\alpha]_D$ −27° (water, c = 0.24). Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 51.97; H, 7.86; N, 12.16.

(4*R*)-1-(*tert*-Butoxycarbonyl)-4-[[[[(*p*-toluenesulfonyl)imino]aminomethyl]amino]methyl]-D-proline (41). Amino acid **40** (1.40 g, 5.74 mmol) was converted to **41** as for **13**. The residue was recrystallized from EtOAc/Et$_2$O/hexane to give 1.87 g of **25** (59% yield): mp 132–133 °C; ^{1}H NMR (d_6-DMSO) δ 1.33–1.38 (2 s, 9 H), 1.74 (m, 1 H), 2.34 (s, 3 H), 2.97 (m, 1 H), 3.33 (m, 1 H), 3.63 (m, 1 H), 4.08 (m, 2 H), 6.65 (bs, 2 H), 6.93 (bs, 1 H), 7.27 (d, J = 8 Hz, 2 H), 7.64 (d, J = 8 Hz, 2 H). Anal. Calcd for $C_{19}H_{28}N_4SO_6 \cdot H_2O$: C, 49.77; H, 6.59; N, 12.22. Found: C, 50.54; H, 6.37; N, 11.39.

(4*R*)-4-(Guanidinomethyl)-L-proline (42). Tosyl derivative **38** (50 mg, 0.11 mmol) and 0.25 mL of anisole were cooled to −78 °C in a Teflon vessel, under a stream of nitrogen. Anhydrous hydrogen fluoride gas was then condensed into the vessel.[9b] The reaction was allowed to warm to −20 °C and stirred at that temperature for 30 min. The reaction was allowed to warm to 0 °C, and the HF was allowed to evaporate under a stream of nitrogen. At this point 25 mL of water was added and the resulting solution was extracted three times with 75 mL of ethyl ether. The aqueous phase was frozen and lyophilized to give the crude title compound. This material (25 mg) was >90% pure by ^{1}H NMR and analytical HPLC. The crude product was purified by using reverse-phase high-performance chromatography on a 10 μm 300 Å pore size C-18 packing. The column was eluted with a aqueous gradient of 0.1% trifluoroacetic acid going from 0% to 10% acetonitrile (containing 0.1% trifluoroacetic acid) over 20 min. Lyophilization gave the title compound as a white solid (25 mg, 55% yield): ^{1}H NMR (D$_2$O) δ 2.08 (m, 1 H), 2.28 (m, 1 H), 2.60 (m, 1 H), 2.94 (m, 1 H), 3.03 (m, 1 H), 3.26 (d, J = 7 Hz, 2 H), 3.63 (m, 1 H), 4.21 (dd, J = 5.7, 9.3 Hz, 1 H); ^{13}C NMR (D$_2$O) δ 35.9, 40.1, 45.8, 51.7, 64.4, 160.5, 177.6. Anal. Calcd for $C_7H_{14}N_4O_2 \cdot 2TFA$: C, 31.89; H, 3.89; N, 13.52. Found: C, 32.05; H, 4.34; N, 14.18.

Acknowledgment. We thank Peter L. Barker and Eugene D. Thorsett for helpful discussions and Jim Bourell and John Stults for the mass spectral measurements. We also thank Pureza Vallar for assistance with the hydrogen fluoride reaction.

Registry No. **2**, 37813-30-2; **3**, 132622-63-0; **4a**, 132622-64-1; **4a**·HCl (*N*-deprotected), 132623-02-0; **4b**, 132623-01-9; **5a**, 132623-03-1; **5b**, 132622-65-2; **6**, 132622-66-3; **7**, 132622-67-4; **8a**, 132623-04-2; **8b**, 132622-68-5; **9**, 132622-69-6; **10**, 132622-70-9; **11a**, 132623-05-3; **11b**, 132622-71-0; **12**, 132622-72-1; **13**, 132622-73-2; **14**, 132622-74-3; **15**, 83548-48-5; **16**, 77450-00-1; **17**, 132622-75-4; **18**, 132622-76-5; **19a**, 132623-06-4; **19b**, 132622-77-6; **20**, 132622-78-7; **21**, 132622-79-8; **22a**, 132623-07-5; **22b**, 132622-80-1; **23**, 132622-81-2; **24**, 132622-82-3; **25**, 132622-83-4; **26**, 132622-84-5; **27**, 132622-85-6; **28**, 132622-86-7; **29**, 132622-87-8; **30**, 132622-88-9; **30** (free acid), 618-27-9; **31**, 132622-89-0; **31** (free acid), 2584-71-6; **32**, 132622-90-3; **33**, 132622-91-4; **34**, 132622-92-5; **35**, 132622-93-6; **36**, 132622-94-7; **37**, 132622-95-8; **38**, 132622-96-9; **39**, 132622-97-0; **40**, 132622-98-1; **41**, 132622-99-2; **42**, 132623-00-8; TsNC(SMe)$_2$, 2651-15-2.

Supplementary Material Available: X-ray data for **11b** (3 pages). Ordering information is given on any current masthead page.

Kinetics of Proton Transfer of 3,5-Heptanedione, 2,6-Dimethyl-3,5-heptanedione, and Dibenzoylmethane with Amines in 50% Me$_2$SO–50% Water. Effect of Steric Crowding and π-Overlap on Intrinsic Rate Constants

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Received November 19, 1990

Rates of reversible deprotonation of 3,5-heptanedione (**6b**), 2,6-dimethyl-3,5-heptanedione (**6c**), and dibenzoylmethane (**6d**) by several primary aliphatic amines, by piperidine and morpholine, and by hydroxide ion (**6b** and **6d** only) have been measured in 50% Me$_2$SO–50% water (v/v) at 20 °C. Apparent pK_a's as well as the pK_a values of the keto and the enol forms, and the enolization equilibrium constants (K_T) were also determined. The pK_a and K_T values show the same trends observed previously in water. The intrinsic rate constants for the reactions of **6b** and **6c** with a given family of amines (primary aliphatic or secondary alicyclic) are the same and also equal to those for the reaction of acetylacetone (**6a**) with the same amines determined previously. These results indicate that steric effects play an insignificant role in the reactions of **6a**, **6b**, and **6c**. The intrinsic rate constants for the deprotonation of **6d** are approximately three fold lower than for **6a–c**. This reduction is shown not to be caused by a steric effect but by π-overlap with the phenyl groups in the enolate ion.

There has been an ongoing interest in the kinetics of proton transfers at carbon in our laboratory.[1-7] A major focus of our work has been an attempt to understand the factors that affect the intrinsic rate constants of reactions of the type shown in eq 1. The intrinsic rate constant is defined as $k_o = k_1/q = k_{-1}/p$ when $pK_a^{BH} - pK_a^{CH_2XY} +$

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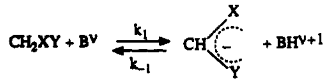


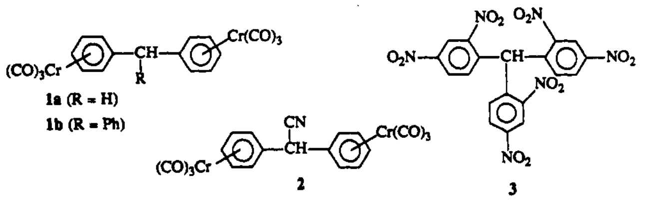
$$CH_2XY + B^v \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH(X)(Y)^- + BH^{v+1} \qquad (1)$$

log $(p/q) = 0$.[8] An important finding has been that there is a distinct inverse relationship between k_o and resonance stabilization/solvation of the carbanion.[5-7,9] This inverse relationship has been attributed to an imbalanced transition state in which the development of resonance and solvation lags behind proton transfer. This effect is a manifestation of the principle of nonperfect synchronization (PNS) which states that a product stabilizing factor whose development lags behind bond formation at the transition state depresses k_o.[9]

Another factor that is believed to affect k_o in proton transfers is the capability (or lack thereof) of the transition state to become stabilized by hydrogen bonding with B^v.[10] Since this capability is likely to diminish with increasing resonance stabilization of the carbanion, this factor tends to reenforce the effect of resonance on k_o.[11]

A third factor that is known to significantly affect the rates of proton transfer is steric hindrance, although, due to the small size of the proton, the steric bulk of either the carbon acid or the base (or both) must be considerable before one can observe significant effects. Well-documented examples of steric retardation of proton transfers include reactions of nitroalkanes and ketones with 2-substituted or 2,6-disubstituted pyridines.[12-14]

Steric hindrance has also been postulated in the reactions of MeO^- with **1**,[15] and of amines with **2**[5b] and **3**.[16] For **3** the intrinsic rate constant for deprotonation by piperidine and morpholine is about 0.8 log units lower than for deprotonation by primary amines which contrasts with the general observation that log k_o for deprotonation of carbon acids by the piperidine/morpholine pair is usually 0.7 to 1.0 units *higher* than with primary aliphatic amines.[2-4,7] Using the same criterion for **2** shows a much smaller steric effect since log k_o(pip/mor) − log (RNH_2) = 0.4 is not much lower than for sterically unhindered systems.



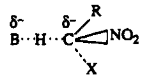
1a (R = H)
1b (R = Ph)

2

3

In all the examples cited above the steric effect may be understood in terms of crowding of the transition state which leads to a reduction in k_o. A few cases are known where steric effects lead to rate *accelerations*.[17,18]

A situation of particular interest is that of an increase in k_o due to steric inhibition of resonance in the carbanion, as in the deprotonation of 1,1-dinitroethane. In 50% Me_2SO–50% water, log k_o with carboxylate ions is ~1.5[1] while log k_o for nitromethane is ~0.73.[6,19] If both nitro groups in the 1,1-dinitroethane anion could be co-planar, the added resonance stabilization by the second nitro group would be expected to decrease k_o relative to that of nitromethane. However, the steric crowding of the anion apparently reduces the resonance quite drastically, thereby diminishing the k_o lowering effect caused by the late development of this resonance. The consequence is a higher k_o. A factor that contributes to the increased k_o is the *polar* effect of the second nitro group; inductively electron-withdrawing groups (X) tend to increase k_o in carbanion-forming reactions that have imbalanced transition states because the group is usually closer to the negative charge in the transition state (**4**) than to that in the product ion (**5**) and hence the stabilization of the transition state is disproportionately stronger than that of the product ion.[9] A similar situation is believed to prevail in the deprotonation of 2,2′,4,4′-tetranitrodiphenylmethane by aryl oxide ions, carboxylate ions, and amines where k_o is about 0.5 log units higher than for the deprotonation of the less crowded 2,4,4′-trinitrodiphenylmethane.[20] However, in a recent reinterpretation, Terrier et al.[21] have deemphasized the resonance-reducing steric effect in favor of the polar effect exerted by the additional nitro group. A similar, even more dramatic k_o-enhancing polar effect was noted when comparing the deprotonation of 2,2′,4,4′,6,6′-hexanitro- and 2,2,4,4′,6-pentanitrodiphenylmethane.[21]



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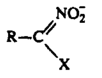
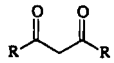


5

The present study was aimed at determining intrinsic rate constants of the deprotonation of 3,5-heptanedione (**6b**), 2,6-dimethyl-3,5-heptanedione (**6c**), and dibenzoylmethane (**6d**) by amines, and to compare our results with those for acetylacetone (**6a**).[3] **6a–d** represent a series of compounds of increasing steric bulk which could potentially either lead to reductions in k_o because of crowding in the transition state, or to increases in k_o due to steric inhibition of resonance in the carbanion which could diminish the k_o-lowering PNS effect of late resonance development. As it turns out steric effects play an insignificant role in these reactions but π-overlap with the phenyl groups in the enolate ion derived from **6d** leads to a lowering of k_o.



6
a $R = CH_3$
b $R = CH_2CH_3$
c $R = CH(CH_3)_2$
d R = Ph

Another major objective of this work was to allow a comparison with the potentially much stronger steric effects on the intrinsic rate constants of the nucleophilic addition of amines to olefins such as **7**.[22]

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(8) p and q are statistical factors, where p = number of equivalent protons on BH^{v+1} and q = number of equivalent basic sites on B^v.

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(19) Log k_o for nitromethane refers to deprotonation by piperidine and morpholine but this value is not expected to be significantly different from that with carboxylate ions if the reactions of 1,3-indandione[4] can be used as a guide.

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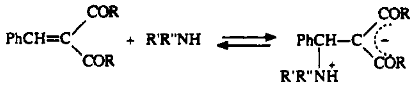
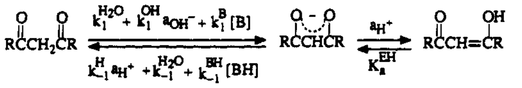

(2)

7 a R = CH_3
b R = CH_2CH_3
c R = $CH(CH_3)_2$
d R = Ph

Results

Kinetics. Just as is the case with acetylacetone (**6a**), **6b**, **6c**, and **6d** exist as equilibrium mixtures of the keto and enol forms, and the reaction scheme for proton transfer can be described by eq 3. Rates of proton transfer were determined with B = piperidine, morpholine, *n*-butylamine, 2-methoxyethylamine, glycine ethyl ester, and cyanomethylamine in 50% Me_2SO–50% water (v/v) at 20 °C. All measurements were made under pseudo-first-order conditions in the presence of excess amine buffers or KOH and at an ionic strength of 0.5 M maintained with KCl. Under these conditions the observed pseudo-first-order rate constant for equilibrium approach is given by eq 4 with K_a^{EH} being the acid dissociation constant of the enol form.


(3)

KH E⁻ EH

$$k_{obsd} = k_1^{H_2O} + k_1^{OH}a_{OH^-} + k_1^{B}[B] + (k_{-1}^{H} + k_{-1}^{H_2O} + k_{-1}^{BH}[BH^+])\frac{K_a^{EH}}{K_a^{EH} + a_{H^+}} \quad (4)$$

k_{obsd} for a given substrate/amine combination was typically determined in a 1:1 buffer at five to seven buffer concentrations. If the pH of the buffer was higher than the pK_a of the keto form (pK_a^{KH}) of the carbon acid, the equilibrium was approached from the KH side; if the pH was lower than pK_a^{KH}, the substrate was first deprotonated with dilute KOH and then mixed with the buffer, i.e., the equilibrium was approached from the E^- side. The reactions were monitored spectrophotometrically in a stopped-flow apparatus.

All plots of k_{obsd} vs [B] gave excellent straight lines with large slopes and small intercepts. The raw data are summarized in Table S1–S3 of the supplementary material.[23] The slopes are given by eq 5. k_1^B was easily calculated

$$\text{slope} = k_1^B\left(1 + \frac{a_{H^+}}{K_a^{KH}}\frac{K_a^{EH}}{K_a^{EH} + a_{H^+}}\right) \quad (5)$$

from eq 5 after K_a^{KH} and K_a^{EH} were determined as described below, and k_{-1}^{BH} was then obtained from $k_1^BK_a^{BH}/K_a^{KH}$. The various rate constants are reported in Table II.

Rate constants for the reaction of **6b** and **6d** with OH^- were also determined. Measurements were carried out in KOH solution where eq 4 simplifies to $k_{obsd} = k_1^{OH}a_{OH^-}$. The data are summarized in Tables S4 of the supplementary material.[23]

Equilibrium Measurements. The apparent acid dissociation constant for the various diketones, which is defined as

$$K_{app} = \frac{[E^-]a_{H^+}}{[KH] + [EH]} \quad (6)$$

is related to K_a^{KH} and K_a^{EH} by eq 7. K_{app} was measured by standard spectrometric procedures. K_a^{KH} and K_a^{EH} could be obtained separately from K_{app} and K_T, the enolization constant defined by eq 8. K_T was measured

$$\frac{1}{K_{app}} = \frac{1}{K_a^{KH}} + \frac{1}{K_a^{EH}} \quad (7)$$

$$K_T = \frac{[EH]}{[KH]} = \frac{K_a^{KH}}{K_a^{EH}} \quad (8)$$

spectrophotometrically by comparing the absorbance of an equilibrium solution of the substrate (A_{eq}) with a solution that corresponds to 100% enol from (A_{EH}). The enol was generated in the stopped-flow spectrophotometer by mixing the enolate ion with dilute HCl; since protonation of the oxygen is many orders of magnitude faster than protonation of the carbon, this procedure assures 100% conversion to the enol form which gradually rearranges to an equilibrium mixture of EH and KH. Assuming that all the absorption of the equilibrium mixture is due to the enol form, K_T is calculated as

$$K_T = \frac{A_{eq}}{A_{EH} - A_{eq}} \quad (9)$$

pK_{app}, pK_a^{KH}, pK_a^{EH}, and K_T values are summarized in Table I.

Table I. Summary of Acid Dissociation and Enolization Constants of Acetylacetone (6a), 3,5-Heptanedione (6b), 2,6-Dimethyl-3,5-heptanedione (6c), and Dibenzoylmethane (6d) in 50% Me_2SO–50% Water (v/v) at 20 °C[a]

	6a[d]	6b	6c	6d
pK_{app}[b]	9.27	10.25	10.66	9.35
pK_a^{KH}[b]	9.12	10.16	10.45	8.72
pK_a^{EH}[b]	8.75	9.52	10.23	9.23
K_T[c]	0.43	0.23	0.61	3.2
pK_{app}(H_2O)[e]	8.84[f]	9.55[f]	9.83[f]	8.95[g]

[a] μ = 0.5 M (KCl). [b] Estimated experimental error ±0.05 or better. [c] Estimated experimental error ±8% or better. [d] Reference 3. [e] In water. [f] Reference 26a. [g] Reference 26b.

Discussion

pK_a Values and Enolization Constants. The various pK_a values and the enolization constants (K_T) are summarized in Table I. Replacing R = CH_3 with CH_3CH_2 and $(CH_3)_2CH$ leads to an increase in pK_a^{KH} and pK_a^{EH} while replacing R = CH_3 with Ph has an acidifying effect on pK_a^{KH}, but not on pK_a^{EH}. The observed trends are quite similar to the ones found in aqueous solution;[24] pK_{app} values in this latter solvent are included in Table I.

A number of explanations has been offered to account for the effect of R groups on the acidity of these and other β-diketones. One factor that may contribute to the reduced acidity in the series $CH_3 \rightarrow CH_3CH_2 \rightarrow (CH_3)_2CH$ is an electron-donating inductive effect.[25,26] However, correlations with Taft's σ^* values are not very good which has been attributed to hyperconjugation[25] or steric effects.[26] Hammond et al.[27] have also emphasized the effect of steric crowding which destabilizes the enolate ion by forcing the negatively charged oxygens into closer proximity, thereby enhancing electrostatic repulsion.

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[23] See paragraph at the end of this paper regarding supplementary material.

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Table II. Summary of Rate Constants for the Reactions of Amines and Hydroxide Ion with 3,5-Heptanedione (6b), 2,6-Dimethyl-3,5-heptanedione (6c), and Dibenzoylmethane (6d) in 50% Me$_2$SO–50% Water (v/v) at 20 °C[a]

		6b (pK_a^{KH} = 10.16)		6c (pK_a^{KH} = 10.45)		6d (pK_a^{KH} = 8.72)	
amine (pK_a^{BH})		k_1^B, M^{-1} s^{-1}	k_{-1}^{BH}, M^{-1} s^{-1}	k_1^B, M^{-1} s^{-1}	k_{-1}^{BH}, M^{-1} s^{-1}	k_1^B, M^{-1} s^{-1}	k_{-1}^{BH}, M^{-1} s^{-1}
piperidine	(11.02)	1.6×10^3	2.2×10^2	1.1×10^3	2.9×10^2	1.9×10^3	9.7
morpholine	(8.72)	1.8×10^2	5.0×10^3	1.7×10^2	9.3×10^3	3.2×10^3	3.2×10^2
n-butylamine	(10.65)	3.0×10^2	9.7×10^1	2.1×10^2	1.3×10^2	4.1×10^2	4.9
2-methoxyethylamine	(9.62)	9.6×10^1	3.3×10^2	9.8×10^1	6.7×10^2	1.6×10^2	21
glycine ethyl ester	(7.87)	12.2	2.4×10^3	9.6	3.7×10^3	27	1.9×10^2
cyanomethylamine	(5.39)	1.4	8.4×10^4	1.2	1.4×10^4	1.8	3.8×10^3
OH$^-$	(17.34)	1.9×10^4	3.4×10^{-3} [b]			1.6×10^4	2.5×10^{-3} [b]

[a] μ = 0.5 M (KCl); estimated error limits of rate constants are ±4% or better. [b] In units of s^{-1}.

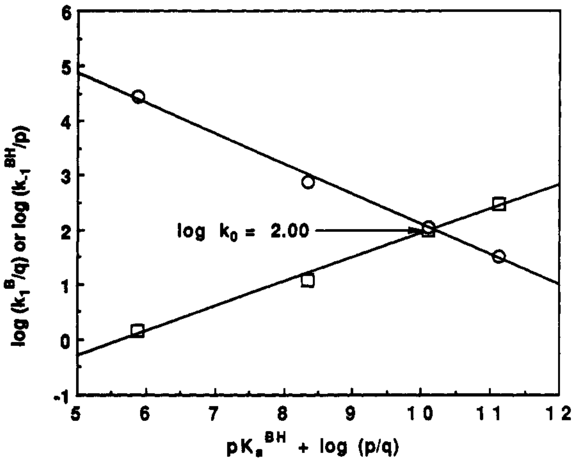

Figure 1. Brønsted plots for the reaction of 3,5-heptanedione (**6b**) with primary amines (k_1^B) and its reverse (k_{-1}^{BH}). Point of intersection corresponds to log k_o.

Table III. Brønsted Coefficients and Intrinsic Rate Constants for the Reactions of Amines with Acetylacetone (6a), 3,5-Heptanedione (6b), 2,6-Dimethyl-3,5-heptanedione (6c), and Dibenzoylmethane (6d)

	6a[a]	6b	6c	6d
	piperidine/morpholine			
β	0.42 ± 0.03	0.41 ± 0.02	0.37 ± 0.04	0.36 ± 0.03
log k_o	2.75 ± 0.06	2.73 ± 0.05	2.76 ± 0.08	2.36 ± 0.08
	1° RNH$_2$			
β	0.45 ± 0.01	0.44 ± 0.02	0.44 ± 0.03	0.45 ± 0.03
log k_o	2.06 ± 0.02	2.00 ± 0.06	2.05 ± 0.08	1.56 ± 0.08

[a] Reference 3.

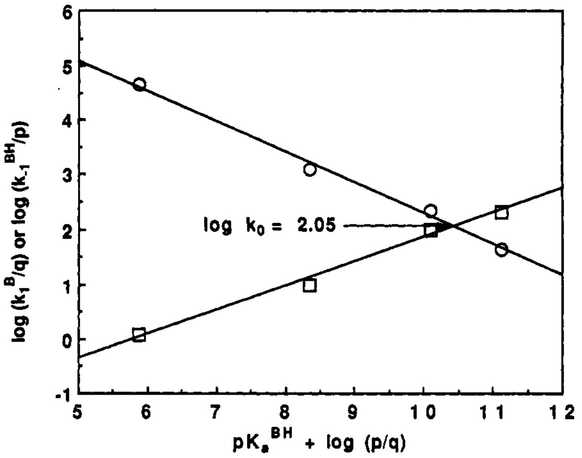

Figure 2. Brønsted plots for the reaction of 2,6-dimethyl-3,5-heptanedione (**6c**) with primary amines (k_1^B) and its reverse (k_{-1}^{BH}). Point of intersection corresponds to log k_o.

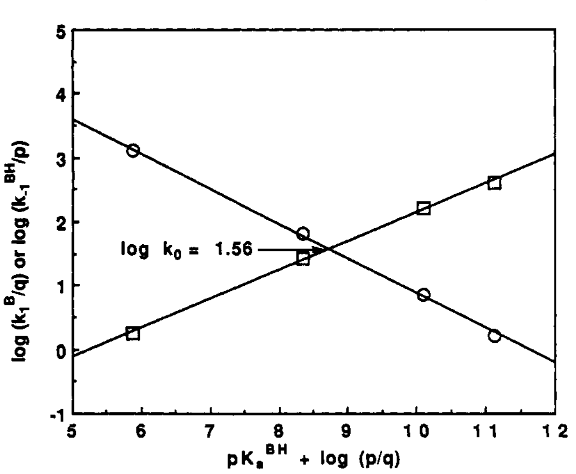

Figure 3. Brønsted plots for the reaction of dibenzoylmethane (**6d**) with primary amines (k_1^B) and its reverse (k_{-1}^{BH}). Point of intersection corresponds to log k_o.

The pK_a^{KH} of **6d** (R = Ph) is lower than that of **6a**, which reflects the electron-withdrawing effect of the phenyl groups. Part of this electronic effect is undoubtedly inductive, but some stabilization of the enolate ion by π-overlap with the phenyl groups is likely to be a contributing factor. Such overlap is indicated by the λ_{max} = 351 nm of the enolate ion which is substantially red-shifted compared to that of the enolate ion of the other diketones (291 nm for **6a**, 296 nm for **6b** and **6c**). Additional evidence for this π-overlap comes from our kinetic results discussed below. One might in fact have expected the pK_a^{KH} of **6d** to be even lower than 8.72 but the steric effect of forcing the two charged oxygens into proximity, as described above for bulky alkyl groups,[27] probably counteracts the electronic effects.

With respect to the enolization constants K_T, we note that they change little from CH$_3$ to CH$_3$CH$_2$ to (CH$_3$)$_2$CH but there is a significant increase for R = Ph. These findings are similar to those reported by others in various solvents,[28] in particular the larger K_T value for **6d**.[29] The shift towards the enol form in **6d** probably reflects the stabilization of the C=C double bond of the enol by π-overlap with the phenyl group. The substantial red-shift of λ_{max} of the enol of **6d** (347 nm) compared to the enol forms of the other diketones (272 nm for **6a**, 275 nm for **6b**, and 277 nm for **6c**), which is similar to the shift in λ_{max} for the respective enolate ions, supports this notion. The increased K_T value of acetophenone relative to that of acetone is likely to have a similar explanation.[30]

Rate Constants. All rate constants determined in this study are summarized in Table II (**6b–d**) while Table III reports Brønsted β values (Brønsted plots for the primary amines are in Figures 1–3) and intrinsic rate constants (log k_o) for **6a–d**. The following conclusions can be drawn.

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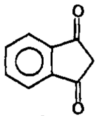
[28] Forsen, S.; Nilsson, M. In *The Chemistry of the Carbonyl Group*; Zabicky, J., Ed.; Wiley-Interscience: New York, 1970; Vol. 2, p 157.

[29] Lowe, J. U., Jr.; Ferguson, L. N. *J. Org. Chem.* **1965**, *30*, 3000.

[30] Keeffe, J. R.; Kresge, A. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1990**, *112*, 4862.

(1) The Brønsted β values with the primary amines do not depend on the R group of the diketones. There is a slight trend in β with the secondary alicyclic amines which, however, is barely outside the estimated error limits. In view of the fact that these latter β values are derived from two-point Brønsted plots, not much significance should be attached to the slight variations. On the other hand, the observation that β for the secondary alicyclic amines are slightly lower than for the primary aliphatic amines is probably real since the same result has been reported for numerous other carbon acid deprotonation reactions.[2-5,7]

(2) The log k_0 values for **6a–c** are the same for a given series of amines and approximately 0.7 ± 0.1 log units higher for the secondary alicyclic amines compared to the primary amines. This difference in log k_0 between primary and secondary amines, which is a well-known phenomenon caused by differences in the solvation energies of the respective protonated amines,[31-33] is about the same as that observed in numerous other proton transfers, including cases where there is little possibility for steric hindrance. For example, for 1,3-indandione (**8**), log k_0(pip/mor) − log k_0(1° RNH_2) ≈ 0.69.[4] The fact that log k_0 does not change for $CH_3 \rightarrow CH_3CH_2 \rightarrow (CH_3)_2CH$ and that the difference between log k_0(pip/mor) and log k_0(1° RNH_2) is constant indicates that steric crowding is not an important factor in these proton transfers.



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(3) For **6d** log k_0 is ~0.4 to ~0.5 units lower than for **6a–c**. A possible explanation of this reduction is that it reflects steric crowding in the transition state, similar to that invoked for the examples cited in the introduction. However, there are several reasons why this is not an attractive explanation. One is that CPK molecular models fail to show substantial crowding in the transition state. Another is that the difference between log k_0(pip/mor) and log k_0(1° RNH_2) is, with experimental error, the same as for **6a–c**; if crowding were a severe problem, the reaction with the more bulky secondary amines should be slowed down more than that with the primary amines, leading to a smaller difference between log k_0(pip/mor) and log k_0(1° RNH_2), as observed with **2** and **3** (see introduction). By the same token, the k_1^{OH}/k_1^{Pip} ratio for **6d** should be significantly larger than for **6a** or **6b**, but this is not borne out by the results (k_1^{OH}/k_1^{Pip} = 13.0, 11.8, and 8.39 for **6a**, **6b**, and **6d**, respectively, Table II).

Other types of steric effects, in particular steric inhibition of resonance in the enolate ion, would tend to *increase* log k_0 because the k_0-lowering effect of the late development of this resonance would be reduced, as has been observed in the comparison of 1,1-dinitroethane with nitromethane (see introduction). We conclude that the depressed intrinsic rate constants for **6d** must have a nonsteric origin.

It seems reasonable to relate this depressed log k_0 to what is the most significant difference between the enolate ion of **6d** and that of the other diketones, namely the overlap between the π-electrons of the phenyl groups with the π-system responsible for the delocalization of the charge. Inasmuch as the development of this overlap depends on the delocalization of the charge, the lag in the development of this latter behind proton transfer also implies a lag in the development of the π-overlap. And just as the lag in the delocalization of the charge reduces log k_0, so will the lag in the development of the π-overlap with the phenyl groups lower k_0 further. Both these effects are manifestations of the PNS in which the intrinsic rate constant is reduced by the late development of a product stabilizing factor.

Experimental Section

Materials. 3,5-Heptanedione (**6b**) and 2,6-dimethyl-3,5-heptanedione (**6c**) were obtained from Eastman, dibenzoylmethane (**6d**) from Aldrich; they were used without further purification. The amines were purified and stored as previously described.[1-4]

Procedures. Kinetic determinations, preparation of solutions, pH measurements, etc., were carried out as described previously.[1-4] All kinetic measurements were performed in a Durrum–Gibson stopped-flow apparatus. Monitoring wavelengths were 294 nm (enolate ion) or 274 nm (enol) for **6b** and **6c**, 382 nm for **6d**. For **6b** and **6c** these wavelengths correspond to λ_{max} of the respective species; for **6d**, 382 nm was the wavelength of largest difference in ϵ between enol and enolate ion, with λ_{max} being 351 nm (enolate ion) and 347 nm (enol).

Acknowledgment. This research was supported by Grant CHE-8921739 from the National Science Foundation.

Supplementary Material Available: Kinetic data, Tables S1–S4 (7 pages). Ordering information is given on any current masthead page.

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[31] This is a PNS effect according to which the stronger solvation of RNH_3^+ compared to $RR'NH_2^+$ reduces k_0 because solvation of the developing positive charge on the amine nitrogen in the transition state lags behind proton transfer.[9,32,33]

[32] Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; p 178.

[33] Bell, R. P. *The Proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1973; Chapter 10.