Separation of Ring Polar and Resonance Effects on the Rate Constants for Uncatalyzed *N*-Arylidenepropylamine Formation in Methanol

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Rate constants are reported for the reaction of a series of 19 ring-substituted benzaldehydes with propylamine in methanol and in *O-d*-methanol at different temperatures and of three of them with 2-methoxyethylamine and 2,2-dimethoxyethylamine. The large direct solvent kinetic isotope effects (KSIE) (2.1–2.9), as well as the $\Delta H^\ddagger$ (4.7–7.6 kcal mol^{-1}) values vary smoothly with substituent. $\Delta S^\ddagger$ (ca. -45 cal mol^{-1} K^{-1}) is almost independent of substituent. These data indicate that there in no change in the rate-limiting step, and since the large KSIE and $|\Delta S^\ddagger|$ can be related to significant solvation of the leading OH$^-$ group at the transition state, they agree with a mechanism involving α-amino alcohol formation in a fast preequilibrium followed by rate-limiting OH$^-$ detachment yielding iminium ions. When corrected for parallel hemiacetal formation, the second-order rate constants are accounted for by the Young–Jencks equation with $\rho^n = 0.08$ and $\rho^r = 0.57$, this equation allowing a separation of the direct resonance effects from the polar effects of the substituted ring. The very low ρ^n value indicates that the polar effects for the rate-limiting OH$^-$ detachment are almost compensated by those on the constant of the α-amino alcohol-formation preequilibrium. In contrast, the relatively large ρ^r coefficient, which means that the overall rate constants depend almost exclusively on resonance, is due to predominance of the direct resonance effects on the preequilibrium. The KSIE and $\Delta S^\ddagger$ data, as well as the β_{nucl} parameters (close to unity) observed when the reacting amine was changed (slopes of the straight lines obtained by plotting the logarithm of the rate constants vs the pK_a of the ammonium ions) favor a late transition state. In contrast, the low ρ^r value for the rate-limiting step (ca. -0.5) shows that the transition state is not iminium ion-like.

Introduction

In the preceding paper of this issue[1] it was shown that the Young–Jencks (YJ) equation[2] (eq 1), based on a

$$\log k \text{ or } \log K = \rho^n \sigma^n + \rho^r \Delta\sigma_R^+ + C \qquad (1)$$

separation of the polar effects of the substituted benzene ring, including resonance-induced polar (RP) effects, from the direct resonance (DR) effects, can be more relevant and informative than the classical DSP equation[3] (eq 2) for dealing with rate and equilibrium data for reactions

$$\log k \text{ or } \log K = \rho_1 \sigma_1 + \rho_R \sigma_R + C \qquad (2)$$

occuring at an sp^2 carbon atom adjacent to the ring and involving a change in hybridization. The advantages are evident when the electron-demand variations of the reaction center require a separation of the DR and RP effects. The opposite signs of these two contributions observed for α-amino ether cleavage cannot be dealt with by the DSP equation since the use of this latter equation requires a DR/RP ratio close to that for the standard reactions which have served to define the σ^0, σ, σ^+, and σ^- sets of parameters. In order to gain further evidence supporting the distinction between the RP and DR effects,

as well as the relevance of the $\Delta\sigma_R^+$ parameters to account for the latter contribution, we examined the dependence on substituent of the rate constants for the reaction of Schiff base formation from primary amines and benzaldehydes in methanol. For this reaction there were some indications in the literature that the rate constant depends mainly on DR effects.

Imine formation in water from aliphatic aldehydes or ketones and primary amines has been examined by many authors.[4–10] Except in the case of unstable aldehydes, the reaction is reversible and lies on the imine side. Forward rate constants were usually measured in the presence of both hydroxylamine and aliphatic primary amine since it was shown that oxime is formed competitively via the intermediate imine. The rate constant for this path corresponds to imine formation since the imine-to-oxime transformation is faster.[8b] In the case of benzaldehydes, 1, data for the reaction in methanol with *n*-butylamine (Scheme 1) have been reported by Santerre et al.[11] The reaction was observed to be complete because of the

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(1) Toullec, J.; Bennour, S. Preceding paper of this issue.
(2) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977,** *99,* 8238. Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1978,** *100,* 1228. Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1979,** *101,* 3288. Young, P. R.; McMahon, P. E. *J. Am. Chem. Soc.* **1979,** *101,* 4678.
(3) (a) Taft, R. W., Jr.; Lewis, I. C. *J. Am. Chem. Soc.* **1858,** *80,* 2436. (b) Taft, R. W., Jr.; Ehrenson, S.; Lewis, I. C.; Glick, R. E. *J. Am. Chem. Soc.* **1959,** *81,* 5352. (c) Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Progr. Phys. Org. Chem.* **1973,** *10,* 1.

(4) Jencks, W. P. *Progr. Phys. Org. Chem.* **1964,** *2,* 63.
(5) Jencks, W. P. *Catalysis in Chemistry and Enzymology;* McGraw-Hill: New York, 1969; p 463.
(6) Zuman, P. *Collect. Czech. Chem. Commun.* **1950,** *15,* 839. Zuman, P. *Chem. Listy* **1952,** *46,* 516. Zuman, P.; Brezina, M. *Chem. Listy* **1953,** *47,* 975. Brezina, M.; Zuman, P. *Chem. Listy* **1953,** *47,* 975.
(7) (a) Bender, M. L.; Williams, A. *J. Am. Chem. Soc.* **1966,** *88,* 2502. (b) Williams, A.; Bender, M. L. *J. Am. Chem. Soc.* **1966,** *88,* 2508.
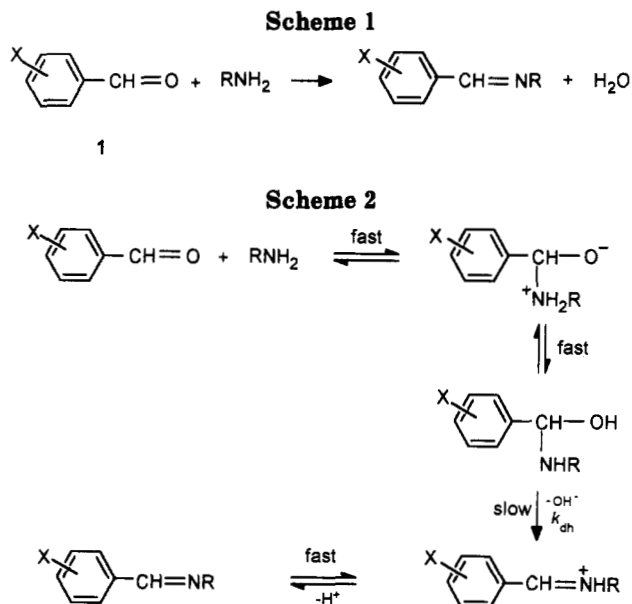(8) (a) Hine, J.; Yeh, C. Y. *J. Am. Chem. Soc.* **1967,** *89,* 2669. (b) Hine, J.; Via, F. A.; Gotkis, J. K.; Craig, J. C. *J. Am. Chem. Soc.* **1970,** *92,* 5186. (c) Hine, J.; Yeh, C. Y.; Schmalstieg, F. C. *J. Org. Chem.* **1970,** *35,* 340. (d) Hine, J.; Zeigler, J. P.; Johnston, M. *J. Org. Chem.* **1979,** *44,* 3540. (e) Hine, J.; Cholod, M. S.; Chess, W. K., Jr. *J. Am. Chem. Soc.* **1973,** *95,* 4270. (f) Hine, J. *Acc. Chem. Res.* **1978,** *11,* 1.
(9) Sander, E. G.; Jencks, W. P. *J. Am. Chem. Soc.* **1968,** *90,* 6154.
(10) Diebler, H.; Thorneley, R. N. F. *J. Am. Chem. Soc.* **1973,** *95,* 896.

Scheme 1

$$X\text{-}C_6H_4\text{-}CH{=}O + RNH_2 \longrightarrow X\text{-}C_6H_4\text{-}CH{=}NR + H_2O$$

1

Scheme 2

$$X\text{-}C_6H_4\text{-}CH{=}O + RNH_2 \underset{\text{fast}}{\rightleftharpoons} X\text{-}C_6H_4\text{-}\underset{\overset{+}{N}H_2R}{CH{-}O^-}$$

↕ fast

$$X\text{-}C_6H_4\text{-}\underset{NHR}{CH{-}OH}$$

slow $\downarrow k_{dh}$ $^{-OH^-}$

$$X\text{-}C_6H_4\text{-}CH{=}NR \underset{\text{-H}^+}{\overset{\text{fast}}{\rightleftharpoons}} X\text{-}C_6H_4\text{-}CH{=}\overset{+}{N}HR$$

absence of significant amounts of water. A plot of the logarithm of the second-order rate constants against the Hammett σ parameters exhibits a peculiar bell-shaped curve, the rate being maximal for X = H and decreasing for both σ-electron-withdrawing and π-electron-donating substituents. This is analogous to the behavior observed in the case of semicarbazone formation,[12] which was explained in terms of changes in the rate-limiting step.[4,5,13] In contrast, Santerre et al. attributed the substituent effects for aldimine condensation to incomplete compensation of the resonance effects on the α-amino alcohol formation prior to equilibrium and on the rate constant for α-amino alcohol dehydration. The reaction was assumed to proceed according to the mechanism shown in Scheme 2 without any change in the rate-limiting step. Since OH$^-$ detachment from α-amino alcohols (carbinolamines) is usually considered to be rate-limiting for the imine formation process at high pH in water, the reaction was assumed to be also controlled by this step when the reaction is conducted in methanol in the presence of primary amines. According to Jencks,[4] "it is not known with certainty whether a single step is rate-limiting for all compounds studied, or whether there is a change in rate-determining step with changing substituents...; however, it is probable that (in this case) the dehydration step is rate-determining and the negative deviations for compounds with electron-donating substituents reflect an incomplete cancellation of substituent effects on the two steps of the reaction, rather than a change in rate-determining step for these substituents". Similar behavior has also been observed for the addition of ammonia to benzaldehyde.[14,15] However, in this case the inversion of the substituent effects was interpreted as being due to a change in the rate-limiting step, from α-amino alcohol formation for aldehydes substituted by electron-donating groups to α-amino alcohol dehydration when the substituent is electron withdrawing.
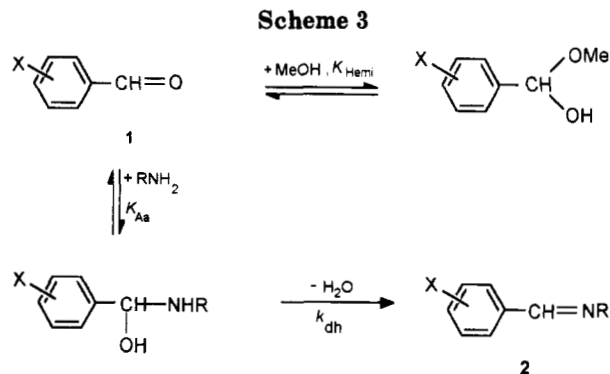
(11) Santerre, G. M.; Hansrote, C. J., Jr.; Crowell, T. I. *J. Am. Chem. Soc.* **1858**, *80*, 1254.

(12) Noyce, D. S.; Bottini, A. T.; Smith, S. G. *J. Org. Chem.* **1958**, *23*, 752.

(13) Anderson, B. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1960**, *82*, 1773.

(14) Ogata, Y.; Kawasaki, A.; Okumura, N. *J. Org. Chem.* **1964**, *29*, 1985.

(15) Ogata, Y.; Kawasaki, A. In *The Chemistry of the Carbonyl Group*; Zabicky, J., Ed.; Wiley: London, 1970; Vol. 2, p 1.

Scheme 3

$$X\text{-}C_6H_4\text{-}CH{=}O \underset{}{\overset{+MeOH, K_{Hemi}}{\rightleftharpoons}} X\text{-}C_6H_4\text{-}\underset{OH}{CH}\overset{OMe}{}$$

1

↕ +RNH$_2$, K_{Aa}

$$X\text{-}C_6H_4\text{-}\underset{OH}{CH{-}NHR} \overset{-H_2O}{\underset{k_{dh}}{\longrightarrow}} X\text{-}C_6H_4\text{-}CH{=}NR$$

2

It is noteworthy that in these studies of the reaction of aliphatic amines or ammonia with aldehydes in alcohols it was not explicitly considered[16] that the reacting aldehydes are in equilibrium with the corresponding hemiacetals (Scheme 3). Kinetic data for this process in methanol for various substituted benzaldehydes[17] make it possible to estimate the forward and reverse rate constants in primary aliphatic amine solutions and to calculate that τ, the reciprocal of the sum of the forward and backward first-order rate constants, is less than 10^{-2} s. It follows that the hemiacetal formation equilibrium can be considered as rapidly established after mixing and that the spectrometrically-determined first-order rate constants for *N*-arylideneamine formation should be corrected by the $(1 + K_{Hemi})$ factor.

This paper describes an extension of Santerre's work. Propylamine was used instead of butylamine and the substituent set was much enlarged. Substituent effects were examined in terms of two-parameter free-energy relationships after taking hemiacetal formation into account. Moreover, in order to examine whether changes in the substituent result in changes in the rate-limiting step, the activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ were measured, as well as the kinetic solvent isotope effects (KSIE) associated with a change in solvent from methanol to *O-d*-methanol. It can be predicted that any change in the rate-limiting step of the overall imine formation process would induce a break in the substituent dependence of the activation parameters and of the KSIEs. Both KSIE and $\Delta S^\ddagger$ data are also expected to give information on the degree of hydrogen bond solvation of the leaving hydroxide ion at the transition state. On the other hand, studies of the dependence of the rate constant on R in RNH$_2$ were thought to provide some indication about the positive charge formed at the nitrogen atom. R was varied from *n*-Pr to 2-methoxyethyl and to 2,2-dimethoxyethyl. Combined with conclusions based on substituent effects, it was expected that these data would make it possible to sketch out a model of the transition state.

Results

The reaction of substituted benzaldehydes, **1a–s**, with 0.02–0.16 M propylamine, **3a**, was followed in methanol by conventional UV spectroscopy. Apparent first-order rate coefficients, k_ψ, were calculated from the exponential increase of absorbance at fixed wavelengths corresponding to maximum differences in molar absorption coefficients

(16) It has been suggested in ref 11 that hemiacetal formation, which reduces the concentration of aldehyde, may have some implication on the observation of a rate constant maximum.

(17) Arota, M.; Cox, B. G.; Sørensen, P. E. *J. Chem. Soc., Perkin Trans.* 2 **1979**, 103.
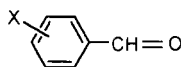
1 (X in) **a**: 4–OH; **b**: 4–NMe$_2$; **c**: 4–OMe;
  d: 4–OPh; **e**: 4–Me; **f**: H; **g**: 3–Me;
  h: 3–OMe; **i**: 4–F; **j**: 4–Cl; **k**: 4–Br;
  l: 3–F; **m**: 3–Cl; **n**: 3–Br; **o**: 4–CF$_3$;
  p: 3–CN; **q**: 4–CN; **r**: 3–NO$_2$; **s**: 4–NO$_2$

of the Schiff base formed and of the starting material. Excellent first-order behavior, corresponding to eq 3, was

$$(A_\infty - A_t) = (A_\infty - A_0)\exp(-k_\psi t) \qquad (3)$$

observed up to 95% reaction. In this equation A_t, A_0, and A_∞ are the absorbance at time t and the extrapolated initial and final absorbances, respectively. The addition of water to methanol, up to 0.5% w/w, did not introduce any change in k_ψ or in A_∞. This indicates that the reaction is complete whatever the substituent. Moreover, in the case of the reaction of **1e**, **1f**, **1m** and **3r** with **2a** it was shown that the final spectra corresponded to those of the corresponding aldimines in methanol.

The pH values of the amine solutions (13.4–13.9 on the 0–16.7 scale, depending on the concentration) were measured; they corresponded to those calculated from the pK_a values (11.7, see below). Under these conditions the relative amounts of the corresponding ammonium ions can be calculated to be always lower than 2%. As shown below, such low ammonium ion concentrations are not sufficient to catalyze the reaction. The small differences between stoichiometric amine concentrations and those of free amine were neglected.

In 0.02–0.16 M propylamine solutions 4-hydroxybenzaldehyde, **1a**, is mostly on the phenolate form **1a⁻**, as calculated by taking into account its pK_a value (pK_a = 12.1[18]). However, since, by reference to **1c**, the phenol form is expected to react more rapidly than **1a⁻**, the k_ψ rate constants measured for the **1a** plus propylamine solutions would need to be corrected for the **1a** contribution to obtain the rate data for **1a⁻**. In order to derive the rate constants associated with **1a** and **1a⁻**, and since k_ψ does not depend on ionic strength, k_ψ was measured in propylamine (0.04 M) and propylammonium nitrate solutions (ionic strength, I, maintained at 0.04 M by adding tetramethylammonium bromide). Under these conditions, k_ψ can be expressed by eq 4,, where $r = [n\mathrm{PrNH_3^+}]/$

$$k_\psi = (k_\psi)_a[r/(r + K)] + (k_\psi)'_a[K/(r + K)] \qquad (4)$$

$n\mathrm{PrNH_2}]$ and $(k_\psi)_a$ and $(k_\psi)'_a$ are the first-order contributions associated with **1a** and **1a⁻**. K is the (**1a** + **3a**)-to-(**1a⁻** + **3a·H⁺**) equilibrium constant calculated from the initial absorbance data at 330 nm at various amine and ammonium ion concentrations ($I = 0.04$ M). The K values obtained, 2.60, 1.96, 1.41, 1.10, and 0.74, at 15, 20, 25, 30, and 37 °C, respectively, are in keeping with the pK_a values for **1a** (12.1[18]) and **3a·H⁺** (11.7, see Experimental Section) if the ionic strength effects on K are taken into account. The rate constants $(k_\psi)_a$ and $(k_\psi)'_a$ were calculated from

the slopes and intercepts, respectively, of the linear plots of $k_\psi[(r + K)/K]$ vs r/K.

Except for **1a** (0.04 M only), the dependence of k_ψ on amine concentration was examined, typically from 0.02 to 0.16 M. The plots of k_ψ against amine concentration were observed to be linear for the lowest concentrations. This is in agreement with what is expected from the mechanism in Scheme 2 if it is assumed that there is no significant buildup of α-amino alcohol. The negative deviations of the k_ψ values from the straight lines that were observed for the highest amine molarities are probably due to some buildup of the adduct. When the mechanism in Scheme 2 is assumed, with rate limited by the OH⁻-detachment step, it is easy to show that k_ψ can be written as in eq 5

$$k_\psi = \frac{K_{\mathrm{Aa}}k_{\mathrm{dh}}[\mathrm{Am}]}{1 + K_{\mathrm{Hemi}} + K_{\mathrm{Aa}}[\mathrm{Am}]} \qquad (5)$$

because rate depends on free aldehyde concentration and not on the stoichiometric aldehyde concentration which includes those of α-amino alcohol and hemiacetal. In this equation, K_{Aa} is the equilibrium constant for the two-step α-amino alcohol formation, [Am] is the concentration of primary amine in excess, and k_{dh} is the rate constant for the OH⁻-detachment step (see Scheme 2). The fact that k_ψ was observed to depend linearly on [Am] at the lowest concentrations used means that the $K_{\mathrm{Aa}}[\mathrm{Am}]$ term can be neglected under these conditions. However, in order to account for the small curvature of the plots of k_ψ vs [Am], the apparent second-order rate constants [$K_{\mathrm{Aa}}k_{\mathrm{dh}}/(1 + H_{\mathrm{Hemi}})$] were calculated as the inverses of the slopes of the small-intercept straight lines observed by plotting $1/k_\psi$ against $1/[\mathrm{Am}]$.

Equation 5 shows that these apparent second-order rate constants should be corrected for the $(1 + K_{\mathrm{Hemi}})$ term in order to get the second-order rate constants k_2 expressed by eq 6.

$$k_2 = K_{\mathrm{Aa}}k_{\mathrm{dh}} \qquad (6)$$

Table 1 lists the k_2 data for **1a–s**, as well as the K_{Hemi} equilibrium constants used to correct the apparent second-order rate constants. These K_{Hemi} values are literature data[17,21] or are calculated by means the YJ relationship observed.[22] When possible, the k_2 values are compared to those reported by Santerre et al.[11] for the reaction of n-butylamine with **1**, also corrected for hemiacetal formation. The agreement is excellent. The differences in reactivity between the two primary amines are small. Figure 1 shows the plot of log k_2 against σ^n.[23] All the points corresponding to the meta substituents fall on a straight line with slope, $\rho^n = 0.08 \pm 0.02$, very close to zero. Those associated with para π-electron-donating substituents are clearly below the line. On the other hand, small positive deviations are observed for the para π-electron-demanding CF$_3$, CN, and NO$_2$ substituents which can be thought to reduce the ability of π-electron donation by

(18) Estimated from the pK_a values for phenol 14.0[19] and 4-nitrophenol (11.20[20]) in methanol. It was assumed that pK_a for substituted phenols in methanol depends linearly on σ^- parameters with a ρ^- value of 2.24 calculated from the above two data.

(19) Charlot, G.; Trémillon, B. *Les Réactions Chimiques dans les Solvants et les Sels Fondus*; Gauthier-Villars: Paris, 1963.

(20) Clare, B. W.; Cook, D.; Ko, E. C. F.; Parker, A. J. *J. Am. Chem. Soc.* **1966**, *88*, 1911.

(21) Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2* **1975**, 185.

(22) Toullec, J.; El-Alaoui, M.; Kleffert, P. *J. Org. Chem.* **1983**, *103*, 4808. Toullec, J.; El-Alaoui, M.; Kleffert, P. *J. Org. Chem.* **1986**, *51*, 2155.

(23) The σ^n values are those given in ref 24a, except for X = 4-O⁻ (–0.50), 4-OH (–0.12), 4-NMe$_2$ (–0.24), 4-OMe (–0.09), 4-OPh (0.09), 4-Me (–0.10), 4-F (+0.18), 4-Cl (+0.29), and 4-Br (0.30) (ref 24b).

(24) (a) van Bekkum, H.; Verkade, P. E.; Wepster, B. M. *Rec. Trav. Chim. Pays-Bas* **1959**, *78*, 815. (b) Hoefnagel, A. J.; Wepster, B. M. *J. Am. Chem. Soc.* **1973**, *95*, 5357.

Table 1. Rate Constants for the Formation of N-Arylidenepropylamine from Substituted Benzaldehydes in Methanol (25 °C)

compd	$k_\psi/[\text{Am}]^a$ (M^{-1} s^{-1})	K_{Hemi}	k_2^b (M^{-1} s^{-1})	k_2^c (M^{-1} s^{-1})
1a	0.0319	ca. 0	0.0319	
1a$^-$	0.0050	ca. 0	0.0050	
1b	0.0149	ca. 0	0.0149	0.0158
1c	0.0432	0.012 ± 0.003^e	0.0437	0.0470
1d	0.0601	0.022^d	0.0614	
1e	0.0820	0.034 ± 0.004^e	0.0848	0.0881
1f	0.0908	0.090 ± 0.005^e	0.099	0.113
1g	0.1048	0.070^d	0.108	
1h	0.0929	0.090 ± 0.005^e	0.101	
1i	0.0615	0.113^d	0.068	
1j	0.0757	0.24 ± 0.02^e	0.094	0.0986
1k	0.0788	0.27 ± 0.03^e	0.100	
1l	0.0706	0.40^d	0.099	
1m	0.0729	0.45 ± 0.06^e	0.106	
1n	0.0733	0.43 ± 0.05^e	0.105	
1o	0.0601	1.13^d	0.128	
1p	0.0434	1.71^f	0.118	
1q	0.0441	1.83^d	0.124	
1r	0.0363	2.1 ± 0.2^e	0.112	0.109
1s	0.0359	3.0 ± 0.2^e	0.144	0.131

^{a} Second-order rate constants at low amine concentration. Standard deviations: ca. 1%. ^{b} Second-order rate constants corrected for hemiacetal concentration (this work). ^{c} Corrected second-order rate constants for the reaction of 1 with butylamine (data from ref 11, corrected for hemiacetal formation). ^{d} Equilibrium constants for hemiacetal formation calculated by interpolation of literature data by means of the YJ equation established in ref 22. ^{e} From ref 21.
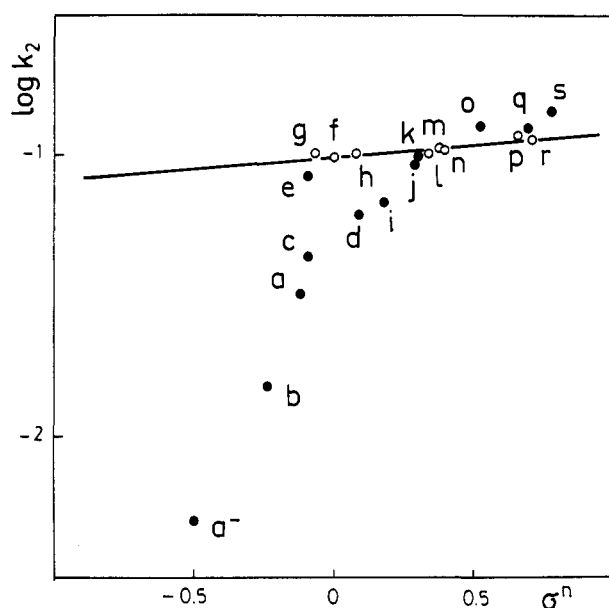

Figure 1. Plot of the hemiacetal formation-corrected second-order rate constants for N-arylidenepropylamine formation against the Wepster σ^n parameters: O, meta substituents; ●, para substituents.

the benzene ring.[25] As shown in Figure 2, a satisfactory linear relationship is observed when, following the Yukawa–Tsuno–Sawada[28] or Young–Jencks[2] procedure, the differences from the straight line are plotted against $\Delta\sigma_R^+$. The ρ^r observed, 0.57, is much larger than ρ^n. This indicates that the DR effects are much the most important. Equation 7 gives the coefficients of the two-parameter

$$\log k_2 = (0.10 \pm 0.07)\sigma^n + (0.62 \pm 0.05)\Delta\sigma_R^+ +$$
$$(-0.975 \pm 0.032) \qquad (r^2 = 0.964) \quad (7)$$

relationship calculated by a least-squares treatment based on Young–Jencks equation (eq 1).[23,29]
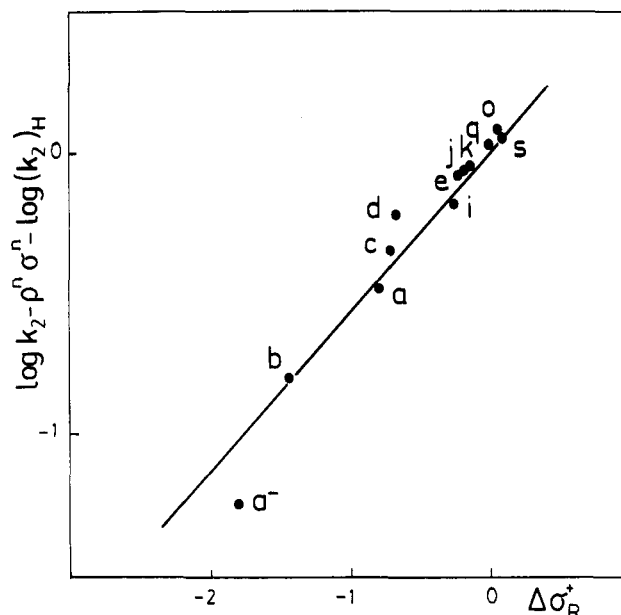
Figure 2. Plot of the deviations for the para substituents from the line on Figure 1 against the direct resonance $\Delta\sigma_R^+$ parameters.

The first-order rate constants for Schiff base formation in methanol were also measured in the case of **1c**, **1h**, and **1q** reacting with 2-methoxyethylamine, **3b**, and 2,2-dimethoxyethylamine (aminoacetaldehyde dimethyl acetal), **3c**. Figure 3 shows the dependence of log k_2 on the pK_a of the ammonium ions.[30] The reaction is slowed down when the entering amine is less basic than propylamine. The Brønsted slopes, β_{nucl}, are close to unity, 0.87, 0.94, and 1.06, respectively.

The dependence of k_ψ on the concentrations of the ammonium ions correspnoding to the amines used was briefly investigated. As shown in Table 2, the addition of propylammonium nitrate in the case of N-(4-methoxy-benzylidene)propylamine formation causes only a small increase in rate. As expected from kinetic data for imine formation in water,[8c,d] which primarily follows the mechanism in Scheme 2 with a slow OH$^-$-detachment step, the reaction is only weakly acid-catalyzed by ammonium ions. This small increase in k_ψ values cannot be ascribed to ionic strength effects. When propylammonium ion nitrate was replaced by tetramethylammonium bromide no change in k_ψ was observed.

(25) Although the σ^+ values[26] for 4-NO$_2$ and 4-CF$_3$ are rather close to the σ^n values[24] (0.790 and 0.612 instead of 0.778 and 0.53, respectively), the differences can be due to the π-electron-demanding effects of these groups, which reduce the ability of the benzene ring to provide π-electrons to the electron-deficient side chain. In the case of the CF$_3$ group, the π-accepting property has been ascribed to carbon–fluorine hyperconjugation. This point has been reviewed in ref 27. For the 4-CN group, the Brown–Okamoto σ^+ value (0.659) is surprisingly lower than that of σ^n (0.67[24b]), but the sum ($\sigma_I + \sigma_R^+$) from ref 3b is 0.69. In the following relationships, $\Delta\sigma_R^+$ was assumed to be zero for this group. As noted in the text, it can be thought that the 4-CF$_3$, 4-CN, and 4-NO$_2$ substituents reduce the π-electron-accepting properties of the phenyl group more when the side chain is much less π-electron-demanding than in the case of a carbenium ion center.

(26) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979.

(27) Stock, L. M.; Wasielewski, M. R. *Progr. Phys. Org. Chem.* **1981**, *13*, 253.

(28) Yukawa, Y.; Tsuno, Y.; Sawada, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 198.

(29) The $\Delta\sigma_R^+$ values are from ref 24b or calculated from σ^n and σ^+ data from refs 24a and 26, respectively.

(30) The pK_a values of the ammonium ions corresponding to **3a**, **3b**, and **3c** (11.95, 11.27 and 10.73, respectively) were measured as described in the Experimental Section.
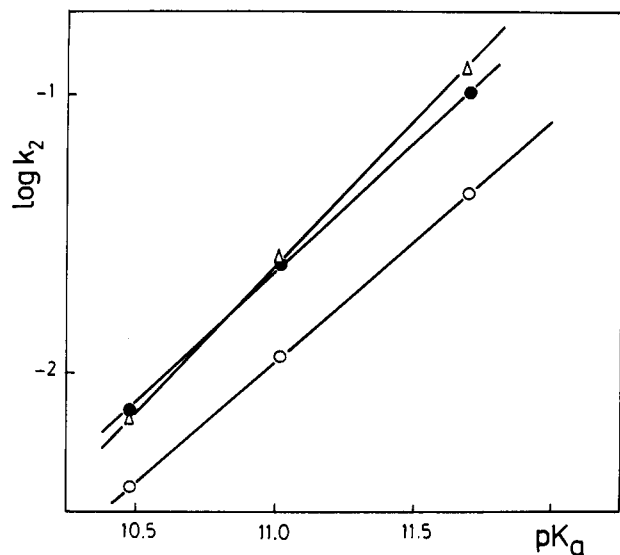
Figure 3. Dependence of the hemiacetal formation-corrected second-order rate constant for N-arylidenealkylamine formation on the pK_a of the corresponding ammonium ion: O, 1c; ●, 1h; △, 1g.[2]

Table 2. Dependence of the Second-Order Rate Constant for the Formation of N-(4-Methoxybenzylidene)propylamine at 25 °C on the Concentration of Ammonium Ion[a]

[RNH$_3^+$] (M)	k_ψ/[RNH$_2$] (M^{-1} s^{-1})	[RNH$_3^+$] (M)	k_ψ/[RNH$_2$] (M^{-1} s^{-1})
0.000	0.0432	0.032	0.0497
0.008	0.0449	0.040	0.0513
0.016	0.0457	0.064	0.0548
0.024	0.0475	0.080	0.0561

Table 3. Substituent-Dependence of the Kinetic Solvent Isotope Effect (KSIE) on the Second-Order Rate Constant for N-Arylideneaniline Formation and of the Enthalpy and Entropy of Activation

compd	KSIE[a]	$\Delta H^{\ddagger}$ [b] (kcal mol^{-1})	$-\Delta S^{\ddagger}$ [b] (cal mol^{-1} K^{-1})
1a		6.3 ● 0.3	44.4 ● 1.0
1a$^-$		7.6 ± 0.5	43.6 ± 1.5
1b	2.07	7.52 ± 0.10	41.6 ± 0.4
1c	2.26	6.10 ● 0.20	44.3 ± 0.7
1d		5.86 ± 0.08	44.4 ± 0.3
1e		5.42 ± 0.06	45.2 ± 0.2
1f	2.51	5.19 ± 0.10	45.6 ● 0.3
1g	2.57	5.16 ● 0.08	45.7 ± 0.2
1h	2.51	5.16 ± 0.10	45.7 ± 0.3
1i	2.26	5.54 ± 0.09	45.3 ± 0.3
1j	2.54	5.08 ● 0.05	46.4 ± 0.2
1k		5.21 ● 0.10	45.5 ± 0.3
1l		5.28 ● 0.08	45.4 ± 0.3
1m	2.61	5.30 ± 0.11	45.2 ± 0.5
1n		5.35 ± 0.07	45.0 ± 0.3
1o		5.40 ± 0.09	44.4 ± 0.4
1p		5.33 ± 0.10	44.9 ● 0.4
1q	2.84	4.99 ± 0.07	45.9 ± 0.3
1r		5.11 ± 0.05	45.7 ± 0.2
1s	2.86	4.66 ± 0.10	46.7 ± 0.3

[a] Average of the [(k_ψ/[RNH$_2$])/(k_ψ/[RND$_2$])] ratios observed for amine concentrations of 0.0394 and 0.0787 M in MeOH and MeOD. Standard deviations = ca. 0.05. Uncorrected for the protium content of the deuteriated solvent (<1%). [b] Calculated from data at 15, 20, 25, 30, and 35 °C. Figures after the ± sign are estimated standard deviations.

Table 3 lists the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values calculated from k_2 data at 15, 20, 25, 30, and 37 °C (±0.1 °C). The equilibrium constants K_{Hemi} at these temperatures were taken from ref 21 or estimated from the K_{Hemi} values at 25 °C. It was assumed that ΔS^0 is constant and equal to

97 J mol^{-1} K^{-1}, the average of the figures obtained for various benzaldehydes. The assumption that hemiacetal formation is isoentropic is based on the fact that the change in entropy is primarily due to loss of degrees of freedom due to methanol addition. Data in Table 3 show that $\Delta S^{\ddagger}$ is very negative and nearly constant throughout the series of the reactants.

Pseudo-first-order rate constants $(k_\psi)_D$ were measured for most of the 1a–s compounds in O-d-methanol for [n-PrNH$_2$] = 0.0394 and 0.0787 M. The mean KSIE values, corresponding to the ratios between k_ψ in MeOH and MeOD at these concentrations, are listed in Table 3. Although it is not known whether solvent isotope composition affects the hemiacetal formation equilibrium constant, it is expected that the effects on K_{Hemi} are small and that the KSIE values in Table 3 correspond to $(k_2)_H/(k_2)_D$. These data show that the change from MeOH to MeOD slows down the reaction by a factor 2.1–2.9 which increases smoothly when X becomes more electron-withdrawing.

Discussion

Mechanism of Schiff Base Formation. The kinetic data observed for imine formation from 1a–s are in agreement with the mechanism shown in Scheme 2 with rate-limiting dehydration of the α-amino alcohol intermediate. The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ data are consistent with those previously reported for similar reactions.[31] For instance, they are close to the figures obtained for oxime formation in water (4.8 kcal mol^{-1} and –45 cal mol^{-1} K^{-1}, respectively) under pH conditions which made α-amino alcohol dehydration rate-limiting; they are very different from those observed (12.9 kcal mol^{-1} and –17 cal mol^{-1} K^{-1}, respectively) for the same reaction when the hydroxylamine addition step was slow.[32] Since a change in rate-limiting step with substituent is therefore expected to induce dramatic variations, the smooth variations of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, as well as those of the solvent kinetic isotope effects, show clearly that there is no change in the rate-limiting step. The $\Delta H^{\ddagger}$ values are low because of compensation between exothermic α-amino alcohol formation and $\Delta H^{\ddagger}_{dh}$. The very negative $\Delta S^{\ddagger}$ values and the large direct KSIEs are typical of what is expected for a reaction which results in significant OH$^-$ release. The $\Delta S^{\ddagger}$ values of ca. –45 cal mol^{-1} K^{-1} can be interpreted as due to cumulative loss of degrees of freedom of the chemical species in the course of the reaction, those associated with preequilibrium (for example, –10 cal mol^{-1} K^{-1} by reference to other addition reactions of uncharged species to carbonyl compounds[33]) and those due to the hydrogen-bonding of methanol molecules to the leaving OH$^-$ ion (for example, –35 cal mol^{-1} K^{-1}). The observed KSIEs stem from the differences in the energies of the hydrogen bonds between OH$^-$ and the MeOH and MeOD solvating molecules (the reverse of what is usually observed for nucleophile-catalyzed reactions which involve OH$^-$ attachment[34]). The fact that the figures for $\Delta S^{\ddagger}$ and KSIE are large suggest that the transition state is late, corresponding to almost

(31) Reference 4, p 118.
(32) Domansky, R.; Juránková, O. *Z. Physik. Chem. (Leipzig)* **1960,** *215,* 133.
(33) Schaleger, L. L.; Long, F. A. *Adv. Phys. Org. Chem.* **1962,** *1,* 1.
(34) Laughton, P. M.; Robertson, R. E. In *Solute–Solvent Interactions*; Coetzee, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969; p 399.

complete C–O bond cleavage and strong solvation of the leaving group. The degree of C–O bond breaking at the transition state does not change much with substituent. ΔS^* is almost substituent-independent due to nearly constant solvation. Although larger than was expected in view of the small variations in ΔS^*, the dependence of KSIE on substituent can also be related to the decrease in the lateness of the transition state when the iminium ion is more stabilized.

The slopes of the Brønsted plots between log k_2 and ammonium ion pK_a are in excellent agreement with the above conclusions. Since they are close to unity, they indicate that the positive charge on the nitrogen atom at the transition state is similar to what it is in the corresponding ammonium ions, this resulting in the same inductive effects of the methoxy groups within R. Although the β_{nucl} values were determined from data for only three amines, the variations observed, from 1.06 for **1q** to 0.94 for **1h** and to 0.87 for **1c**, are in agreement with what is expected. The earlier the transition state, the weaker the positive charge on N. It is noteworthy that these β_{nucl} values are in agreement with those observed for imine formation from aliphatic aldehydes or ketones and primary amines in water. The β_{nucl} values of 0.80, 0.66, 0.60 and 0.59 were reported for isobutyraldehyde, 3-pentanone, cyclopentanone and acetone, respectively.[8d] For the three latter compounds, it is expected that the iminium ions formed are more stable than for aldehydes, this making the transition state earlier. Moreover, since the iminium cation should be less stable in methanol than in water because of the difference in the dielectric properties of the two solvents, the transition state is expected to correspond to a larger extent of C–O bond cleavage. It is interesting to note, however, that values are high as unity are larger than what is expected for a transition state resembling the (iminium ion + OH⁻) molecular system, even for a fully broken C–O bond. The positive charge in iminium ions is partly delocalized on the carbon atom, and the substituent effects of R on pK_a are weaker than for the parent ammonium ions. A straight line with a 0.85 slope was observed when the pK_a values for a series of Schiff bases, derived from benzophenones and various amines, were plotted against the pK_as of the corresponding amines.[35] If a similar 0.85 slope is assumed between the pK_a values for the iminium ions and the corresponding ammonium ions, the slopes of the straight lines between log k_2 and iminium ions pK_a would be 1.25, 1.11 and 1.02, for **1q**, **1h** and **1c**, respectively.[36]

Since the second-order rate constants k_2 are composite, the ρ^n and ρ^r coefficients of eq 7 correspond to the sums of the ρ values for K_{Aa} and k_{dh}. The fact that ρ^n is nearly equal to zero arises from almost complete compensation between the positive coefficient for α-amino alcohol formation and the negative one for the rate constant of the rate-limiting step. This is analogous to what is

Scheme IV
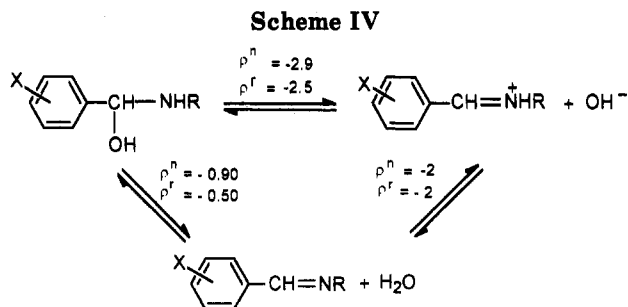
observed for semicarbazone formation in water for benzaldehydes bearing electron-withdrawing substituents.[4,13] The mechanism is similar, and the dehydration of the α-amino alcohol intermediate is also rate-limiting. The low ρ value of 0.09, which was explained in the same ways, is very close to that reported here. In contrast to the polar effects, the ρ^r values on K_{Aa} and k_{dh} do not compensate each other, the resulting ρ^r coefficient being positive, due to predominant effects on K_{Aa}.

Despite the lack of data for α-amino alcohol formation, the ρ^n and ρ^r coefficients for prior equilibrium can be safely estimated. It was shown that the equilibrium constants for the addition of uncharged species to benzaldehydes or acetophenones fit eq 1 with ρ^n and ρ^r values which express the dependence of the starting material energy on polar and DR effects. The polar coefficient, ρ^n, depends only on solvent, ca. 1.0 in water and 1.8–1.9 in methanol or dodecane; the resonance factor, ρ^r, is close to unity whatever the solvent.[22] This makes it possible to estimate the $\rho^n = 1.9$ and $\rho^r = 1.0$ coefficients for α-amino alcohol formation. It follows that ρ^n and ρ^r can be calculated as $-(1.8$–$1.9)$ and $-(0.5$–$0.6)$, respectively, for the OH⁻-detachment rate-limiting step. These latter values can be compared with those expected for a late transition state close to the (iminium ion + OH⁻) system, i.e., for the equilibrium between the α-amino alcohol and the iminium ion. As shown by Scheme 4, the ρ^n and ρ^r coefficients for this equilibrium can be estimated from the dependence on substituent of (i) the iminum ion acidity constant and (ii) of the equilibrium constant for α-amino alcohol formation from Schiff bases.

There is a shortage of data on iminium ion pK_a values. The acidity constants of protonated N-benzylideneanilines substituted at the benzaldehyde residue have been measured in nitromethane and shown to depend on σ^+ with $\rho^+ = -2.4$.[37] On the other hand, a ρ^+ value of -1.6 was reported for N-arylidene-2,2-dimethylethylamines in water.[38] In view of these data, it seems likely that the pK_a of the N-arylideneammonium ions should depend on σ^+ with ρ^+ about 2 in methanol.

It is reported in ref 1 that the equilibrium constants for methanol addition to N-arylideneanilines in methanol are accounted for by the YJ equation with $\rho^n = 0.87$ and $\rho^r = 0.54$. Because α-amino alcohol formation is analogous to α-amino ether formation, similar values for the imine-to-α-amino alcohol step are likely. As in the case of carbonyl compounds, the equilibrium constants for methanol or water addition depend primarily on the stability of the starting materials. The replacement of R = alkyl by R = phenyl is not expected to have a dramatic consequence

(35) Okuyama, T.; Shibuya, H.; Fueno, T. *J. Am. Chem. Soc.* **1982**, *104*, 730.

(36) It can be argued, however, that these coefficients do not correspond to the slopes of the lines between log k_2 and the logarithm of the α-amino alcohol-to-iminium ion equilibrium constant, which would express the degrees of resemblance of the transition state with products. It can be considered that iminium ion pK_as also depend on the polar effects of R on imine stability. These are expected to be fairly large because of the polarizability of the C=N group. It was reported that the equilibrium constant for methanol addition to N-benzylideneanilines substituted at the aniline moiety depends on σ^+ with a large ρ^+ coefficient (1.58) which can be attributed to polar and resonance effects on Schiff base energy (Ogata, Y.; Kawasaki, A. *J. Org. Chem.* **1974**, *39*, 1058) (see also ref 1).
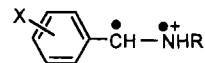
(37) Stepanov, B. I.; Korolev, B. A.; Rozanel'skaya, N. A. *J. Gen. Chem. USSR* **1969**, *39*, 1128.

(38) Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 832.

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on the effects of X.[39] It follows, as shown in Scheme 4, that the ρ^n and ρ^r coefficients can be estimated as –2.9 and –2.5, respectively.

Even though the above estimates are rough, they show that the ρ^n and ρ^r coefficients for the α-amino alcohol-to-iminium ion equilibrium constants are much larger than those derived for the rate constant k_{dh}. The ring polar effects on rate are only a little larger than half those estimated for full equilibrium; the direct resonance effects are surprisingly much weaker ($\rho^n = -0.5$ instead of –2.5). This means that the stabilization of the transition state by the DR effects is much less than that expected in view of the KSIE, $\Delta S^\ddagger$ and β_{nucl} data which favor a (iminium ion + HO⁻) transition-state model. Since the DR effect term is related to the change in carbon hybridization in the course of the reaction, it can be thought that this sp³-to-sp² change is not very advanced at the transition state. It is noteworthy that a similar conclusion can be drawn from reported data for Schiff base formation from cyclopentanone and 3-pentanone. The ratio between the rate constants k_2, 0.0534 and 0.001 38 M^{-1} s^{-1},[8d] respectively, which can be thought to depend on the differences in strain in iminium ions and carbonyl compounds, is much larger than that expected for a late transition state; it is close to that estimated (ca. 10–50[40]) if the rate were controlled by the ratio of the equilibrium constants for α-amino alcohol formation, resulting in a full sp²-to-sp³ change. Here also, even though the β_{nucl} are relatively large, the transition state can be considered as α-amino alcohol-like as far as the hybridization of the central atom is concerned. The unexpectedly small dependence of k_{dh} on conjugative effects is also in agreement with Hine's conclusions regarding the relative reactivities of acetone and isobutyraldehyde.[8d] Despite the resonance stabilization of the iminium ion intermediate by the two methyl groups of acetone, the k_{dh} constants are similar.

The lack of consistency between the conclusions drawn from the free energy relationships and other pieces of evidence is reminiscent of what is observed for many reactions and referred to as "imbalance phenomena" or manifestations of "imperfect synchronization".[41] Changes in molecular geometry and charge delocalization due to resonance interactions are not directly related to the degrees of bond breaking or bond formation. The kinetic data reported in this paper suggest a transition-state model with almost complete OH⁻ detachment from α-amino alcohol, but with a cationic moiety resembling the singlet biradical 4 instead of the iminium ion. The positive charge lies mainly on the nitrogen atom, and the hybridization

(39) It can be expected that the electron-withdrawing phenyl group of the aniline residue in benzylideneanilines increases the carbenium-ion character of Schiff bases and of the corresponding iminium ions. It follows that the ρ values for the formation of the α-amino alcohols might be a little lower than those indicated in Scheme 4. However, since—for the same reasons—the assumed ρ^+ value for imine protonation is probably a lower limit, the change of R from phenyl to alkyl is not expected to introduce major errors in the estimates ρ values for the rate constant of the α-amino ether-to-iminium ion step.

(40) Schneider, H. J.; Schmidt, G.; Thomas, F. *J. Am. Chem. Soc.* **1983**, *105*, 3556. Toullec, J.; Mladenova, M.; Gaudemar-Bardone, F.; Blagoev, B. *J. Org. Chem.* **1985**, *50*, 2569. For instance, ratios of ca. 20 were observed between the equilibrium constants for methanol (Garrett, R.; Kubler, D. G. *J. Org. Chem.* **1985**, *50*, 2569) or hydrogen cyanide (Prelog, V.; Kobelt, M. *Helv. Chim. Acta* **1949**, *32*, 1187) addition to cyclohexanone and cyclopentanone or between the rate constants for the reduction of these cycloalkanones by NaBH₄, a process which occurs via a product-like transition state (Brown, H. C.; Ichikawa, K. *Tetrahedron* **1957**, *1*, 221.

(41) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511. Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119 and references cited therein.

4

of the α carbon atom is closer to sp³ than to sp². When the reverse reaction between iminium ions and OH⁻ is considered, this means that the reaction is initiated by C=N double bond cleavage with only small OH⁻ transfer at the transition state.

Relevance of the Young–Jencks Treatment. The main point of this paper lies in the fact that the direct resonance (DR) effects on rate constants can be very predominant if the polar effects of a substituted phenyl ring, including the resonance-induced polar effects, are weak because of compensation phenomena. This point allows us to emphasize the necessity of distinguishing the RP effects from the DR effects and of using two- or three-parameter relationships involving such a separation. In contrast, the Taft DSP equation (eq 2) cannot be used since no σ_R parameter can cope with such a situation. The RP effect contribution is too small to allow the use of σ_R^+, the resonance parameter usually considered when dealing with strong electron demand of the side-chain reaction center. It is important to emphasize that the $\Delta\sigma_R^+$ parameters are used with success to express the DR effect associated with π-electron-donating substituents. This point is not trivial since, as stressed in ref 1, the σ^+ parameters have been defined from kinetic data for a carbenium ion-forming reference reaction for which the separation between the DR and RP effects is questionable. The electron transfers from or to the substituent to or from the aromatic ring are expected to be dependent on the electron donation to the highly electron-deficient side chain. It is possible, however, that some deviations from the straight line in Figure 2 stem from the relatively weak π-electron-demanding character of the reacting side chain. For instance, it can also be noted that the points for the 4-CN and 4-NO₂ substituents are slightly above the line. This might indicate that these groups alter the π-donating ability of the ring more than when the nucleus is much polarized by the presence of an adjacent positive charge.

General Conclusions

As a general conclusion of this and the preceding paper, it can be said that the Young–Jencks equation is probably the best way to deal with rate and equilibrium constants for situations analogous to those encountered here. In contrast to the DSP equation, it is possible to trace the variations of resonance between the aromatic ring and the reacting side chain associated with changes in the hybridization of the next-to-ring carbon atom. Moreover, the fact that the differences in ρ^n and ρ^r values for the direct and reverse rate constants correspond to those for full equilibrium is in this context a fundamental advantage. Although the basic assumptions, as well as the statistical least-squares treatments, are the same as when the Yukawa–Tsuno equation is used, we believe that the examination of the ρ^n and ρ^r coefficients is more informative than that of the r coefficient. This parameter corresponds to the ρ^n/ρ^r ratio of eq 1; it can be high, far beyond the usual 0–1 range (ca. 7 in the case of the title reaction), or even negative (–0.27 for α-amino ether cleavage[1]) when ρ^n and ρ^r have opposite signs.

The basic assumption behind the YJ and Yukawa–Tsuno–Sawada attempts to separate polar and resonance

effects lies in the assumption that the DR and RP effects are additive contributions to free energies. We thoroughly examined this point in ref 1 and concluded that this should not be rigorously true, especially when the resonance interactions between the reacting side chain and the ring are large. This does not mean that this treatment cannot be used, but that care should be taken when interpreting the coefficients in terms of cross-resonance energies, especially when these are large. As emphasized above, the success of the $\Delta\sigma_R^+$ parameters in expressing the DR effect is a little surprising but, as a matter of fact, they work.

The YJ treatment is clearly limited to situations such that the ratios between the inductive effect (ρ_I) and RP effect (ρ_R^0) coefficients in the three-term eq 8 can be taken

$$\log k \text{ or } \log K = \rho_I\sigma_I + \rho_R^0\sigma_R^0 + \rho^r\Delta\sigma_R^+ + C \quad (8)$$

as unity. When this assumption is not valid eq 8 (or that with a $\rho_R^n\sigma_R^n$ term equivalent to $\rho_R^0\sigma_R^0$) is an interesting alternative to the DSP equation. Its use cannot be avoided when the relative RP and DR contributions to the overall resonance term differ too much from those to the different σ_R parameters.

In these two papers, we have only considered reactions involving an electron-deficient reacting site at the initial, final, or transition state, with rate and equilibrium constants depending on π-electron-donating effects. It is evident that a similar YJ equation using a $(\rho^r)^-\Delta\sigma_R^-$ term [with $\Delta\sigma_R^- = (\sigma^- - \sigma^n)$] can be used for reactions depending on π-electron-demanding resonance effects. It can even be thought that the $\Delta\sigma_R^-$ and $\Delta\sigma_R^+$ contributions should coexist in one of the following situations: (i) when the energies of the transition state (or products) and of the initial state both depend on resonance effects, one of the two on π-electron-donating effects and the other on π-electron-demanding ones, or (ii) when there is overlap between the π-orbitals of the substituted ring and two different localized orbitals within the reacting side chain. In such situations the three-term eq 9 is expected to deal

$$\log k \text{ or } \log K = \rho^n\sigma^n + (\rho^r)^+\Delta\sigma_R^+ + (\rho^r)^-\Delta\sigma_R^- + C \quad (9)$$

with the experimental data. We shall show in a forthcoming paper that this behavior is observed in the case of reactivity data for *N*-benzylideneanilines **5**. For these

5
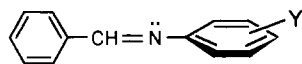
compounds the π-orbitals of the Y-substituted rotated ring interact both with the π orbitals of the C=N bond and with the nitrogen lone-pair orbital. It is clear that neither the DSP equation nor the Yukawa–Tsuno–Sawada equation can be used in this case.

Experimental Section

Reagents. Substituted benzaldehydes were obtained from Aldrich or Janssen Chimica and were kept under nitrogen. "Analyzed Baker Reagent" methanol was used as received. **3a–3c**, supplied by Janssen Chimica, were distilled before use. Purity was checked by GC. Primary ammonium nitrate solutions were prepared by neutralization of the corresponding amine by nitric acid (Fluka, 100%). *O-d*-Methanol was obtained from the CEA, France (deuterium ≥99.0%; D_2O content ≤0.1%).

Kinetic Measurements. UV–vis absorption spectra and kinetics were recorded either with (i) a Varian/Cary 210 spectrometer, equipped with the Wavelength Programmer 954100, the Temperature Readout 954300, and a laboratory-designed digital acquisition unit,[42] or (ii) a Perkin-Elmer Lambda 2 spectrophotometer equipped by a PTP-6 Peltier temperature programmer. In the latter case, temperature (25 ± 0.05 °C) was checked in the cell by a Portable Thermistor thermometer, Cole Parmer Instrument Co., Model 8502-16 (thermistance detector YSI 400). After microsyringe addition of 10–25 μL of the substituted benzaldehyde in dioxane (ca. 10^{-2} M) in the 1-cm cell containing the amine solution, kinetic runs were recorded at the following wavelengths (λ in nm): **1a**, 330; **1b**, 345; **1c**, 268; **1d**, 260; **1e**, 256; **1f**, 246; **1g**, 248; **1h**, 248; **1i**, 247; **1j**, 254; **1k**, 255; **1l**, 245; **1m**, 244; **1n**, 244; **1o**, 240; **1p**, 240; **1q**, 257; **1r**, 235; and **1s**, 240. Rate constants were calculated by microcomputer by means of a program based on the Guggenheim or phase plane[42,43] methods.

The pK_a values for the ammonium ions derived from **3a** (11.70), **3b** (11.02), and **3c** (10.48) were measured spectrophotometrically from the absorbance at 390 nm of 4-nitrophenol ($pK_a = 11.20$[19]) in buffer solutions prepared by mixing amine and ammonium nitrate solutions. The apparent differences between ammonium ion pK_a values and that of the indicator used were taken as corresponding to half-absorbance on the curve of the apparent molar absorption coefficients of the partially dissociated phenol vs log ([Am]/[AmH$^+$]). Since the proton-transfer equilibrium between the indicator and the primary amine results in the formation of charged species, the pK_a data were corrected, as described in ref 44, for ionic strength. This correction amounts to -0.50 pK_a unit.[45] For **3a**, the data obtained are very close to those reported in the literature for other primary alkylamines in methanol[39] (e.g., 11.78 for *n*-butylamine[47]).

(42) Meyer, J. J.; Paumard, J. L.; Milin, D.; Levoir, P.; Fontaine, J. C. *Talanta* **1988**, *35*, 869.

(43) Bacon, J. R.; Demas, J. N. *Anal. Chem.* **1983**, *55*, 653.

(44) Gold, V.; Toullec, J. *J. Chem. Soc., Perkin Trans. 2* **1979**, 596.

(45) Uncorrected pK_a values were used in ref 46.

(46) Toullec, J.; Razafindralambo, R. *J. Org. Chem.* **1987**, *52*, 1646.

(47) Goodhue, L. D.; Hixon, R. M. *J. Am. Chem. Soc.* **1934**, *56*, 1329.