ability is in turn only one of the many complex interacting factors influencing pK_a's.

Experimental Section

Ultraviolet absorption spectra were determined on a Cary Model 14 recording spectrophotometer with matched 1-cm silica cells. Concentrations were $3–5 \times 10^{-5}$ *M*. The reported data represent the average of two determinations for each spectrum, with occasional checks that λ_{max} did not vary with concentration. All solvents were Spectro Grade or the best grade commercially available and were checked by glpc to confirm the absence of significant impurities.

Registry No.—4-Nitroaniline, 100-01-6; *N*,*N*-diethyl-4-nitroaniline, 2216-15-1; *N*-ethyl-4-nitroaniline, 3665-80-3; 4-nitrophenol, 100-02-7; 4-nitroanisole, 100-17-4.

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Substituent and Secondary Deuterium Isotope Effects for Hydrolysis of Schiff Bases[1]

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The inverse kinetic secondary deuterium isotope effect, k_D/k_H, for attack of hydroxide ion on the conjugate acids of substituted *N*-benzylidene-1,1-dimethylethylamines is near 1.22 and is independent of the nature of the polar substituent. The same isotope effect for the attack of water on the conjugate acid of *N*-4-methoxybenzylidene-1,1-dimethylethylamine is 1.20. Thus, transition states for these reactions resemble the adducts more closely than the substrates. Second-order rate constants for the attack of hydroxide ion on substituted *N*-(substituted)-benzylideneanilines are correlated by the Hammett σ constants. Values of ρ near 2.7 were obtained in all cases except for the Schiff bases derived from 4-nitrobenzaldehyde, for which a value of 1.9 was found. These large values are consistent with adduct-like transition states for Schiff base hydrolysis.

Previous studies of addition of nucleophilic reagents to Schiff bases derived from aromatic aldehydes have sufficed to establish a number of points pertinent to these reactions.[3] Some general conclusions include (i) the rate-determining step for hydrolysis changes from nucleophile attack to intermediate decomposition as the solution pH is lowered;[4-9] (ii) the conjugate acids of Schiff bases are very much more reactive toward nucleophilic attack than are the free bases;[6-10] (iii) the basicity of the departing amine has a marked influence on the kinetics of Schiff base hydrolysis—decreasing basicity decreases reactivity under basic but increases reactivity under acidic conditions;[6,8,9] and (iv) the addition of nucleophilic reagents to Schiff bases is subject to general acid–base catalysis.[5,8,9,11,12]

Having a general understanding of the course and kinetics of these reactions, it appears desirable to begin to probe the structure of the associated transition states and the variation in such structures with substrate reactivity in more detail. This manuscript reports the results of some efforts in this direction. Two approaches have been employed: kinetic secondary deuterium isotope effects and effects of polar substituents. The former have been studied employing *N*-benzylidene-1,1-dimethylethylamines deuterated at the aldehydic carbon as substrates and the latter using *N*-benzylideneanilines. In both cases the magnitude of the observed effects has been probed as a function of the nature of the polar substituent in the benzaldehyde moiety.

Experimental Section

Materials.—Substituted *N*-(substituted)-benzylideneanilines were prepared by the direct condensation of the appropriate aldehydes and anilines. All such substrates were recrystallized to constant melting point or carefully redistilled prior to use. *N*-Benzylidene-1,1-dimethylethylamines were prepared as previously described.[8] Benzaldehyde-*1-d* was prepared by oxidation of benzoin-*1-d* in tetrahydrofuran at 17° by the slow addition of D_5IO_6, prepared by exchanging H_5IO_6 with D_2O. Following completion of the reaction, the solvent was removed on a rotary evaporator and the benzaldehyde-*1-d* was isolated as the bisulfite complex. The deuterated benzoin substrate was prepared by refluxing for 24 hr a solution of 0.43 mol of benzoin, 1.00 mol of D_2O, and 0.001 mol of NaOH in 450 ml of dioxane. The dioxane–water azeotrope was removed by distillation and the exchange process was repeated. 4-Methoxybenzaldehyde-*1-d* was prepared in the same way, beginning with 4,4′-dimethoxybenzoin. 3-Bromobenzaldehyde-*1-d* was prepared by the bromination of benzaldehyde-*1-d*.[13] Proton magnetic resonance spectra of neat benzaldehyde-*1-d* samples revealed that each had an isotopic purity of at least 98%. Reagent grade salts and distilled water were employed throughout.

Kinetic Methods.—All reactions were followed spectrophotometrically employing Zeiss PMQ II spectrophotometers equipped with cell holders through which water from a constant-temperature bath was continuously circulated. Reactions were ordinarily monitored at wavelengths near the absorption maximum of the Schiff base under study. Spectra recorded at the conclusion of the hydrolysis reactions corresponded to those of a mixture of the appropriate aldehyde and amine. For those reactions not involving determination of secondary isotope effects, first-order rate constants were obtained from semilogarithmic plots of the difference in optical density and infinite time optical density

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[2] Career Development Awardee of the National Institutes of Health.

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TABLE I

SECONDARY DEUTERIUM ISOTOPE EFFECTS FOR THE HYDROLYSIS OF *N*-(SUBSTITUTED)-BENZYLIDENE-1,1-DIMETHYLETHYLAMINES AT 25°

Substituent	Registry no.	pH	Solvent[a]	k_D/k_H[b]	σ_{mean}
3-Bromo	28405-57-4	0.1 *M* NaOH	45.7% aqueous ethanol	1.224	±0.004
Unsubstituted	6852-58-0	0.1 *M* NaOH	58.2% aqueous ethanol	1.222	±0.005
4-Methoxy	15875-74-8	0.1 *M* NaOH	64.2% aqueous ethanol	1.224	±0.004
4-Methoxy		4.62	Water	1.199	±0.002

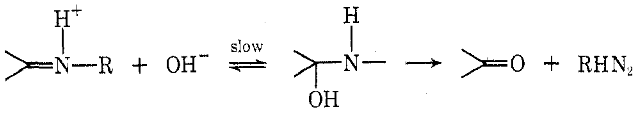
[a] Solvent composition was chosen so as to obtain reaction half-lives near 30 min. [b] Mean of five observations.

against time in the usual way. Second-order rate constants were calculated from slopes of plots of first-order rate constants against the concentration of hydroxide ion. In those cases involving determination of secondary deuterium isotope effects, first-order rate constants were obtained by linear regression analysis as previously described.[14] These rate constants were reproducible to within ±1%.

Results and Discussion

Kinetic secondary deuterium isotope effects have been successfully employed in a number of cases, particularly solvolytic reactions, to define transition state structures.[15,16] This technique has been applied in relatively few cases for the study of reactions involving substrates at the carbonyl level of oxidation, and a conflicting pattern of results has emerged from these studies in some cases.[17-19] A recent study of secondary deuterium isotope effects for acetal hydrolysis has provided new insight into these reactions.[14] These findings have prompted our study of such effects for Schiff base hydrolysis.

It has been established that the rate-determining step for pH-independent hydrolysis of *N*-benzylidene-1,1-dimethylethylamines involves the attack of hydroxide ion on the conjugate acids of the substrates.[8]



In Table I, secondary deuterium isotope effects are collected for the attack of hydroxide ion on the protonated Schiff bases derived from 3-bromo, 4-methoxy, and unsubstituted benzaldehydes. As expected, the isotope effect is inverse; *i.e.*, the deuterio substrates react more rapidly than the protio ones. In each case the rate ratio is near 1.22. While the maximal isotope effect for the addition of oxygen nucleophiles to carbon–nitrogen double bonds has not been experimentally established, analogy to related systems suggests that the observed value is close to the maximal one.[16] Thus, the sp^2 carbon atom of the substrate has been largely converted to sp^3 geometry in the transition state; *i.e.*, carbon–oxygen bond formation is nearly complete in the transition state. The extent of carbon–oxygen bond formation, as measured by the isotope effect, is independent of the nature of the polar substituent. This result contrasts with the observation that the extent of carbon–oxygen bond cleavage in the hydrolysis of diethyl acetals of benzaldehydes changes markedly as a function of the nature of the polar substituent.[14]

Under more acidic conditions, the attack of water, rather than hydroxide ion, on the protonated Schiff bases becomes the predominant reaction pathway.[3,8] The secondary deuterium isotope effect for the hydrolysis of *N*-4-methoxybenzylidene-1,1-dimethylethylamine at pH 4.62 is included in Table I. Under these conditions the rate of carbinolamine decomposition contributes not more than 10% to the overall reaction rate. The magnitude of the isotope effect is similar to that for the attack of hydroxide ion, indicating that, in this case too, the carbon–oxygen bond is well-formed in the transition state. This is certainly the expected result based on the earlier observations. It would be hard to rationalize an observation suggesting that the transition state for the attack of water on the Schiff base occurred appreciably sooner along the reaction coordinate than that for attack of hydroxide ion.[20] A previous investigation has established that the attack of water on protonated *N*-benzylidene-1,1-dimethylethylamines is slightly more sensitive to the nature of polar substituents than is the attack of hydroxide ion.[8] This would suggest that the transition state for the former reaction is reached somewhat later along the reaction coordinate than is that for the former. However, the secondary deuterium isotope effects do not provide support for this suggestion. It is possible that factors other than degree of carbon–oxygen bond formation, particularly electrostatic factors, may account for the observed difference in ρ values.

Within a series of closely related reactions, such as the attack of the same nucleophilic reagent on structurally related substrates, values of ρ potentially yield useful information concerning transition state structures, and the variation in ρ with substrate reactivity may indicate how these structures vary as a function of reactivity.[6] There have, in fact, been rather few studies of the effect of the variation in substrate reactivity on values of ρ. A model study of this type has been carried out by Kirsch, *et al.*, who have examined the alkaline hydrolysis of acyl- and aryl-substituted phenyl benzoates.[21] These workers observed that the values of ρ for alkaline hydrolysis of aryl-substituted phenyl benzoates did not vary detectably as a function of the nature of the polar substituent in the acyl moiety. In efforts to more fully define the transition state for Schiff base hydrolysis, we have studied a related set of reactions: the alkaline hydrolysis of substituted *N*-(substituted)-benzylideneanilines.

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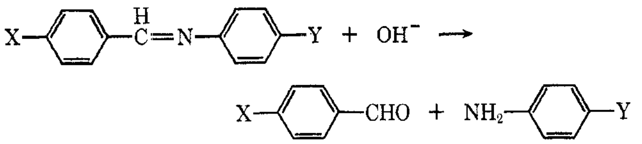
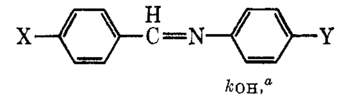


It has previously been established that hydrolysis of these substrates under alkaline conditions exhibits both pH-independent and base-catalyzed reaction routes.[6,8] The former reflects attack of hydroxide ion on the protonated substrates and the latter reflects the attack of this nucleophile on the corresponding free bases. In Table II second-order rate constants for the base-catalyzed reaction and first-order rate constants for the pH-independent hydrolysis for a series of substituted *N*-benzylideneanilines are collected. In each case, the rate constants have been calculated, respectively, from the slope and intercept of plots of first-order rate constants against hydroxide ion concentration. Base concentrations of 0.05, 0.10, 0.20, and 0.40 *M* were generally employed. For those Schiff bases possessing electron-donating substituents, the pH-independent reaction was frequently so great as to mask the basic reaction; for those possessing electron-withdrawing substituents, the converse was frequently true.

TABLE II

RATE CONSTANTS FOR THE pH-INDEPENDENT AND BASE-CATALYZED HYDROLYSIS OF SUBSTITUTED BENZYLIDENEANILINES IN WATER AT 30° AND IONIC STRENGTH 0.50



X	Y	k_{OH},[a] M^{-1} min^{-1}	k_0,[b] min^{-1}
CH_3O	CH_3O		0.029
	CH_3		0.033
	H	0.054	0.022
	Cl	0.088	0.023
	CH_3CO	1.52	0.025
	NO_2	5.8	
CH_3	CH_3O		0.020
	CH_3		0.050
	H	0.09	0.013
	CH_3CO	1.96	
	NO_2	10.6	
H	CH_3	0.045	0.023
	H	0.076	0.014
	Cl	0.25	
	CH_3CO	3.75	
	NO_2	9.5	
Cl	CH_3	0.061	0.043
	H	0.185	0.010
	COOH	0.90	0.038
	Cl	1.07	
	CH_3CO	5.3	
	NO_2	17.3	
NO_2	CH_3O	0.37	
	CH_3	0.57	
	H	1.03	
	Cl	3.0	
	NO_2[c]	26.0	

[a] Second-order rate constants for the attack of hydroxide ion on the Schiff bases. [b] First-order rate constants for the pH-independent hydrolysis reaction. [c] *m*-Nitro.

Note that the values of the pH-independent rate constants vary rather little with the nature of polar substituent in either the aldehyde or amine moiety, in accord with previous observations.[22] This finding reflects the opposing effects of polar substituents on substrate protonation and hydroxide ion attack. In contrast, second-order rate constants for hydroxide ion attack on the free bases increase rapidly with increasing electron withdrawal. Plots of the logarithm of these rate constants against σ values for aniline-substituted Schiff bases yield fair (but not excellent) straight lines from which values of ρ have been calculated. (Surprisingly, corresponding plots of rate constants for benzaldehyde-substituted Schiff bases did not yield satisfactory Hammett plots.) The following values of ρ were obtained for the indicated benzaldehyde-substituted substrates: 4-methoxy, 2.6; 4-methyl, 2.7; unsubstituted, 2.6; 4-chloro, 2.7; and 4-nitro, 1.9. Two points are of note here. First, these are the largest values of ρ observed for the attack of a nucleophile on Schiff bases. For example, rate constants for attack of water, hydroxylamine, and methoxyamine on protonated benzhydrylidenemethylamines yield values of ρ^+ near unity;[9] attack of water on protonated benzhydrylideneimines generates a ρ value of 2.0;[23] and on protonated *N*-benzylidene-1,1-dimethylethylamines a value of ρ^+ of 1.7 is obtained.[8] Finally, rate constants for attack of hydroxide ion on protonated *N*-benzylidene-1,1-dimethylethylamines are correlated by a ρ^+ value of 1.26.[8] All of the above substrates, reacting as the conjugate acids, are substantially more reactive than those studied here; the variation in sensitivity to polar substituents may reflect a difference in extent of carbon–oxygen bond formation in the transition state, although other factors may be important as well. Additional studies of secondary deuterium isotope effects for the pertinent reactions would be of interest. At any event, the large values suggest a good deal of carbon–oxygen bond formation in the transition states.

Second, values of ρ are, with the exception of those for the substrates derived from 4-nitrobenzaldehyde, independent of the nature of the polar substituent on the benzaldehyde moiety, a situation similar to that encountered by Kirsch, *et al.*[21] Only the slightly smaller value for the 4-nitro derivatives, the most reactive substrates, provides a suggestion of a detectable change in transition state structure with changing substrate reactivity.

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