0.05, *i.e.*, indistinguishable from 1. For the system of eq 1 a similar inversion plot in 65% DMSO had afforded an intercept of 1.35 from which K_2 was calculated.[3] We now have serious reservations about this value because of a possibly erroneous extinction coefficient (ϵ_3). For lack of any better value we were forced to use ϵ_3 determined in 85% DMSO. Our present study indicates that ϵ_6 decreases from 32,200 in 80% DMSO to 21,000 in 50% DMSO. If ϵ_3 depends in a similar way on the solvent as does ϵ_6, the true intercept of said inversion plot would become indistinguishable from 1.

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Equilibrium Additions of Nucleophiles to Carbon-Nitrogen Double Bonds in Nonaqueous Solutions. Addition of Alcohols to Substituted Benzylideneanilines

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Received September 25, 1973

Rate and equilibrium constants for the base-catalyzed addition of methanol to benzylideneanilines in methanol–acetonitrile (90:10 v/v) were determined by means of spectrophotometry. The equilibrium constant increases by electron-withdrawing substituents in the aniline ring as well as in the benzylidene ring, showing a correlation with the σ^+ constants. Also the rate constant increases by electron-withdrawing groups, showing a correlation with σ in this case. The solvent deuterium isotope effects are 0.98 for K_0^{MeOH}/K_0^{MeOD} and 0.60 for k_f^{MeOH}/k_f^{MeOD}. The structural change of alcohol leads to the Taft equation for equilibrium constant, K_0: log $(K_0^X/K_0^{Me}) = -8.2\sigma^* + 0.48E_s$. The rate decreases in the order *n*-BuOH > EtOH > MeOH > *sec*-BuOH > *t*-BuOH > *i*-PrOH, showing no simple correlation. The observed base catalysis, substituent effect, and solvent isotope effect are best explained by a mechanism involving a rate-determining attack by the alkoxide ions on the imino carbon atom. Thermodynamic parameters are calculated.

Equilibrium additions of nucleophiles to C═O bonds have been extensively studied[1] but the studies on the additions to C═N bonds are few except for the hydrolysis of Schiff bases[2-5] and for the additions of amines[5] and of hydrogen cyanide.[6,7] Only a few reports have paid attention to the addition of alcohols to C═N.[2,8,9] Because of the higher basicities[2-4] and lower electrophilicity of C═N than those of C═O,[1] these reactions involve the protonated Schiff bases, where negative ρ values have been observed.[2-7]

The present report describes the base-catalyzed equilibrium addition of alcohols to benzylideneanilines **1–11** in which no subsequent reactions such as C—N cleavage in hydrolysis occur.

$R^1C_6H_4CH{=}NC_6H_4R^2$

Compd	R¹	R²	Compd	R¹	R²
1	*p*-NO₂	*m*-NO₂	**7**	H	*m*-NO₂
2	*p*-NO₂	*m*-Cl	**8**	H	*m*-Cl
3	*p*-NO₂	*p*-Cl	**9**	H	*p*-Cl
4	*p*-NO₂	H	**10**	H	H
5	*p*-NO₂	*p*-Me	**11**	*p*-Cl	H
6	*p*-NO₂	*p*-OMe			

Results

Base-Catalyzed Addition of Methanol. The stoichiometry of equilibrium addition of methanol to benzylideneanilines was confirmed by the decrease in extinction at 340 nm in the uv spectrum and appearance of the CH proton at *ca.* τ 4.5 with a decrease in the CH═ proton at τ 1.7 in the nmr spectrum. The addition in neutral methanol solution requires several days to reach an equilibrium, while in the presence of a basic catalyst it is much more rapid. Addition of acetonitrile to the basic equilibrium solution causes the extinction at 340 nm to increase until a new equilibrium position is established, because of the decrease in methanol concentration. Moreover, the value of equilibrium constant, K_0, evaluated in terms of a following stoichiometry from the decrease in extinction of a Schiff base, is consistent with that evaluated from the relative strengths of the CH proton signal *vs.* the -CH═ proton signal in the nmr spectrum of the solution. Hence

$$R^1C_6H_4CH{=}NC_6H_4R^2 + MeOH \overset{K_0}{\rightleftharpoons} R^1C_6H_4CH(OMe){-}NHC_6H_4R^2$$

Although rapid solvolysis of Schiff bases occurs in acidic methanol to afford the corresponding benzaldehyde dimethyl acetals and anilines, no solvolysis occurs in alkaline methanol.

Effect of Substituent in Benzylideneanilines. The equilibrium and rate constants for addition of methanol to benzylideneanilines are shown in Table I. *N*-Benzylideneanilines with a single electron-releasing group such as methyl or methoxy have very small equilibrium constants showing only poor addition of the alcohol ($K_0 \leq 10^{-3}\ M^{-1}$ based on ≤1% conversion of Schiff base).

The equilibrium constants show a good correlation with the Brown–Okamoto's σ^+ constant,[10] giving a ρ^+ value of 1.42 (r = 0.993) at 15°, 1.41 (r = 0.994) at 25°, and 1.43 (r = 0.995) at 30° for *N*-(*p*-nitrobenzylidene)(substituted anilines), 1.58 for *N*-benzylidene(substituted anilines), and

Table I
Equilibrium and Rate Constants for the Addition of Methanol to Benzylideneanilines at 25° in Methanol–Acetonitrile (90:10 v/v)[a]

Compound	Registry no.	Substituent R^1	Substituent R^2	10^3K_0, M^{-1}	$10^5k_f^{\mathrm{MeOH}}$,[b] M^{-1} sec^{-1}	k_f^{MeOH},[c] M^{-1} sec^{-1}
1	10480-07-6	p-NO$_2$	m-NO$_2$	65 ± 1	176 ± 6	6.6
2	10480-21-4	p-NO$_2$	m-Cl	31.5 ± 0.5	23.5 ± 0.5	0.88
3	14796-61-3	p-NO$_2$	p-Cl	16.4 ± 0.1	9.5 ± 0.1	0.36
4	785-80-8	p-NO$_2$	H	7.1 ± 0.1	1.6 ± 0.2	0.06
5	730-39-2	p-NO$_2$	p-Me	3.6 ± 0.2	1.03 ± 0.04	0.04
6	5455-87-8	p-NO$_2$	p-OMe	0.6 ± 0.2	~0.04	~0.015
7	5341-44-6	H	m-NO$_2$	23 ± 1	7.5 ± 0.3	0.28
8	7519-65-5	H	m-Cl	8.6 ± 0.2	1.35 ± 0.10	0.051
9	780-21-2	H	p-Cl	3.5 ± 0.1	0.54 ± 0.06	0.020
10	538-51-2	H	H	1.5 ± 0.05	0.39 ± 0.07	0.015
11	2362-79-0	p-Cl	H	2.6 ± 0.2	0.28 ± 0.02	0.011
2		p-NO$_2$	m-Cl	32[d]	39[d]	

[a] [KOH] = 0.006 M. [b] Apparent second-order rate constants calculated from the concentration of MeOH. [c] Second-order rate constants calculated from experiments at a single KOH concentration. [d] In MeOD–MeCN (90:10 v/v). Solvent deuterium isotope effect is 0.98 for $K_0^{\mathrm{MeOH}}/K_0^{\mathrm{MeOD}}$ and 0.60 for $k_f^{\mathrm{MeOH}}/k_f^{\mathrm{MeOD}}$.

Table II
Base Catalysis for the Addition of Methanol to *N*-(*p*-Nitrobenzylidene)-*m*-chloroaniline (2) at 25° in Methanol–Acetonitrile (90:10 v/v)

KOH, M	10^2K_0, M^{-1}	$10^5k_f^{\mathrm{MeOH}}$,[a] M^{-1} sec^{-1}
0.0006	3.15	1.60
0.0012	3.2	3.54
0.0030	3.2	10.5
0.0048	3.2	17.3
0.0060	3.2	23.1

[a] Apparent second-order rate constant based on the concentration of MeOH.

Table III
Equilibrium and Rate Constants for the Addition of Alcohols to *N*-(*p*-Nitrobenzylidene)-*m*-chloroaniline (2) at 25° in ROH–MeCN (90:10)[a]

R in ROH	Registry no.	10^2K_0, M^{-1}	10^5k_f, M^{-1} sec^{-1}
Me	67-56-1	3.2 ± 0.05	23 ± 0.1
Et	64-17-5	2.4 ± 0.1	58 ± 0.1
n-Bu	71-36-3	3.7 ± 0.1	140 ± 8
i-Pr	67-63-0	11 ± 1	1.9 ± 0.1
sec-Bu	78-92-2	7.6 ± 0.2	5.0 ± 0.4
t-Bu	75-65-0	22 ± 1	4.8 ± 1.5

[a] [KOH] = 0.0006 M.

0.86 for *N*-(substituted benzylidene)anilines at 25°. An electron-withdrawing group both in the aniline and benzylidene rings increases the equilibrium constants, and the polar effect of the substituent in the aniline ring is a little larger than in the benzylidene ring. On the other hand, the forward rate constants are correlated with σ, giving a ρ value of 2.66 (r = 0.995) at 15°, 2.65 (r = 0.994) at 25°, and 2.80 (r = 0.999) at 30° for *N*-(*p*-nitrobenzylidene)(substituted anilines) and 1.7 for *N*-benzylidene(substituted anilines). An electron-withdrawing group (p-NO$_2$ and p-Cl) in the benzylidene ring also increases the rate constant.

Base Catalysis. The apparent second-order rate constant based on the concentration of methanol is proportional to the concentration of added potassium hydroxide. As methanolic KOH contains a much larger amount of the methoxide ions than the hydroxide ions,[7] the rate equation is $v_f = k_f^{\mathrm{MeO^-}}[\mathrm{C{=}N}][\mathrm{MeO^-}]$, where C=N is benzylideneaniline. The value of $k_f^{\mathrm{MeO^-}}$ for *N*-(*p*-nitrobenzylidene)-*m*-chloroaniline was calculated to be 0.88 M^{-1} sec^{-1} at 25° from the plotted data in Table II.

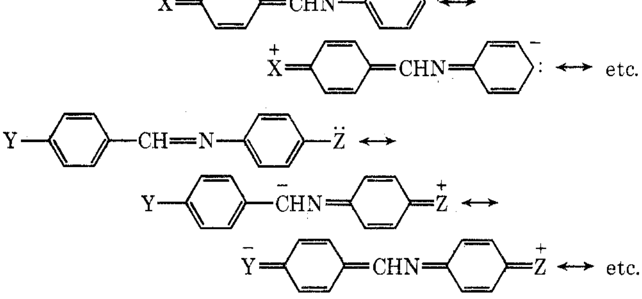
Solvent Isotope Effect. Table I shows that the solvent deuterium isotope effects on the equilibrium constant $K_0^{\mathrm{MeOH}}/K_0^{\mathrm{MeOD}}$ and rate constant $k_f^{\mathrm{MeOH}}/k_f^{\mathrm{MeOD}}$ for the base-catalyzed addition of methanol to *N*-(*p*-nitrobenzylidene)-*m*-chloroaniline (**2**) are 0.98 and 0.60, respectively.

Effect of Structure of Alcohols. The equilibrium and rate constants with some alcohols are presented in Table III. Application of the Taft equation to the equilibrium constants gave a ρ^* value of −8.2 and a δ value of 0.48 in the Taft equation,[11] $\log (K_0^{\mathrm{X}}/K_0^{\mathrm{ME}}) = \rho^*\sigma^* + \delta E_{\mathrm{S}}$, where σ^* and E_{S} are polar and steric substituent constants, and ρ^* and δ are polar and steric reaction constants, respectively. The polar effect on the equilibrium constant is larger than the steric effect. Methanol showed a positive deviation from the line. On the other hand, application of the Taft equation to the rate constant is less satisfactory in the case where the steric effect is larger than the polar effect. Thus, the rate constants for primary alcohols are larger than those for secondary and tertiary alcohols.

Effect of Temperature. Thermodynamic properties were calculated from the data at 15, 25, and 30° in methanol–acetonitrile (90:10 v/v) and are shown in Table IV.

Discussion

These reactions are base-catalyzed equilibrium additions. A few examples of such base-catalyzed additions to carbon-nitrogen double bonds have been reported, *e.g.*, the addition of diethyl phosphonate to benzylideneanilines,[12] dehydration of carbinolamine intermediates (the reverse of the addition of water)[13,14] and hydrolysis of some benzylideneanilines with strong electron-withdrawing groups.[2] The observed correlation of the equilibrium constant with σ^+ suggests that the following resonance



X = Z = OMe; Y = NO$_2$

Table IV
Temperature Effect for the Addition of Methanol to *N*-(*p*-Nitrobenzylidene)-(substituted anilines) in Methanol–Acetonitrile (90:10 v/v)[a]

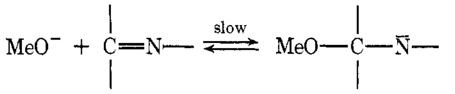
Compd	Substituent R^2	$\Delta F°$, kcal mol^{-1}	$\Delta H°$, kcal mol^{-1}	$\Delta S°$, eu	ΔF^*, kcal mol^{-1}	ΔH^*, kcal mol^{-1}	ΔS^*, eu
1	*m*-NO_2	1.6	1.5 ± 0.3	0 ± 0.8	21.0	8.3 ± 0.5	−44 ± 2
2	*m*-Cl	1.8	3.0 ± 0.3	4.2 ± 0.8	22.1	7.3 ± 0.4	−51 ± 1
3	*p*-Cl	2.2	2.8 ± 0.3	2.1 ± 0.9	22.6	7.8 ± 0.9	−51 ± 3
4	H	2.7	2.7 ± 0.3	0 ± 0.8	23.6	6.9 ± 2.1	−58 ± 7
5	*p*-Me	3.1	2.1 ± 0.9	−3.4 ± 3.1			
6	*p*-OMe	4.2	2.3 ± 3.1	−6.6			

[a] [KOH] = 0.0006 *M*.

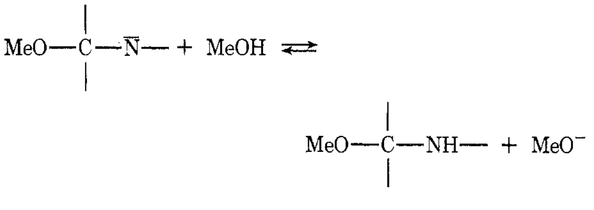
stabilization of benzylideneanilines by both R^1 and R^2 is important to make the equilibrium constant smaller, although benzylideneanilines have been reported to have nonplanar conformations,[15,16] composed of the planar benzylideneamino and anilino parts. Correlation with σ^+ for equilibria for the substituent attached to the benzylidene part is well known,[4,5] but such a correlation with σ^+ for the substituent attached to the anilino part (R^2) is unknown. The former resonance between X and C=N is similar to that in carbonyl compounds, and the latter between Z and N=C resembles that in stilbenes and azobenzenes[17] but not in carbonyl compounds.

The deuterium solvent isotope effect on equilibrium constant, $K_0^{\mathrm{MeOH}}/K_0^{\mathrm{MeOD}} = 0.98$, can be explained by virtually no change in zero-point energies between the O–H and the N–H vibrations,[18] since $\nu_{\mathrm{OH}} = \nu_{\mathrm{NH}} = 3400$ cm^{-1} in methanol and α-methoxybenzylanilines can be assumed.

The observed base catalysis and the positive ρ value can exclude the possibility of the participation of the conjugate acid of the Schiff base. Hence a probable mechanism is



$$\mathrm{MeO^- + \overset{|}{\underset{|}{C}}{=}N{-}\ \overset{slow}{\rightleftharpoons}\ MeO{-}\overset{|}{\underset{|}{C}}{-}\bar{N}{-}} \quad (1)$$



$$\mathrm{MeO{-}\overset{|}{\underset{|}{C}}{-}\bar{N}{-} + MeOH \rightleftharpoons MeO{-}\overset{|}{\underset{|}{C}}{-}NH{-} + MeO^-} \quad (2)$$

A noncatalyzed mechanism involving preequilibrium formation of methoxide ion and protonated Schiff base from methanol and Schiff base, followed by a slow reaction between these ions, is less plausible because the reaction should be independent of base. Also, the reaction involving such a preequilibrium, followed by a reaction between free Schiff bases and methoxide ion, would require second-order kinetics in Schiff bases, which is not the case.

The value of 0.60 for $k_f^{\mathrm{MeOH}}/k_f^{\mathrm{MeOD}}$ is close to the value of 0.71 for $k^{\mathrm{H_2O}}/k^{\mathrm{D_2O}}$ reported for an attack of hydroxide ions on the Schiff base,[19] which supports the above mechanism. Since potassium hydroxide (a strong base) is used, the concentration of the methoxide ions in methanol is the same as that in methanol-d_1 and hence the value of 0.60 corresponds to the effect of solvent on the methoxide ion attack, that is, desolvation of the methoxide ions may be easier in methanol-d_1 than in methanol, which is a stronger acid than methanol-d_1.[20] It is known that the rate of specific base catalysis is lower in protiated solvent than in deuterated solvent.[21] Hydrogen bonding to the imino nitrogen in the transition state, if any, would be unimportant because it would lead to an isotope effect over unity.

The correlation of rates by σ in contrast to the correlation of equilibria by σ^+ may be explained by the transition state structure of

$$(\mathrm{MeO^{\delta-}\text{-----}C{=\!=}N^{\delta-}})$$

Since partial negative charge may appear at the carbon and nitrogen atoms, the electron-releasing resonance by a substituent is not so important for the transition state stability.

The entropy of reaction ($\Delta S° \sim 0$) and the enthalpy of reaction ($\Delta H° \sim 3$) are small. Although it is difficult to explain the changes of entropy and enthalpy of reaction with varying substituent, electron-withdrawing groups tend to increase the enthalpy and entropy of reaction at any rate. On the other hand, the rate is controlled by entropy of activation rather than enthalpy of activation. This trend is the reverse of that for the hydrolysis rate of aromatic amides[22] and anhydrides.[23] The solvation of the transition state may be stronger with an electron-releasing substituent and cause a decrease in the degree of freedom in the transition state.

The equilibrium constant is influenced by polar substituents in alcohols ($\rho^* = -8.2$, $\delta = 0.48$), while the rate constant decreases in the order *n*-BuO$^-$ > EtO$^-$ > MeO$^-$ > *sec*-BuO$^-$ > *t*-BuO$^-$ > *i*-PrO$^-$. No parallelism between equilibrium and rate constants was observed. This order would result from overlapping of steric, polar, and solvent effects. The failure of the Taft relationship for the rates may be ascribed in part to the rate measurement in each alcohol itself, *i.e.*, in a different solvent, because of low conversion in equilibrium in other solvents. For the addition of nucleophiles to the carbonyl compounds, where the steric effect is larger, γ value or a measure of the affinity of nucleophiles for carbon[1] decreases in the order MeOH > EtOH > *i*-PrOH > *t*-BuOH. In contrast, the following reactivity order has been observed for an attack of alkoxide ions on acrylonitrile or butenone, where the polar effect is larger: MeO$^-$ > EtO$^-$ > PrO$^-$ > *i*-PrO$^-$.[24,25]

Experimental Section

Uv spectra were recorded on a Hitachi spectrophotometer Model 124 and nmr spectra on a JEOL spectrometer Model C-60 HL.

Materials. Substituted benzylideneanilines **1–11** were prepared as reported previously[6,7] and stored as an acetonitrile solution. Alcohols and acetonitrile were purified according to the literature.[26]

Nmr Spectra of the Solution. The nmr spectrum of *N*-benzylidene-*m*-chloroaniline in *tert*-butyl alcohol shows signals of α-*tert*-butoxybenzyl)-*m*-chloroaniline at τ 4.62 (CH) and at 3.3–3.6 (aromatic H) together with signals of *N*-benzylidene-*m*-chloroaniline at τ 1.70 (–CH=). Signals assigned to the NH proton of the adduct are obscure because of the overlap with strong signals of the OH protons. Also the nmr spectrum of *N*-benzylidene-*m*-nitroaniline in methanol shows signals of the CH protons at τ 4.33 together with those of the –CH= protons at τ 1.43. From relative strengths of these two signals the equilibrium constant for *N*-benzylidene-*m*-nitroaniline is calculated to be 0.028 M^{-1} which is close to 0.023 M^{-1} at 25° obtained by uv spectrophotometry. These facts indicate the stoichiometry of the reaction described above.

Rate and Equilibrium Measurements. The reaction was carried out in methanol–acetonitrile (90:10 v/v) and followed in a cell compartment of a spectrophotometer. The reaction was started when methanolic potassium hydroxide (0.1 ml) was added to a thermostated solution of benzylideneanilines (2.9 ml) and the extinction (E) at an appropriate wavelength (320–340 nm) was followed. Because of the excess methanol the equilibrium constant (K_0) was calculated by the following equation

$$K_0 = \frac{E_0 - E_\infty}{E_\infty[\mathrm{MeOH}]}$$

where subscripts 0 and ∞ refer to time 0 and equilibrium state, respectively.

Plot of log ($E_t - E$) *vs.* time t gave a good straight line from which pseudo-first-order rate constant for a reversible reaction, k_{obsd}, was obtained. Using the values of [MeOH], K_0, and k_{obsd}, apparent forward second-order rate constant, k_f^{MeOH}, was calculated by means of the equations

$$k_{\mathrm{obsd}} = \frac{2.303}{t} \log \frac{E_0 - E_\infty}{E_t - E_\infty}$$

and

$$k_f^{\mathrm{MeOH}} = \frac{k_{\mathrm{obsd}}K_0}{[\mathrm{MeOH}]K_0 + 1}$$

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Steroidal Nitrones

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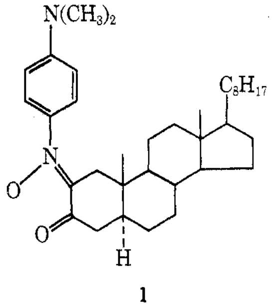
Received September 21, 1973

Steroidal 6- and 20-aldonitrones were prepared. 3-Ketonitrones were also prepared, and, in the case of Δ^4-3-ketonitrones, stereoisomers were separated and configurations assigned on the basis of uv and nmr spectroscopy.

Bambury, *et al.*, have published several reports on heterocyclic containing nitrones having antimicrobial activity.[1] Nitrone groups increase water solubility and the ability of a molecule to penetrate cell membranes.[2] For these reasons, we extended our work to the steroid field, and report here some of our findings on the preparation of 6-aldonitrones, 20-aldonitrones, and 3-ketonitrones.

Several steroidal nitrones are reported as intermediates in the Kröhnke reaction.[3] For example, the ketonitrones **1**[4] and **2**[5] were prepared and converted to the corresponding α-diketones. Similarly, the 21-aldonitrones **3**,[6] **4**,[6] and **5**[7] were prepared and converted to the 21-aldehydes. Other examples of steroid-like nitrones in which the nitrone is an integral part of the ring system, such as **6**,[8] **7**,[8] and **8**,[9] have also been reported. Subsequent to the completion of this work, Barton and coworkers[10] reported the conversion of 3-ketonitrones **9** *via* a Beckmann-type rearrangement to amides **10**, but no details for preparing **9** were given.

6-Aldonitrones. Steroidal 6-carboxaldehydes are readily available from Vilsmeier–Haack formylation of the corresponding 3-enol ethers **11** according to Burn, *et al.*[11] Experimentation showed that nitrone formation was best accomplished by heating a mixture of **12**, *N*-alkylhydroxylamine salt, and sodium bicarbonate in aqueous methanol containing pyridine. The resulting nitrones **13** are crystal-



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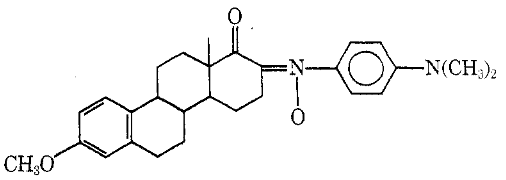

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