Registry No.—(−)-**1**, 52075-14-6; **2** (R = cyclohexyl), 53480-81-2; **2** (R = *o*-MeOPh), 69795-83-1; (*E*)-**3** (R = Me), 57403-82-4; (*Z*)-**3** (R = Me), 69853-65-2; (*E*)-**3** (R = ·Et), 57403-83-5; (*Z*)-**3** (R = Et), 69853-66-3; (*E*)-**3** (R = *i*-Pr), 69795-84-2; (*Z*)-**3** (R = *i*-Pr), 69795-85-3; (*E*)-**3** (R = *t*-Bu), 69795-86-4; (*E*)-**3** (R = cyclohexyl), 69814-85-3; (*Z*)-**3** (R = cyclohexyl), 69795-87-5; (*E*)-**3** (R = $MeOCH_2CH_2$), 61198-39-8; (*Z*)-**3** (R = $MeOCH_2CH_2$), 69880-56-4; (*E*)-**3** (R = Ph), 57403-84-6; (*E*)-**3** (R = *o*-MeOPh), 61198-40-1; **4**, 69795-88-6; **5a**, 16958-25-1; **5b**, 57403-74-4; **5c**, 52075-16-8; **5d**, 772-15-6; **5e**, 57403-75-5; **5f**, 16460-78-9; **5g**, 69795-89-7; **5h**, 69795-90-0; **5i**, 16497-93-1; **5j**, 69795-91-1; **5k**, 61198-41-2; **5l**, 69795-92-2; **5m**, 61198-42-3; **5n**, 61198-43-4; **5o**, 2845-27-4; **5p**, 57403-76-6; **5q**, 61198-44-5; **5r**, 61198-45-6; **5s**, 61198-46-7; **5k** methyl ester, 61198-55-8; **5l** methyl ester, 69795-93-3; **5m** methyl ester, 61198-56-9; **5n** methyl ester, 61198-57-0; **5q** methyl ester, 61198-58-1; **5r** methyl ester, 61198-59-2; **5s** methyl ester, 61198-60-5; **6** (R = Me, R′ = *n*-hexyl), 69795-94-4; (4*S*)-**7**, 61999-29-9; (±)-**7**, 69853-67-4; (4*R*)-**8**, 61999-31-3; (±)-**8**, 69853-68-5; (4*R*)-**9**, 61999-33-5; (±)-**9**, 69853-69-6; (*R*)-**10**, 62174-10-1; **11a**, 61198-47-8; **11b**, 69853-70-9; **11c**, 61198-48-9; **11d**, 61198-49-0; **12a**, 61198-50-3; **12b**, 61198-51-4; **12c**, 61198-52-5; MeCHO, 75-07-0; EtCHO, 123-38-6; *i*-PrCHO, 78-84-2; *t*-BuCHO, 630-19-3; $C_6H_{11}CHO$, 2043-61-0; $MeOCH_2CH_2CHO$, 2806-84-0; PhCHO, 100-52-7; *o*-MeOPhCHO, 135-02-4; EtLi, 811-49-4; *n*-BuLi, 109-72-8; *n*-HexLi, 21369-64-2; PhLi, 591-51-5; *n*-PrLi, 2417-93-8; *n*-propyl chloride, 540-54-5; *n*-hexyl chloride, 544-10-5; diisopropyl phosphonochloridate, 2574-25-6; triisopropyl phosphite, 116-17-6; ethylacetimidate hydrochloride, 2208-07-3; L-serine ethyl ester hydrochloride, 26348-61-8; (*S*)-(+)-3-phenylheptanoic acid, 61999-35-7.

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Physicochemical Properties of Schiff Bases. 4. Tautomeric Equilibrium and Kinetics of Hydrolysis of *N*-Benzylideneaniline Derivatives

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The kinetics of hydrolysis of *N*-(X-benzylidene)aniline, with X = OH or OCH_3 in the ortho, meta, or para position, have been investigated in the pH range from −1 to 14 at 30 °C by means of ultraviolet spectrophotometry. The mechanism of hydrolysis of these Schiff bases was found to be critically dependent on the presence of the ketoamine tautomer in some of these compounds, as was the case for the Schiff bases derived from isopropylamine.[1] The tautomeric constants have been estimated by various methods and consistent results have been obtained when comparison was possible.

In previous studies of *N*-benzylidene-2-aminopropane derivatives,[1] it has been shown that the presence of an hydroxy substituent in ortho or para positions in the benzaldehyde ring produces a tautomeric equilibrium between the phenolimine and the ketoamine form of the Schiff bases and that this equilibrium has an important effect on the hydrolysis of these Schiff bases at various pHs. The tautomeric equilibrium of Schiff bases has been studied by various workers,[2] while others[3] have denied its existence.

In the case of Schiff bases derived from aromatic amines, other mechanisms have been proposed[4,5] for the hydrolysis reaction. In order to see if special mechanisms are required in the latter case, we have investigated the reaction of hydrolysis of *N*-(X-benzylidene)aniline with X = OH or OCH_3 in ortho, meta, and para positions in the whole pH range from −1 to 14. We have also tried to estimate the amount of the ketoamine tautomer present in the various compounds in order to see if this amount is relevant in the interpretation of the observed variation of k_{obsd} with pH.

Experimental Section

The Schiff bases were prepared by condensation of commercially available aniline carefully distilled, with the appropriate aldehyde, following known procedures.[6]

Acetate, phosphate, borate, and carbonate buffers were used in their appropriate range.[7] Buffer concentrations were typically 0.05 M in acetate, dihydrophosphate, and hydrophosphate and 0.025 M in borax and bicarbonate. Buffer catalysis was never important except for the *o*-hydroxy compound as mentioned below. Extrapolated values of k_{obsd} at zero buffer concentration were at least 90% of the values corresponding to maximum buffer concentration. For the *o*-hydroxy

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Table I. Spectroscopic Determination of the Formation Constants of *N*-(X-Benzylidene)anilines by Hydrolysis of the Schiff Base (Initial Concentration 10^{-4} mol L^{-1}) in the Presence of Increasing Amounts of Aniline (Temperature 30 °C, Ionic Strength 0.1) [a]

	aniline concn, M	A_0	A_∞	$x_A \times 10^4$	$x_S \times 10^4$	K_f(spectroscopic)
X = *o*-OH	0	0.283	0	1	0	
pH 7	0.025	0.274	0.121	0.549	0.451	32.1
λ 432 nm	0.05	0.273	0.163	0.397	0.603	30.4
	0.10	0.292	0.205	0.240	0.760	31.7
	0.15	0.230	0.220	0.185	0.815	29.4
	0.2	0.270	0.234	0.133	0.867	32.6
	mean:	0.270				31.2
X = *o*-OCH_3	0	0.825	0.1377	1	0	
pH	0.025	0.781	0.200	0.906	0.094	4.15
λ 350 nm	0.05	0.818	0.260	0.816	0.184	4.51
	0.1	0.810	0.330	0.710	0.290	4.09
	0.2	0.792	0.443	0.542	0.458	4.23
	mean:	0.805				4.24
X = *o*-OCH_3	0	1.11	0.34	1	0	
pH 10	0.025	1.12	0.425	0.891	0.109	4.89
λ 325 nm	0.05	1.13	0.480	0.820	0.180	4.39
	0.1	1.12	0.578	0.694	0.306	4.41
	0.15	1.10	0.660	0.589	0.411	4.65
	0.2	1.12	0.702	0.535	0.465	4.35
	mean:	1.12				4.53
X = *m*-OH	0	1.16	0.276	1	0	
pH 7	0.1	1.249	0.616	0.624	0.376	6.02
λ 320 nm	0.2	1.213	0.758	0.467	0.533	5.71
	0.3	1.108	0.840	0.366	0.634	5.77
	mean:	1.182				5.83
X = *m*-OCH_3	0	1.132	0.255	1	0	
pH 7	0.1	1.084	0.550	0.624	0.376	6.03
λ 320 nm	0.2	1.150	0.729	0.461	0.539	5.84
	0.3	1.181	0.805	0.375	0.625	5.55
	mean:	1.136				5.81
X = *p*-OH	0	1.572	0.340	1	0	
pH 6.6	0.1	1.573	0.498	0.871	0.129	1.48
λ 320 nm	0.2	1.586	0.638	0.758	0.242	1.6
	0.3	1.559	0.718	0.693	0.307	1.48
	mean	1.573				1.52
X = *p*-OH	0	0.396	0	1	0	
pH 6.6	0.1	0.396	0.048	0.874	0.126	1.44
λ 410 nm	0.2	0.360	0.084	0.780	0.220	1.41
	0.3	0.378	0.122	0.681	0.319	1.56
	mean:	0.383				1.47
X = *p*-OCH_3	0	1.745	0.0785	1	0	
pH 6.6	0.05	1.525	0.152	0.949	0.051	1.07
λ 320 nm	0.1	1.58	0.267	0.871	0.129	1.48
	0.15	1.57	0.346	0.817	0.183	1.49
	0.2	1.57	0.467	0.735	0.265	1.80
	0.3	1.37	0.561	0.671	0.329	1.63
	mean:	1.548				1.49

[a] A_0 is the initial absorbance and A_∞ the final absorbance at the indicated wavelength; x_A and x_S are the equilibrium concentration of the aldehyde and of the Schiff base; the formation constant is given in unit mol^{-1} L.

compound, however, it was not possible to use the borate buffer in its normal range 8–10.8 owing to excessive buffer catalysis. In the range 9.6–10.8, bicarbonate buffers were used; no satisfactory buffers were found for the range 8–9.6.

Kinetic measurements were carried out spectroscopically, at 30 °C, on a Unicam SP 1800 spectrophotometer and a Durrum D 110 stopped flow spectrophotometer. Unless otherwise indicated, ionic strength was adjusted to 0.1 in the pH range 1–13. Real absorbance of the Schiff bases in water was found by extrapolation to zero time of the hydrolysis curve. The hydrolysis reaction was studied in 2% dioxane–water (v/v) medium.

For measurements in the pH range where the observed rate constant is larger than 5 min^{-1}, a special technique must be devised for the mixing of the diluted Schiff base with the buffer in the stopped flow spectrophotometer. The *o*-OH Schiff base was first diluted in a phosphate buffer (pH 7.8) having a concentration ten times less than the normal value and corresponding to the minimum of the kinetic curve. Rapid mixing was then made of this solution with a buffer where enough acid has been added to obtain the intended pH value in the mixture. The same method was used for the other compounds, but the base was first diluted in borate buffer at pH 9.6. Under these conditions it was naturally not possible to extrapolate absorbances

at zero time and to determine spectroscopically the dissociation constants.

Dissociation constants of conjugate acids of the free bases and of their anions defined as:

$$SH^+ \overset{K_1}{\rightleftharpoons} S + H^+$$

$$S \overset{K_2}{\rightleftharpoons} S^- + H^+$$

were determined from the curves giving the variation of the rate of hydrolysis with pH. In addition, the pK_2 values of the meta and para hydroxy derivatives were determined spectroscopically from the variation with pH of the absorbance at 265 nm.

The formation equilibrium constant K_f defined as

$$K_f = \frac{[\text{Schiff base}]}{[\text{aldehyde}][\text{amine}]}$$

has been calculated from the variation of the observed rate constant with increasing aniline concentration, at a pH where the concentration of ionized forms is negligible (Figure 1):

$$k_{obsd} = k_h + k_f[\text{aniline}]$$

$$K_f(\text{kinetic}) = k_f/k_h$$

The value of K_f has also been obtained from apparent absorptivities at characteristic wavelengths and is given as K_f(spectroscopic). Pertinent results for the application of this method are given in Table I.

Results and Discussion.

In Figure 2, the observed rate constants for the hydrolysis of *N*-(X-benzylidene)aniline, with X = OH or OCH_3 in ortho, meta, and para positions, are plotted as a function of pH over the range −1 to 14. The hydrolysis reaction may be formulated as:

$$SH^+ + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} XH^+ \quad (1)$$

and

$$SH^+ + OH^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} X \quad (2)$$

where X is the carbinolamine intermediate. Reactions 1 and 2 are valid for the methoxy as well as for the hydroxy derivatives. For the latter, however, an additional reaction becomes important at neutral and alkaline pHs:

$$Q + OH^- \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} X^- \quad (3)$$

where Q represents the quinoid tautomer. Finally, for the *o*-OH derivative at neutral pH, the predominant reaction is:

$$Q + H_2O \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} X \quad (4)$$

Reactions 2 and 4 refer to kinetically indistinguishable mechanisms; they can be disentangled however through comparison of hydroxy with methoxy derivatives (see below). In addition, it has been demonstrated[1,8] that at very acidic pHs, the rate-determining step is the decomposition of the carbinolamine intermediate:

$$X \xrightarrow{k_{5a}} \text{ald} + \text{am} \quad (5a)$$

$$X^- \xrightarrow{k_{5b}} \text{ald}^- + \text{am} \quad (5b)$$

$$XH^+ \xrightarrow{k_{5c}} \text{ald} + \text{amH}^+ \quad (5c)$$

A first indication of the correctness of the proposed mechanism is that the kinetic curves calculated on these premises

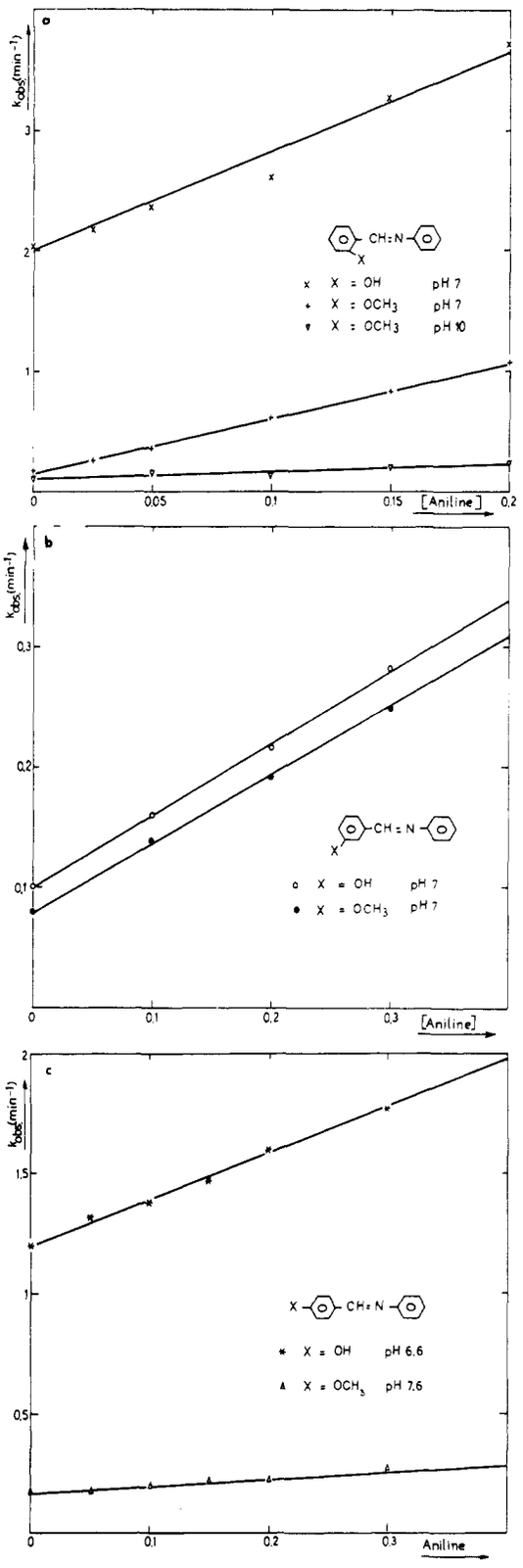


Figure 1. Kinetic determination of the formation constants of *N*-(X-benzylidene)anilines: $k_{obsd} = k_h + k_f[\text{aniline}]$.

by eq 6, 7, and 8 are in agreement with the experimental points (see Figure 2)

$$k_{obsd} = \frac{\{k_1[H_2O][H^+] + k_2K_W + k_3K_1[OH^-] + k_4K_1[H_2O]\}\{k_{5a} + k_{5b}K_X/[H^+]\}}{\{K_1 + [H^+] + K_1K_2/[H^+]\}\{k_{-1}[H^+]/K_{XH} + k_{-2} + k_{-3}K_X/[H^+] + k_{-4} + k_{5a} + k_{5b}K_X/[H^+]\}} \quad (6)$$

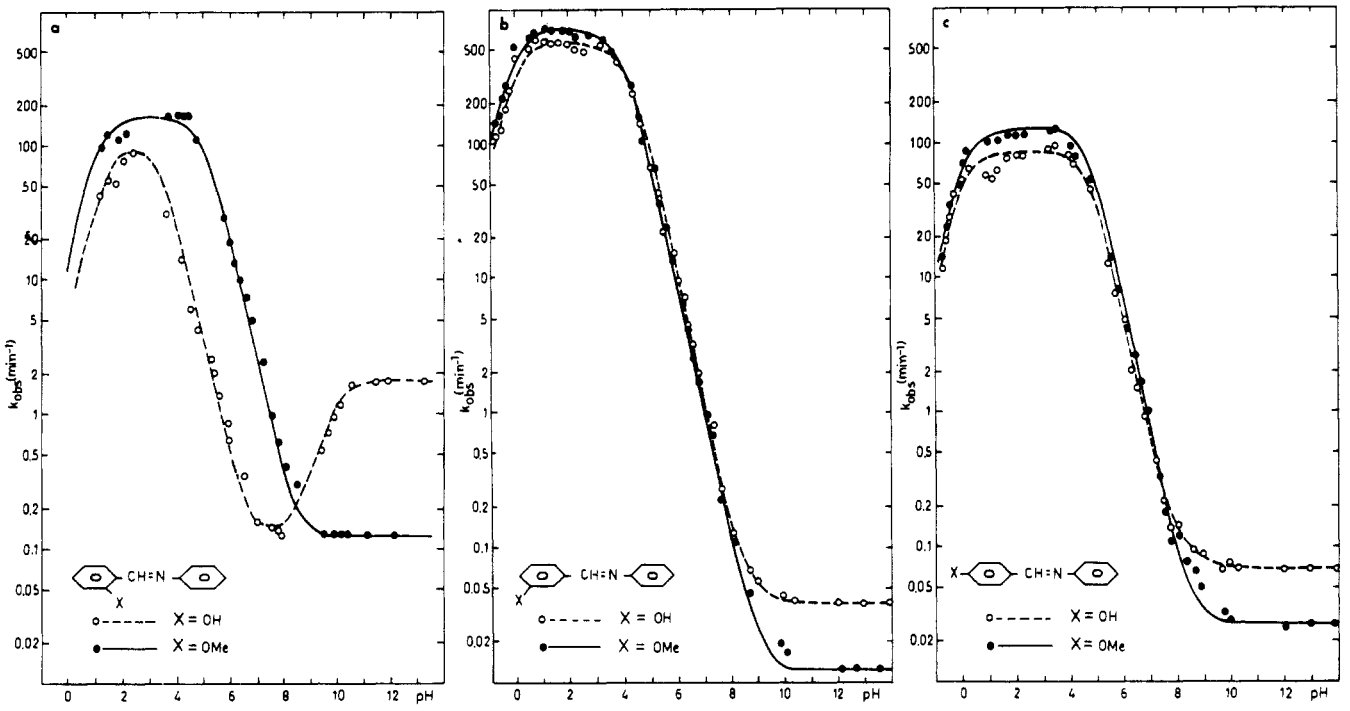


Figure 2. Logarithm of the first-order rate constants for the hydrolysis of *N*-(X-benzylidene)aniline with X = OH or OCH_3 in ortho, meta, and para position as a function of pH. Curves are calculated from eq 7 and 8 (temperature = 30 °C; ionic strength 0.1).

Table II. Dissociation Constants of *N*-(X-Benzylidene)-anilines and Rate Constants for the Hydrolysis of the Same Schiff Bases [a] (30 °C and Ionic Strength 0.1)

X	pK_1	pK_2	k_1, min^{-1} mol L^{-1}	k_2, min^{-1} mol^{-1} L	$k_{-1}/K_{XH}k_{5a}$, mol^{-1} L
o-OH	3.6	9.75	1.88	(3.2×10^9) [b]	23
o-OCH_3	5.2		3	7.6×10^7	13.2
m-OH	4.3	9.51 (9.50) [c]	10.4	2.4×10^8	0.87
m-OCH_3	4.2		12.6	8.9×10^7	0.83
p-OH	4.8	8.51 (8.50) [c]	1.54	1.6×10^8	0.9
p-OCH_3	4.7		2.3	5.2×10^7	1.2

[a] Symbols are defined by eq 1–10 in the text. [b] This value is calculated without taking into account the predominant reaction 4. [c] These values are determined from the variation with pH of the absorbance at 265 nm.

which reduces in the acidic region where $K < [H^+]$ to

$$k_{obsd} = \frac{k_1[H_2O]}{1 + k_{-1}[H^+]/k_{5a}K_{XH}} \quad (7)$$

and when $K_1 \geq [H^+]$ to

$$k_{obsd} = \frac{k_1[H_2O][H^+] + k_2K_W + k_3K_1[OH^-] + k_4K_1[H_2O]}{K_1 + [H^+] + (K_1K_2/[H^+])} \quad (8)$$

The dissociation constants of the carbinolamine intermediate are defined as:

$$X \overset{K_X}{\rightleftharpoons} X^- + H^+ \quad (9)$$

$$XH^+ \overset{K_{XH}}{\rightleftharpoons} X + H^+ \quad (10)$$

The values obtained for the significant constants are given in Table II, except for k_3 and k_4 which will be discussed later.

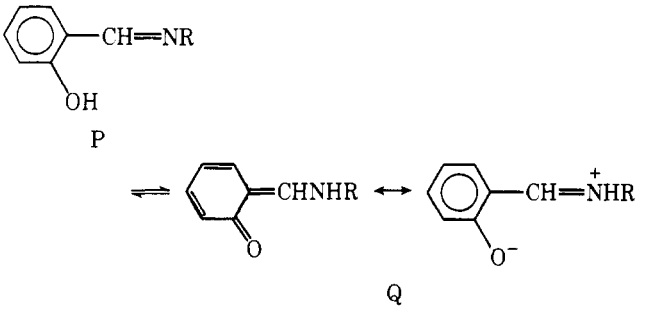
Our investigation of the kinetics of hydrolysis provides additional evidence regarding some important steps of the reaction.

At alkaline pHs, the hydroxy compounds are hydrolyzed mainly through step 3.[1] The importance of reaction 3 in the case of the benzylideneanilines is illustrated by the numerical values obtained for k_3 through eq 11 for the rate constant at pH 14:

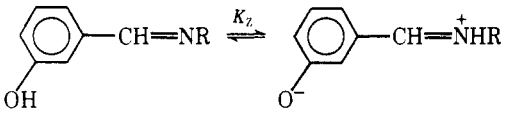
$$k_{(14)} = \frac{k_3K_W}{K_2(1 + 1/K_T)} \quad (11)$$

where the tautomeric constant K_T is defined as

$$K_T = [Q]/[P]$$



with analogue formulas for the para hydroxy derivative. The values of K_T were estimated as explained below. For the *m*-OH compound, K_T is replaced by K_Z:



The values obtained for the rate constants are given in Table III. It should be emphasized that eq 11 was obtained by supposing that the form Q is the only important one for the attack by OH^-. It seems reasonable to admit that this attack is easier on the para than on the ortho compound. The fact that the apparent constant k_3' is lower in the case of *p*-hydroxybenzylideneaniline than for the corresponding ortho compound

Table III. Rate Constants in min^{-1} mol^{-1} L for the Addition of OH^- on $XC_6H_4CH{=}NR$ (temperature 30 °C; Ionic Strength 0.1)

	$k_3' = k_3/(1 + 1/K_T)$	K_T[a]	k_3
R = $-CH(CH_3)_2$			
X = *o*-OH	800[b]	16	850
X = *m*-OH	66 000[b]		
X = *p*-OH	11 400[b]	15	12 160
R = $-C_6H_5$			
X = *o*-OH	32 000	6.3	37 000
X = *m*-OH	1 270		
X = *p*-OH	25 360	0.05	532 560

[a] See Table VI. [b] Reference 1a.

is an indirect proof that the amount of the Q form is very low in the case of the para compound; for the isopropylamine derivatives, the observed values of k_3' are in the expected order. For the meta compound, addition of water on the anionic form is not to be excluded as a competitive reaction.

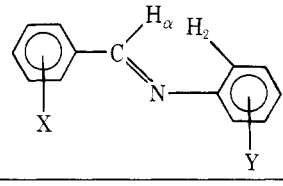
For the *o*-hydroxy compound, another important reaction appears at neutral pH, i.e., addition of water on the quinoid neutral tautomer. Without this contribution, the calculated value of the rate constant at pH 8, using k_2(*o*-OH) = k_2(*o*-OMe) as approximation, would be 0.007, whereas the observed value is 0.15. Additional evidence for the importance of reaction 4 is provided by the study of the influence of the ionic strength f_i on the observed rate constant. At pH 7, the observed rate remains independent of the ionic strength as f_i is varied by addition of KCl at concentrations 0.1, 0.2, and 0.4, which is what one expects for a reaction between neutral species. In contrast, at pH 5 where mechanism 1 is dominant, the observed rate varies as follows with ionic strength: 4.84 without KCl; 7.33 with KCl (0.1 M); 8.25 with KCl (0.2 M); and 8.45 with KCl (0.4 M). The values of the corresponding second-order rate constant k_4 obtained from the simplified equation

$$k_{(7)} = k_4'[H_2O] \qquad (12)$$

are as follows (in min^{-1} mol^{-1} L) for *o*-$OHC_6H_4CH{=}NR$: with R = $-CH(CH_3)_2$, k_4' = 0.00108;[1c] with R = -Ph-*p*-CH_3, k_4' = 0.0022; with R = $-C_6H_5$, k_4' = 0.0027; with R = -Ph-*m*-Br, k_4' = 0.0027; and with R = -Ph-*p*-NO_2, k_4' = 0.0052. These values increase with the electron-withdrawing power of R, in accordance with the model previously proposed[1c] of a two-center mechanism.

It may be concluded from the above considerations that at neutral and alkaline pHs the presence of the tautomeric equilibrium must be taken into account for the interpretation of the hydrolysis reaction of some of the aromatic Schiff bases. Before discussing further the importance of this equilibrium, mention must be made of the interpretation proposed by other workers. Hoffmann and Sterba[5] have investigated the hydrolysis of substituted salicylideneanilines. From the nonlinearity of the plot k_{obsd} vs. σ, they infer that a different mechanism is at play for electron-donating and electron-withdrawing substituents. However it seems to us that nonlinearity of Hammett's correlation for Schiff bases derived from anilines must be interpreted with caution. Indeed, nonlinearity has been observed for other properties of aromatic imines. Herkstroeter[9] has investigated the mechanism of syn-anti isomerization of azomethine dyes and he has reported nonlinear correlation. Ledbetter[10] has found no linear correlation between λ_{max} and σ for compounds of this type. Inamoto[11] has also observed anomalous ρ values for the chemical shifts ^1H and ^{13}C of benzylideneanilines. From these observations we conclude that nonlinearity is not to be attributed to changes in reaction mechanisms but rather to structural characteristics of these Schiff bases and specifically

Table IV. Torsional Angle between the Two Rings in *N*-Benzylideneanilines



X	Y	angle, deg	ref
p-OH	H	53.8	13
H	*p*-OH	17.6	13
p-NO_2	*p*-OCH_3	52.5	14
H	H	44.9	15
H	*p*-COOH	27.3	15
p-CH_3	*p*-NO_2	42.1	15
p-NO_2	*p*-$N(CH_3)_2$	5.6	16
p-CN	*p*-CN	90	16

to the fact that the two aromatic rings are not coplanar. The π electrons of the aniline ring may be conjugated with the π electrons of the C=N bond or, in the perpendicular direction, with the lone pair of the nitrogen atom. X-ray determinations can be found for a number of Schiff bases derived from aniline. The results are collected in Table IV. One can see that all these molecules are twisted more or less, as could be expected from the steric hindrance of hydrogens α and 2. In addition, it may be mentioned that Inamoto[12] has reported that NMR shifts of H_α were influenced by through-space effects. In conclusion, it seems that using Hammett's type correlations for the purpose of determining mechanisms of reaction is unwarranted in this case. As a matter of fact, the general behavior of the kinetic curves for *N*-benzylideneanilines is in accordance with the mechanism previously proposed for the Schiff bases derived from isopropylamine. A striking difference however appears: in the ortho position, hydroxy and methoxy substituents have a very different effect on the hydrolysis reaction. On the contrary, when they are in the para position, these substituents give kinetic curves which are nearly coincident at neutral and acidic pHs as is the case for the meta-substituted compounds. The obvious interpretation is that the quinoid tautomer which has been shown to play the leading role at neutral and alkaline pHs is predominant in the ortho and practically absent in the para derivatives. One is thus led to estimate the tautomeric equilibrium constant K_T. Three methods are at hand for this determination. The spectroscopic method as used by Bidegaray and Viovy[17] has the disadvantage that it supposes the constancy of the absorptivity in various solvents. In order to minimize this error, we have applied a correction as explained in part 2.[1b]

The tautomeric constant can also be estimated by comparing the dissociation constants of the hydroxy with those of the methoxy compounds. We define

$$K_{1P} = [P][H^+]/[SH^+]$$

and

$$K_{1Q} = [Q][H^+]/[SH^+]$$

taking advantage of the fact that the conjugate acid is the same for both tautomers. Hence, $K_T = K_{1Q}/K_{1P}$. The K_1 values for the meta-substituted compounds show no difference between the hydroxy and the methoxy derivatives. It may thus be safely inferred that K_1 for the phenolic form of the *p*-OH compound is about the same as the K_1 of the corresponding methoxy compound. This method does not apply so well in the case of ortho substitutent owing to the fact that the strong intramolecular hydrogen bridge in the salicylidene derivative may enhance the value of its K_1 as compared to the

Table V. Formation Constants of *N*-(X-Benzylidene)-anilines (mol^{-1} L) at 30 °C

X	pH	wavelength, nm	K_f(kinetic)	K_f(spectroscopic)
o-OH	7	432	31.3	31.2
o-OCH_3	7	350	4.55	4.24
	10	325	4.5	4.53
m-OH	7	320	5.9	5.83
m-OCH_3	7	320	5.9	5.81
p-OH	6.6	320	1.56	1.52
	6.6	410	1.56	1.47
p-OCH_3	7.6	320	1.47	1.49

Table VI. Tautomeric Constants of Schiff Bases $XC_6H_4CH{=}NR$ (Temperature 30 °C; Ionic Strength 0.1)

	K_T spectroscopic UV	K_T spectroscopic IR	K_T from K_1	K_T from K_f
R = $-CH(CH_3)_2$ [d]				
X = *o*-OH	16	*a*	(631) [b]	*c*
X = *m*-OH	0	0	0	
X = *p*-OH	*a*	15	13	*c*
R = $-C_6H_5$				
X = *o*-OH	*a*	*a*	(40) [b]	6.3
X = *m*-OH	0		0	0
X = *p*-OH	*a*		0	0.05

[a] The method cannot be used because of the absence of an isolated characteristic band. [b] This value is overestimated; see text. [c] The method cannot be used because of the absence of a pH range where all compounds are non-ionized. [d] Reference 1b.

methoxy derivative. Consequently, the values of K_T obtained by this method for the *N*-salicylidene derivatives are too large. They are given in parentheses in Table V.

A third method of quantitative study of the tautomeric equilibrium consists of comparing the formation constants of the various Schiff bases, defined as

$$K_{fP} = [P]/[Ald][Am]$$

and

$$K_{fQ} = [Q][/[Ald][Am]$$

while the observed value (taken as the mean of all values in Table V) is

$$K_{fS} = K_{fP} + K_{fQ}$$

The validity of this method depends on the assumption that the formation constant of the phenolic form of the hydroxy Schiff base is about equal to the formation constant of the corresponding methoxy Schiff base. This assumption is corroborated by the fact that the constants are equal in the case of meta derivatives. In the course of kinetic measurements of the formation constants, one can also measure the absorptivities at characteristic wavelengths and calculate independently the value of K_f. The latter is given in Table V as K_f(spectroscopic).

In Table VI, the values of K_T are given as estimated by the various approximate methods. Values obtained from previous measurements on Schiff bases derived from isopropylamine are given for comparison purpose. The experimental error may attain 50% in the case of the *p*-hydroxybenzylideneaniline; for the other compounds, it is less than 5%. Even if the values obtained are only approximate, a fact clearly borne out by Table VI is that the *N*-(*p*-hydroxybenzylidene)aniline exists mainly in the phenolic form and this is sufficient to explain its "anomalous" kinetic behavior without need to introduce some special mechanism for its hydrolysis at neutral and alkaline pHs.

As far as we know, tautomeric constants have not been previously measured in water. Our results may be compared with the one obtained by Dudek and Dudek[18] for salicylideneaniline in ethanol where they found $K_T = 0.16$. While going from methanol to water as a solvent, the value of K_T goes from 0.25 to 16 in the case of salicylideneisopropylamine.[1b] One can also determine the absorptivity of the quinoid form: $\epsilon^{432} = 3129$, which may be compared with the value (2400) found by Viovy[17] for the same Schiff base in methanol.

Some of our results on the kinetics of hydrolysis may be compared with the one obtained by other workers. For salicylideneaniline, Dash and Nanda[19] measured $k_{obsd} = 0.48$ min^{-1} at pH 6.1 and 30 °C and Bellobono and Favini[20] found $k_{obsd} = 0.68$ min^{-1} at pH 6.16 and 25 °C. Our value is $k_{obsd} = 0.45$ at pH 6.1.

In conclusion, one may state that the mechanism of hydrolysis of Schiff bases derived from aromatic amines is determined by the same reactions as those for Schiff bases derived from aliphatic amines. The presence of a quinoid tautomer plays a determining role in some cases. The fact that this quinoid tautomer is less abundant in the case of anils must be related to the difference in the basicity of the corresponding amines: $pK_b = 10.72$ for isopropylamine and 4.63 for aniline.

Registry No.—*N*-(*o*-Hydroxybenzylidene)aniline, 779-84-0; *N*-(*o*-methoxybenzylidene)aniline, 3369-37-7; *N*-(*m*-hydroxybenzylidene)aniline, 13206-60-5; *N*-(*m*-methoxybenzylidene)aniline, 17637-72-8; *N*-(*p*-hydroxybenzylidene)aniline, 1689-73-2; *N*-(*p*-methoxybenzylidene)aniline, 836-41-9; *N*-(*o*-hydroxybenzylidene)-isopropylamine, 5961-35-3; *N*-(*m*-hydroxybenzylidene)isopropylamine, 13033-49-3; *N*-(*p*-hydroxybenzylidene)isopropylamine, 5961-39-7; *N*-benzylidene-*p*-hydroxyaniline, 588-53-4; *N*-(*p*-nitrobenzylidene)-*p*-methoxyaniline, 5455-87-8; *N*-benzylideneaniline, 538-51-2; *N*-benzylidene-*p*-carboxyaniline, 3939-41-1; *N*-(*p*-methylbenzylidene)-*p*-nitroaniline, 20192-50-1; *N*-(*p*-nitrobenzylidene)-*p*-dimethylaminoaniline, 896-06-0; *N*-(*p*-cyanobenzylidene)-*p*-cyanoaniline, 69622-68-0; *o*-hydroxybenzaldehyde, 90-02-8; *o*-methoxybenzaldehyde, 135-02-4; *m*-hydroxybenzaldehyde, 100-83-4; *m*-methoxybenzaldehyde, 591-31-1; *p*-hydroxybenzaldehyde, 123-08-0; *p*-methoxybenzaldehyde, 123-11-5; benzaldehyde, 100-52-7; *p*-nitrobenzaldehyde, 555-16-8; *p*-methylbenzaldehyde, 104-87-0; *p*-cyanobenzaldehyde, 105-07-7; isopropylamine, 75-31-0; aniline, 62-53-3; *p*-hydroxyaniline, 123-30-8; *p*-methoxyaniline, 104-94-9; *p*-carboxyaniline, 150-13-0; *p*-nitroaniline, 100-01-6; *p*-dimethylaminoaniline, 99-98-9; *p*-cyanoaniline, 873-74-5.

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Studies on the Synthesis and Resolution of γ-Carboxyglutamic Acid Derivatives[1,2]

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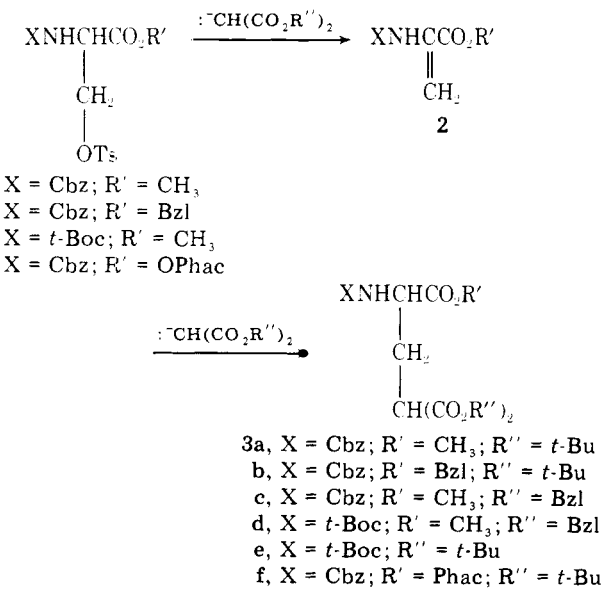
The synthesis and resolution of *N*-(benzyloxycarbonyl)-γ,γ-di-*tert*-butyl-*d,l*-γ-carboxyglutamic acid (**5a**) is described. Resolution using quinine allowed separation of the D enantiomer from the racemic mixture in 15% yield from *N*-(benzyloxycarbonyl)-*O*-tosyl-*d,l*-serine methyl ester (**1a**). Liberation of the L enantiomer from the remaining oily quinine salt followed by purification of the L-tyrosine hydrazide salt of **5a** provided an overall yield of 13% of the L enantiomer from **1a**. The synthesis of *N*-(benzyloxycarbonyl)-γ,γ-di-*tert*-butyl-D-γ-carboxyglutamyl-γ,γ-di-*tert*-butyl-D-γ-carboxyglutamic acid (**19**) is described.

Since the identification of γ-carboxyglutamic acid (Gla)[4] in 1974, the synthesis of Gla derivatives has been the target of several laboratories.[5-7] To date two synthetic approaches have yielded the desired amino acid. One route utilizes a procedure developed by Wheland[8] for the preparation of glutamic acid (Scheme I). As might be expected from similar syntheses of cysteine[9] and selenocysteine,[10] loss of leaving groups from the β carbon of alanine derivatives was accompanied by extensive racemization at the α-carbon atom.[5b,c] The second approach and the only reported asymmetric synthesis of Gla[5g] utilized a modified Strecker synthesis to afford γ,γ-di-*tert*-butyl-L(−)-*N*-phthaloyl-γ-carboxyglutamate. In spite of the high optical purity of the product obtained by this route, the primary source of optically pure Gla for further synthetic studies has been via Scheme I and classical resolution.[7] This report describes in detail our studies on the development of routes to optically pure Gla derivatives on a synthetically useful scale.

Results and Discussion

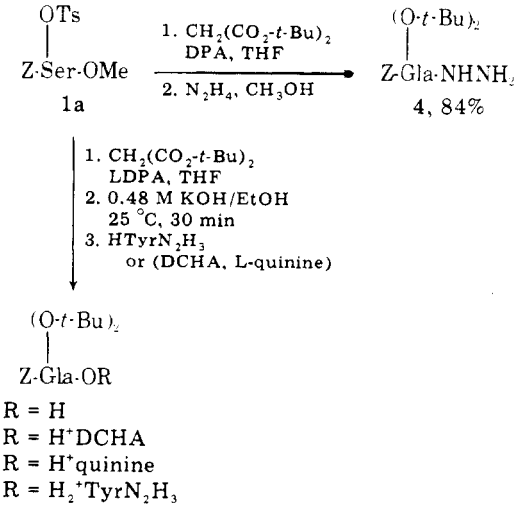
Synthesis. The preparation of the *O*-tosyl-L-serine derivatives (**1a–d**, Scheme I) was based on general procedures previously reported.[9a,b,10] The tosylation reaction was temperature dependent; reactions carried out below −5 °C were more successful. Although **1c** and **1d** were generated and used as in Scheme I, they were not easily purified without losses. The presence of pyridine particularly hampered purification.

Scheme I



Treatment of the appropriate *O*-tosyl-L-serine derivative with excess di-*tert*-butyl malonate using either sodium hydride or lithium diisopropylamide as the base provided the crude Gla derivatives. Of these esters, the *N*-(benzyloxycarbonyl)-γ,γ-di-*tert*-butyl-*d,l*-γ-carboxyglutamic acid α-methyl ester (**3a**) and the *N*-(*tert*-butyloxycarbonyl)-γ,γ-dibenzyl-γ-methyl ester (**3d**) seemed to have properties appropriate for further study. In order to evaluate the stability of the amine triester, solutions of **3a** and **3d** were deblocked at the amino group with palladium and hydrogen and trifluoroacetic acid, respectively, followed by neutralization of the amine salt. The γ,γ-di-*tert*-butyl methyl ester resulting from **3a** exhibited a substantially longer lifetime (TLC, ninhydrin) than the dibenzyl methyl ester resulting from **3d**. Thus, **3a** was utilized in subsequent studies since the rate of apparent cyclization to the pyro-γ-carboxyglutamic acid derivative should be repressed relative to **3d**.

The triester, **3a**, was smoothly converted to the hydrazide, **4**. Hydrazinolysis could be performed on the crude reaction mixture resulting from the reaction of excess di-*tert*-butyl



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