

tamine at a rate which suggests that activated glutamic acid may be bound to the enzyme in a γ -ester link.

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Concerning the Mechanism of the Hydrolysis and Aminolysis of Schiff Bases¹

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The pH-rate profiles and the effect of structure on reactivity for the hydrolysis of Schiff bases derived from benzophenone and aliphatic amines are similar to those previously obtained for the hydrolysis of benzylidene-1,1-dimethylethylamines. The second-order rate constant for the attack of hydroxide ion on the cationic Schiff base, benzhydrylidenedimethylammonium ion, is similar to those calculated from the first-order rate constants for the pH-independent reaction above pH 9 for the attack of hydroxide ion on protonated benzhydrylideneamines. This finding, together with the observed lack of dependence of the first-order rate constants for the pH-independent reaction on the nature of polar substituents, strongly suggests that this reaction does involve the attack of hydroxide ion on the protonated substrates rather than the attack of water on the free base of the substrate. The attack of water on benzhydrylidenedimethylammonium ion is subject to general base catalysis by carboxylate ions. The Brønsted β -value for this reaction is 0.27. Under conditions in which the Schiff bases exist as the conjugate acids, the reactivity of Schiff bases derived from benzophenone and ammonia, methylamine, and dimethylamine, toward hydroxylamine, methoxyamine, semicarbazide, and water decreases with increasing methyl substitution on nitrogen. Values of ρ^+ for the reaction of water, hydroxylamine, and methoxyamine with the conjugate acids of a series of substituted benzhydrylideneethylamines are 1.1, 0.92, and 0.96, respectively. The similarity of the effect of structural alteration in either the amine or carbonyl component of the Schiff base on reaction rates for the reaction with water, for which attack of the nucleophilic reagent is rate determining, and for the reactions with the amines suggests that the attack of the amines is also rate determining. This suggestion is also supported by the finding that the aminolysis reactions, like the hydrolysis reaction, are subject to general base catalysis. The reaction of a series of substituted benzaldehyde semicarbazones with hydroxylamine and the reaction of a series of substituted benzaldehyde oximes with semicarbazide are dependent upon acid catalysis. Both sets of data are correlated by Hammett ρ -values of -1.7 . The pK_a values for the conjugate acids of benzaldehyde oximes have been determined.

Introduction

Numerous studies have established that imines, particularly when present in cationic form $>C=N^+<$, readily undergo reaction with a variety of nucleophilic reagents.³⁻⁸ By their apparent involvement in numerous biochemical processes, attention has been focused on two classes of such reactions, those involving water and amines, as nucleophilic reagents. Enzymatic aldolization,⁹⁻¹² enzymatic decarboxylation,¹³⁻¹⁵ and, perhaps, the visual process^{16,17} all appear to involve Schiff base formation and hydrolysis. In addition, pyridoxal phosphate-dependent enzymatic reactions very probably involve both the hydrolytic and aminolytic cleavage of Schiff bases.¹⁸⁻²⁰

The formation and hydrolysis of Schiff bases, particularly those involving benzaldehydes as carbonyl components, have received considerable study and, in consequence, the basic features of the mechanism and catalysis of these reactions are reasonably well understood.²¹⁻²⁷ On the other hand, the mechanism and catalysis of transamination reactions, the reactions of Schiff bases with amines, are considerably less well understood although such reactions have received some study.^{3,4,7,28}

Results reported herein are concerned principally with the mechanism of the reactions of Schiff bases derived from benzophenone with water and with weakly basic amines. The reaction of these Schiff bases with water was studied for two reasons: first, to extend previous investigations of the mechanism of hydrolysis of Schiff bases to substrates involving benzophenone as the carbonyl component; second, to establish relationships between structure and reactivity for a reaction with these substrates which is reasonably well understood. This reaction, then, will serve as a standard of com-

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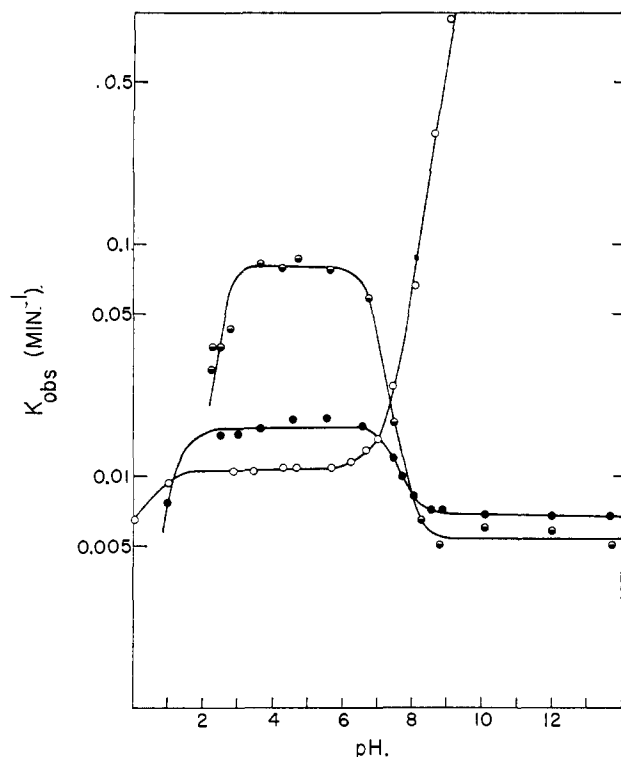


Fig. 1.—First-order rate constants for the hydrolysis of benzhydrylidenedimethylammonium ion, O, benzhydrylidene methylamine, ●, and benzhydrylidene amine, ◐, at 25° and ionic strength 0.50 plotted against pH; 0.02 *M* carbonate, borate, phosphate, acetate, and chloroacetate buffers employed in appropriate pH ranges.

parison for structure-reactivity correlations observed in the less well understood reactions involving amines as nucleophilic reagents. Such comparisons have permitted preliminary conclusions concerning the mechanism of the aminolytic reactions to be drawn.

Experimental

Materials.—Benzhydrylidene methylamine, *p*-methylbenzhydrylidene methylamine, and benzhydrylidenedimethylammonium iodide were prepared by the method of Hauser and Lednicer.⁵ *p*-Chloro- and *p*-methoxybenzhydrylidene methylamines were prepared in similar fashion. Benzhydrylideneamine²⁹ and oximes and semicarbazones of substituted benzaldehydes³⁰ were prepared as previously described. Other reagents, except reagent grade inorganic salts, were redistilled or recrystallized before use. Solutions of nitrogen bases were prepared just prior to use. Distilled water was employed throughout.

Kinetic measurements were carried out spectrophotometrically with a Zeiss PMQ II spectrophotometer equipped with a cell holder thermostated at 25° as previously described.^{21,22} In all kinetic runs, unless specified otherwise, ionic strength was maintained at 0.50 by the addition of KCl; 0.02 *M* chloroacetate, acetate, phosphate, borate, or carbonate buffers were employed in the appropriate pH ranges for the maintenance of constant pH. All reactions were conducted in distilled water containing approximately 3% ethanol or acetonitrile. Measurements of pH were carried out with the glass electrode and a Radiometer PHM 4c pH meter.

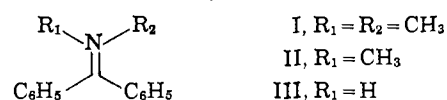
Product Identification.—The products of all of the reactions studied were identified by comparison of ultraviolet spectra of the products with those of authentic samples.

p*K*_a Determinations.—The p*K*_a values for the conjugate acids of the benzophenone Schiff bases were determined spectrophotometrically as previously described.²³ p*K*_a values for the conjugate acids of a series of benzaldehyde oximes were

determined from spectral measurements on these substrates in solutions of hydrochloric or sulfuric acid containing 0.1 *M* hydroxylamine hydrochloride in a fashion similar to that described by Wolfenden and Jencks.³¹ Values of p*K*_a were obtained from plots of optical density differences at two convenient wave lengths against values of *H*₀.^{32,33}

Results

The logarithm of the first-order rate constants for the hydrolysis of benzhydrylidenedimethylammonium ion (I), benzhydrylidene methylamine (II), and benzhydrylideneamine (III) at 25° are plotted as a function of pH in Fig. 1. The pH-rate profiles for II and III are similar to those previously obtained for the hydrolysis



of benzylidene-1,1-dimethylethylamines substituted with electron-withdrawing substituents.²³ The pH-rate profiles for II and III exhibit a pH-independent reaction above pH 9, which may be accounted for either in terms of rate-determining water attack on the free substrates or in terms of rate-determining hydroxide ion attack on the protonated substrates,²³ as well as a pH-independent reaction under slightly acidic conditions, in which the Schiff bases are nearly completely converted to the conjugate acids, which may be accounted for as rate-determining attack of water on the protonated substrates.²³ Under still more acidic conditions, the first-order rate constants decrease with decreasing pH, suggesting a transition in rate-determining step to rate-determining carbinolamine decomposition.²³ First-order rate constants for the hydrolysis of III at values of pH below 1 (not shown on graph) are somewhat larger than expected on the basis of data under less acidic conditions. The reasons for this behavior are not known. The pH-rate profile for the hydrolysis of I, which cannot, of course, be converted to a free base form, exhibits a base-catalyzed reaction, due to rate-determining attack of hydroxide ion on this substrate, as well as the water reaction observed for the hydrolysis of II and III. The first-order rate constants for the attack of water on the cationic substrates decrease as the methyl group substitution on the nitrogen of the amine component increases. In contrast, the relative reactivities are reversed under conditions in which carbinolamine decomposition is rate determining (Fig. 1). The dissociation constants for the conjugate acids of II and III, the first-order rate constants for the pH-independent reactions, and the observed, in the case of I, or calculated, in the cases of II and III, second-order rate constants for the attack of hydroxide ion on the cationic Schiff bases are collected in Table I. The last values were obtained from the p*K*_a values for the protonated substrates and first-order rate constants under basic conditions.²³ Of particular interest is the fact that the observed second-order rate constant for the attack of hydroxide ion on I is similar to the corresponding calculated values for the attack of hydroxide ion on the conjugate acids of II and III. The dissociation constant for the conjugate acid of III and the rate of hydrolysis of the protonated substrate are similar to values previously obtained by Culbertson.³⁴

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TABLE I
RATE CONSTANTS FOR THE HYDROLYSIS OF BENZOPHENONE
SCHIFF BASES AND DISSOCIATION CONSTANTS FOR THE
PROTONATED SCHIFF BASES AT 25° AND IONIC STRENGTH 0.50

Substrate	$K_{SBH^+}^a$ M	k_1^b min. ⁻¹	$k_{calcd.}^c$ M. ⁻¹ min. ⁻¹	$k_{H_2O}^d$ min. ⁻¹
	6.4×10^{49}	0.011
	1.0×10^{-7f}	0.0054	5.4×10^4	.080 ^f
	0.63×10^{-7}	.0068	4.3×10^4	.016
	2.8×10^{-7}	.0047	1.3×10^5	.029
	0.45×10^{-7}	.0084	3.8×10^4	.0072
	0.27×10^{-7}	.0067	1.8×10^4	.0028

^a Dissociation constants for the protonated Schiff bases. ^b First-order rate constants for the pH-independent reaction above pH 9. ^c Calculated second-order rate constants for the attack of hydroxide ion on the protonated Schiff bases. ^d First-order rate constants for the attack of water on the protonated Schiff bases, estimated from the hydrolysis rates in the pH region 4-5. ^e Observed, rather than calculated, rate constant. ^f See also ref. 34.

TABLE II
CATALYTIC CONSTANTS FOR THE GENERAL BASE CATALYZED
ATTACK OF WATER ON BENZHYDRYLIDENEDIMETHYLAMMONIUM
ION AT 25° AND IONIC STRENGTH 1.0

Catalyst	pK _a ^a	Concn. range, M	pH	$k_{cat.}^b$ M. ⁻¹ min. ⁻¹
Acetate	4.76	0.2-1.0	5.25	0.021
3-Bromopropionate	4.02	.2-1.0	4.45	.015
Formate	3.77	.2-1.0	4.15	.012
Chloroacetate	2.86	.2-1.0	3.30	.0071
Cyanoacetate	2.43	.2-1.0	2.90	.0054

^a Of the conjugate acid. ^b No corrections for statistical factors have been made.

The first-order rate constants for the hydrolysis of several substituted benzhydrylidenedimethylamines were determined at 25° under slightly acidic and slightly alkaline conditions. These values are also collected in Table I. In the case of each reaction, first-order rate constants were determined at more than one value of pH to ensure that the measured rates corresponded to the pH-independent reactions illustrated in Fig. 1. The dissociation constants for the protonated benzhydrylidenedimethylamines and the calculated second-order rate constants for the reaction of these substrates with hydroxide ion are also presented in Table I. The dissociation constants and the second-order constants for the hydroxide ion reactions are correlated by the Hammett σ -constants with σ values of 2.0 and 1.8, respectively. On the other hand, the first-order rate constants for the attack of water on the protonated substrates are correlated somewhat better by the σ^+ -substituent constants with a ρ^+ -value of 1.1 (Fig. 2).

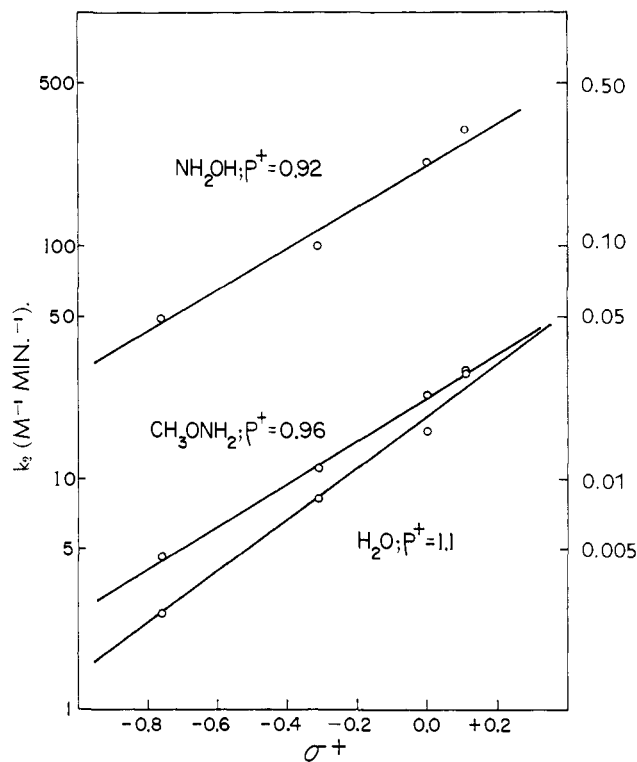
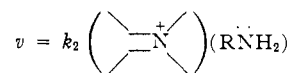


Fig. 2.—Second-order rate constants for the reaction of water, hydroxylamine, and methoxyamine with the conjugate acids of a series of substituted benzhydrylidenedimethylamines at 25° plotted against the σ^+ -substituent constants. The legend on the left applies to the reactions involving amines while that on the right applies to the water reaction.

The attack of water on benzhydrylidenedimethylammonium ion is subject to general base catalysis. The catalytic constants for five carboxylate anions, together with the conditions for their determination, are collected in Table II. These catalytic constants are correlated by a single straight line in a Brønsted plot with a slope, β , of 0.27.

The reactions of hydroxylamine, methoxyamine, and, in some cases, semicarbazide with the conjugate acids of several Schiff bases were studied. These reactions adhere to the rate law



Representative data for the reaction of methoxyamine with benzhydrylidenedimethylammonium ion, which demonstrate the validity of this rate law, are collected in Table III. In some cases, discussed below, this

TABLE III
KINETICS OF THE REACTION OF METHOXYAMINE WITH
BENZHYDRYLIDENEDIMETHYLAMMONIUM ION AT 25°

pH	(CH ₃ ONH ₂) free base, M	$k_{obsd.}^a$ min. ⁻¹	k_2 M. ⁻¹ min. ⁻¹
5.02	0.018	0.047	2.6
	.036	.086	2.4
	.072	.16	2.2
	.14	.31	2.2
	.21	.56	2.6
6.25	.016	.037	2.3
	.062	.13	2.1
	.090	.19	2.1
	.11	.30	2.7

rate law must be modified to include general base catalysis by a second molecule of amine. Second-order

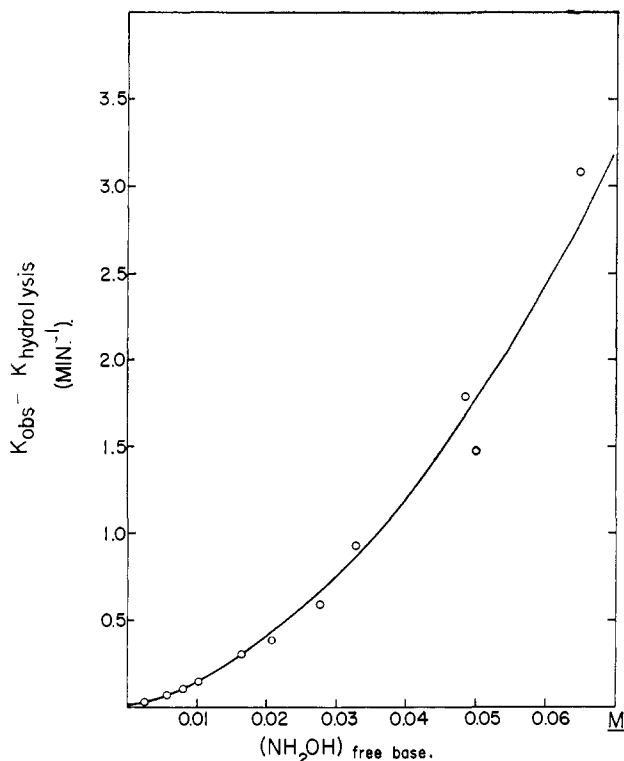


Fig. 3.—First-order rate constants for the reactions of hydroxylamine with benzhydrylidenedimethylammonium ion at 25° plotted against the concentration of hydroxylamine free base. The rate constants have been corrected for a small concomitant hydrolysis reaction. The solid line is a calculated line based on a rate law derived from these data (see Results). These results were taken from experiments performed at pH 6.00 and 6.60.

rate constants for the reactions indicated above are collected in Table IV. The appropriate oxime, O-methyl oxime, or semicarbazone was identified as the product of all reactions of this type. In all cases, the

TABLE IV
SECOND-ORDER RATE CONSTANTS FOR THE AMINOLYSIS OF
BENZOPHENONE SCHIFF BASES AT 25°^a

Substrate	$k_2^{\text{NH}_2\text{OH}}$, $M^{-1} \text{ min.}^{-1}$	$k_2^{\text{NH}_2\text{OCH}_3}$, $M^{-1} \text{ min.}^{-1}$	$k_2^{\text{NH}_2\text{NHCONH}_2}$, $M^{-1} \text{ min.}^{-1}$
	9.0	2.4	...
	590	45	9.0
	230	23	0.7
	320	29	...
	100	11	...
	49	4.6	...

^a All reactions run under conditions in which the substrates were converted nearly quantitatively to their conjugate acids; ionic strength maintained at 0.50 for the reactions involving hydroxylamine and methoxyamine, 1.0 for those involving semicarbazide.

concentration of the attacking amine was adjusted so that the aminolysis reaction was at least an order of magnitude more rapid than the concomitant hydrolysis reaction. All rate constants were measured for at least three concentrations of amine at two or more values of pH. Values of pH were maintained sufficiently low, in the range pH 3 to 6, in all cases so that the Schiff bases were essentially completely converted to the conjugate acids. As in the case of the hydrolysis reaction under conditions in which the attack of water is rate determining, increasing methyl group substitution in the amine component of the Schiff base causes a decrease in the aminolysis rates. Second-order rate constants for the reaction of hydroxylamine and methoxyamine with the substituted benzhydrylidenemethylammonium ions are correlated by the σ^+ -substituent constants as indicated in Fig. 2. Values of ρ^+ of 0.92 for the hydroxylamine and 0.96 for the methoxyamine reaction were calculated from the slopes of these plots. The data for the attack of water on these substrates are included in this figure for comparative purposes.

First-order rate constants for the reactions of hydroxylamine with benzhydrylidenedimethylammonium ion and hydroxylamine and methoxyamine with *p*-methoxybenzhydrylidenemethylammonium ion increase more rapidly than the concentration of the nucleophilic reagent. The apparent catalysis of these reactions by a second molecule of amine was investigated more thoroughly in the case of the first reaction indicated above. Studies of this reaction at pH 6.00 and 6.61 indicated that the catalysis became increasingly marked as the fraction of hydroxylamine as the free base was increased. The catalysis is, therefore, of the general base, rather than general acid, type. First-order rate constants for the reaction of hydroxylamine with benzhydrylidenedimethylammonium ion, corrected for the small contribution of a hydrolysis reaction, are plotted against the concentration of hydroxylamine free base in Fig. 3. The solid line in Fig. 3 is a calculated line based on the derived rate law: $k_{\text{obsd}} (\text{min.}^{-1}) = 9.0(\text{NH}_2\text{OH}) + 530 \cdot (\text{NH}_2\text{OH})^2$. It is likely that many or all of the aminolysis reactions listed in Table IV are subject to general base catalysis by a second molecule of amine. Such catalysis might not be detected as a result of the lower concentrations of amine employed in the studies with the more reactive substrates.

Although this reaction has not been studied extensively, the aminolysis of Schiff bases may also be detected under basic conditions. For example, hydroxylamine reacts with benzhydrylidenemethylamine, yielding the oxime, in a reaction which is independent of pH from pH 11.6 to 13. The second-order rate constant for this reaction at 25° and ionic strength 0.50 is $0.3 M^{-1} \text{ min.}^{-1}$.

The reaction of semicarbazide with a series of substituted benzaldehyde oximes, yielding the semicarbazones, and the reaction of hydroxylamine with a series of substituted benzaldehyde semicarbazones, yielding the oximes, are dependent upon acid catalysis under slightly acidic conditions. Third-order rate constants for these reactions at 25° and ionic strength 0.50 are collected in Table V. These rate constants were determined at several concentrations of nucleophilic reagent over the concentration range 0.02–1.0 *M*. These third-order rate constants are plotted against the

σ -substituent constants in Fig. 4. Both reactions are characterized by ρ -values of -1.7 , indicating that the over-all equilibrium constants for the interconversion of oximes and semicarbazones are independent of the nature of polar substituents.

TABLE V

THIRD-ORDER RATE CONSTANTS FOR THE ACID-CATALYZED REACTIONS OF SUBSTITUTED BENZALDEHYDE SEMICARBAZONES WITH HYDROXYLAMINE AND SUBSTITUTED BENZALDEHYDE OXIMES WITH SEMICARBAZIDE AT 25° AND IONIC STRENGTH 0.50

Substituent	Nucleophilic reagent	pH range	k_3 , $M^{-2} \text{ min.}^{-1}$
<i>p</i> -Dimethylamino	Hydroxylamine	5.1–6.7	2.3×10^6
<i>p</i> -Methoxy	Hydroxylamine	3.4–4.9	6.1×10^5
<i>p</i> -Methyl	Hydroxylamine	3.3–4.7	4.2×10^5
H	Hydroxylamine	1.7–8.1	2.1×10^5
<i>p</i> -Chloro	Hydroxylamine	3.8–4.9	9.7×10^4
<i>p</i> -Nitro	Hydroxylamine	3.1–4.2	7.5×10^3
<i>p</i> -Methoxy	Semicarbazide	2.7–4.9	3.6×10^3
<i>p</i> -Methyl	Semicarbazide	2.2–3.8	2.6×10^3
H	Semicarbazide	2.6–4.3	1.3×10^3
<i>p</i> -Chloro	Semicarbazide	2.4–3.8	6.7×10^2
<i>p</i> -Nitro	Semicarbazide	2.7–4.9	6.0×10^1

Values of pK_a for the conjugate acids of a series of substituted benzaldehyde oximes, determined as indicated in the Experimental section, are collected in Table VI. These values are correlated by the σ -substituent constants with a ρ -value of -1.9 .

TABLE VI

VALUES OF pK_a FOR THE CONJUGATE ACIDS OF SUBSTITUTED BENZALDEHYDE OXIMES^a

Substituent	pK_a
<i>p</i> -Nitro	-2.40
<i>p</i> -Chloro	-1.25
H	-1.20
<i>p</i> -Methyl	-0.65
<i>p</i> -Methoxy	-0.25

^a Determined in the presence of 0.1 *M* hydroxylamine hydrochloride.

Discussion

A. Hydrolysis Reactions.—The character of the pH-rate profiles and the effect of structure on reactivity for the hydrolysis of benzhydrylidemethylamines are quite similar to those previously obtained for the hydrolysis of benzylidene-1,1-dimethylethylamines.²³ The extended discussion, presented in reference 23, concerning the mechanistic features of the latter group of reactions is equally pertinent to the hydrolysis of the benzophenone Schiff bases. In brief, the principal conclusions which are particularly relevant to the following discussion are as follows. The pH-independent reaction which is observed under basic conditions is very probably the consequence of rate-determining attack of hydroxide ion on the protonated Schiff base. Under more acidic conditions, in which the Schiff bases are predominantly protonated, the attack of water, rather than hydroxide ion, on the protonated Schiff base becomes the important reaction pathway. Finally, under still more acidic conditions, in which the first-order rate constants decrease with decreasing pH, a transition in rate-determining step occurs and carbinolamine decomposition becomes rate determining.

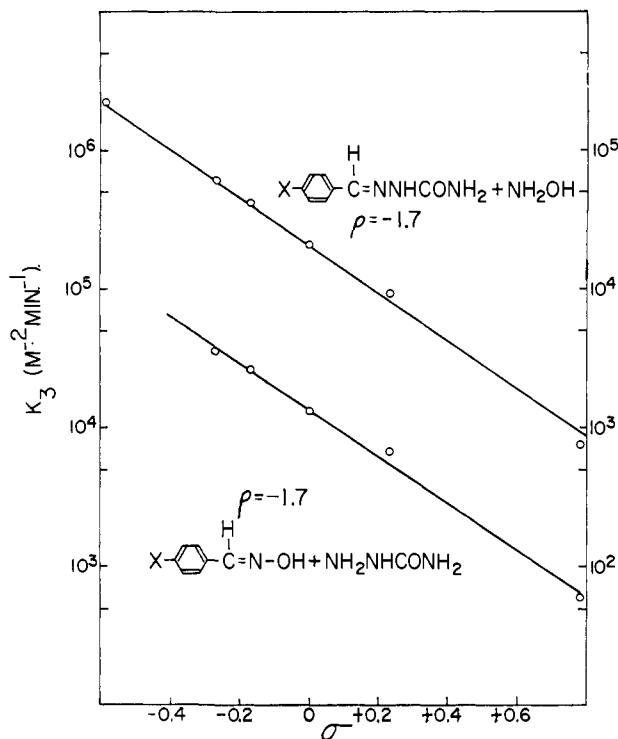
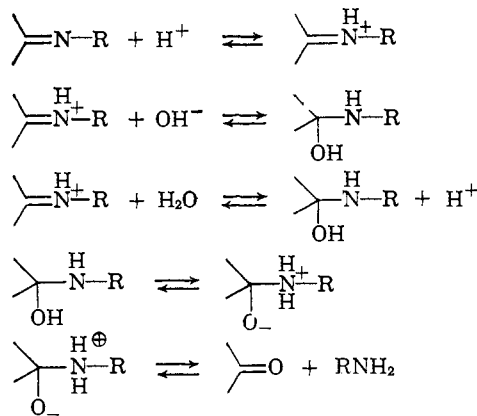


Fig. 4.—Third-order rate constants for the reaction of hydroxylamine with a series of substituted benzaldehyde semicarbazones and for the reaction of semicarbazide with a series of substituted benzaldehyde oximes at 25° and ionic strength 0.50 plotted against the σ -substituent constants. The legend on the left applies to the former reaction while that on the right applies to the latter reaction.

The formulation of the pH-independent reaction under basic conditions as the attack of hydroxide ion on the protonated Schiff base, rather than as the kinetically indistinguishable attack of water on the free

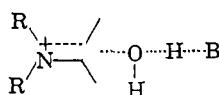


Schiff base, was first suggested by Willi²⁵ and strongly supported by the finding that the first-order rate constants for the hydrolysis of benzylidene-1,1-dimethylethylamines and benzylideneanilines increase slightly with increasing electron-donating power of polar substituents in the benzaldehyde moiety.²³ In the present case, the first-order rate constants for the hydrolysis of benzhydrylidemethylamines in basic solution are essentially independent of the nature of the polar substituent (Table I). These results may be accounted for in terms of the opposing effects of polar substituents on substrate protonation and on hydroxide ion attack but are not consistent with rate-determining attack of water on the free base of the substrate.²³ Under con-

ditions in which the attack of water on the protonated Schiff bases becomes the predominant reaction pathway, the first-order rate constants increase with increasing electron-withdrawing power of the polar substituent, as expected (Table I).²³ The observation that the *measured* second-order rate constant for the attack of hydroxide ion on the cationic Schiff base benzhydrylidenedimethylammonium ion (I) is nearly identical with the *calculated* second-order rate constants for the attack of hydroxide ion on the protonated species of benzhydrylidenedimethylamine and -amine provides very strong support for the above arguments. In these studies, the nondissociable methyl group is employed as a model for a dissociable proton in order to provide a means of distinguishing between otherwise kinetically indistinguishable reaction pathways. This technique has been previously employed to distinguish between alternate pathways for nucleophilic reactions of acetyl-imidazolium.³⁵

Under more acidic conditions, in which the attack of water on the Schiff bases is the predominant reaction pathway, the first-order rate constants decrease with increasing methyl group substitution on the imino nitrogen (Table I, Fig. 1). Although the substitution of methyl for hydrogen may clearly effect the reactivities of these substrates in several ways, these data may be accounted for by presuming that the predominant effect of the substitution is the stabilization of the ground state relative to the transition state by inductive or hyperconjugative electron release from the methyl groups. On the other hand, under still more acidic conditions, in which decomposition of the carbinolamine is rate determining, the order of reactivity is reversed, the dimethyl compound being most reactive (Fig. 1). Since the substitution of methyl for hydrogen may affect two pre-equilibria as well as the rate of carbinolamine decomposition, it is difficult to specify precisely why one obtains the observed order of reactivity. Regardless of the explanation, the important point, to be employed later, is that the relative reactivities of these substrates change as the nature of the rate-determining step is altered.

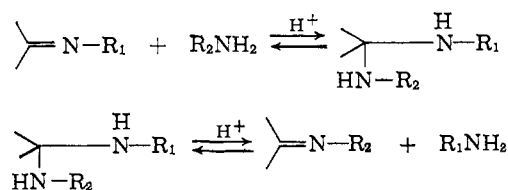
The attack of water on benzhydrylidenedimethylammonium ion is subject to general base catalysis by carboxylate ions with a Brønsted coefficient of 0.27 (Table II). General acid-base catalysis of Schiff base formation and hydrolysis has been observed previously in several instances.^{23,24,26,36,37} For the present reaction, as in the case of general base catalysis for the attack of water on fully protonated benzylidene-1,1-dimethylethylamine,²³ the base catalysis must involve partial removal of the proton from the attacking water molecule in the transition state. The alternative general acid-specific base mechanism, involving proton transfer to the nitrogen atom, is impossible for this



reaction. In the reverse reaction, the above mechanism corresponds to general acid catalysis for carbinolamine

dehydration with a Brønsted coefficient, α , of 0.73. General acid catalysis for carbinolamine dehydration has been observed for benzylideneaniline,^{24,38} oxime,³⁹ semicarbazone,^{22,39-41} and, probably phenylhydrazones formation.³⁹ The general acid-catalyzed reaction for carbinolamine dehydration is largely overshadowed quantitatively by catalysis by the solvated proton suggesting, in accordance the above observation, that the α -value for this reaction is close to unity.

B. Aminolysis Reactions.—The replacement of the amine component of a Schiff base by another amine, transimination, is a symmetrical reaction. Although the existence of an intermediate in these reactions has yet to be demonstrated, the nature of the reactions almost certainly requires that they proceed *via* a two-step reaction path involving a *gem*-diamine as intermediate. Such an intermediate is analogous to the carbinolamine intermediate for Schiff base formation and hydrolysis. Under conditions in which formation and decomposition



of the *gem*-diamine exhibit a similar dependence on acidity, one may expect that, for nearly all cases, the rate-determining step in transimination reactions will involve either the attack of the weaker amine on the Schiff base involving the stronger amine or *vice versa*. Clearly, if the two steps of the reactions depend on acidity in different fashions, one may experience changes in rate-determining step, as in Schiff base hydrolysis,²³ as a function of pH. Since, as is indicated in the Results section, the transimination reactions investigated in this study occur principally *via* a reaction pathway involving the protonated substrate regardless of whether the attacking amine is a stronger or weaker base than the resident amine, the nature of the rate-determining step in such transimination reactions will be considered below. Several lines of evidence suggest, but do not prove, that for reactions of this type the attack of the weaker amine on the Schiff base involving the stronger amine is rate determining. (1) The effect of increasing methyl group substitution on the imino nitrogen atom on the rates of reaction of semicarbazide, hydroxylamine, and methoxyamine with the benzophenone Schiff bases is qualitatively similar to that on the rate of water attack on these substrates (Tables I and IV). This finding suggests that the rate-determining step for the reactions involving the amines is also attack of the nucleophilic reagent. This suggestion is considerably strengthened by the fact that, under conditions in which carbinolamine decomposition becomes rate-determining in the water reaction, the order of reactivities is reversed.

(2) Values of ρ^+ for the reaction of substituted benzhydrylidenedimethylamines with hydroxylamine (0.92) and methoxyamine (0.96) are close to that for the attack of water (1.1) on these substrates (Fig. 2). This

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finding also suggests that the attack of the amines is the rate-determining step.

(3) Both the attack of water and the reactions of the amines with benzhydrylidenedimethylammonium ion and other cationic benzophenone Schiff bases (Results) are subject to general base catalysis. This finding is consistent with and support for rate-determining amine attack. It is, of course, quite possible to account for general base catalysis of the aminolysis reactions by a specific base-general acid catalyzed decomposition of the *gem*-diamine intermediate (in the reverse reaction, this corresponds to general base catalysis of the attack of dimethylamine on the unprotonated oxime), or by a general base-catalyzed decomposition of the protonated *gem*-diamine intermediate (general acid catalysis of the attack of dimethylamine on the oxime in the reverse direction).

(4) No evidence has been found, despite a reasonably careful search, for the accumulation of a detectable amount of the *gem*-diamine intermediate in the reactions of the benzophenone Schiff bases with weakly basic amines. This finding is consistent with rate-determining attack since only in the case of rate-determining *gem*-diamine decomposition would the intermediate accumulate.

In summary, the similarity of the effect of alteration of the structure of either the amine or carbonyl component of the Schiff bases on reaction rates for the attack of water and for the reactions with the amines, together with the finding that these reactions have similar catalytic pathways available to them, suggests that the attack of the amines is rate determining.

The above conclusions are consistent with data obtained for the acid-catalyzed interconversions of oximes and semicarbazones. Third-order rate constants for the acid-catalyzed formation of semicarbazones from benzaldehyde oximes and for the acid-catalyzed formation of oximes from benzaldehyde semicarbazones are correlated by Hammett σ -constants with identical ρ -values of -1.7 (Fig. 4). According to the above arguments, the attack of semicarbazide on the oximes should be rate determining rather than *vice versa*. Since the observed ρ -value of -1.7 must be the sum of ρ -values for oxime protonation and for semicarbazide attack on the protonated substrate, it follows that the ρ -value for the protonation of benzaldehyde oximes must have a value more negative than -1.7 since the ρ -value for the attack reaction is certainly positive. The observed ρ -value of -1.9 for the dissociation constants of protonated benzaldehyde oximes is consistent with this expectation.

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cis-Azoxybenzenes. I. Synthesis and Structure

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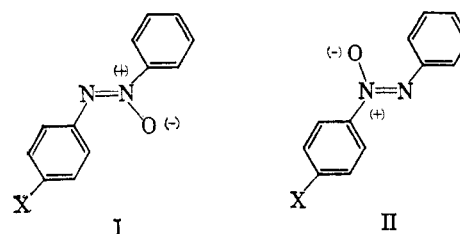
Nuclear magnetic resonance spectra are used to establish the configuration of the *cis*-azoxy group and to show the existence of two isomers in the monosubstituted compounds of this class. All the known monosubstituted and disubstituted *p*-methylazo and azoxy compounds were prepared and the chemical shifts of the methyl peaks, in c.p.s. downfield from tetramethylsilane, were obtained. In the compound *cis-p,p'*-dimethylazoxybenzene two methyl peaks were seen (at 112.7 and 105.2 c.p.s.), clearly eliminating the possibility of a symmetrical structure A and strongly indicating the structure B for the *cis*-azoxy group, analogous to the



known configuration of the corresponding *trans* isomers. This contention is further strengthened by the spectral evidence for two isomeric *cis*-azoxybenzenes from the oxidation of *cis-p*-methylazobenzene. Two methyl peaks of approximately the same intensity were seen (at 112.6 and 105.4 c.p.s.). Only the compound whose methyl resonance occurred at 112.6 c.p.s. was isolated, and on decomposition formed α -*trans-p*-methylazoxybenzene (I, X = CH₃). Two other *cis* monosubstituted compounds were isolated from the oxidation of *p*-bromo- and *p*-chloroazobenzene, respectively. We believe these to be the first reported examples of monosubstituted *cis*-azoxybenzenes.

The chemistry and the configuration of the *trans*-azoxybenzenes have been known for several years. Angeli¹ and co-workers have shown that the monosubstituted and the dissymmetrically substituted compounds exist in two isomeric forms, designated as " α " (I), and " β " (II), which differ only in the relative position of the oxygen atom. These results have recently been corroborated by the independent, unequivocal synthesis of each of the isomeric forms of *trans-p*-bromo- and *-p*-ethoxyazobenzene.²

However, reports of the geometric *cis* isomers have been scarce and pertain only to the unsubstituted or the symmetrically disubstituted compounds.³ To our



knowledge no *cis* monosubstituted azoxybenzenes have been reported. This paper presents a general synthetic method for the preparation of these compounds, albeit in small yields, and reports a preliminary study of their structure.

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