Internal Catalysis in the Reaction of *N,N,N'*-Trimethylethylenediamine with Phenylglyoxal Hydrate to Give *N*-(2-Dimethylaminoethyl)-*N*-methylmandelamide[1a]

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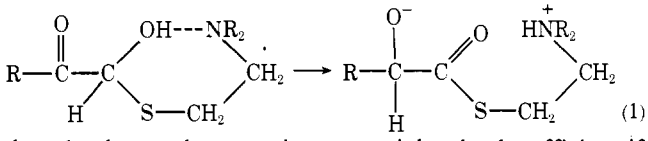
Abstract: The transformation of phenylglyoxal hydrate to mandelate ions was found to be subject to general base catalysis by trimethylamine. The kinetics of the reactions with pyrrolidine, morpholine, and 2-methoxy-*N*-methylethylamine were also analyzed, revealing additional reaction paths, some of which give amides of mandelic acid. Equilibrium constants for the formation of carbinolamines from these secondary amines and phenylglyoxal hydrate were determined. The reaction of *N,N,N'*-trimethylethylenediamine with phenylglyoxal hydrate was found to proceed almost entirely by a pathway that is first order in unprotonated amine and first order in electrically neutral hydrate. This reaction, which gives *N*-(2-dimethylaminoethyl)-*N*-methylmandelamide as a major product, is about 100 times as fast as would be expected from the results obtained with the other secondary amines. The high rate is believed to result from the reversible formation of the carbinolamine $PhCOCH(OH)NMeCH_2CH_2NMe_2$, whose dimethylamino group acts as an internal basic catalyst, removing the hydroxylic proton and thus facilitating hydride migration to the carbonyl group via a transition state such as **3**.

The suggestion that a cancer cell is a cell that has lost its ability to bind its glyoxalase[2] has stimulated interest in the mechanism by which enzymes catalyze the transformation of glyoxal derivatives to α-hydroxy acids. Franzen had earlier shown that certain 2-dialkylaminoethanethiols are relatively efficient nonenzymatic catalysts for some such reactions and described evidence that their mechanism for catalysis is similar to that followed by enzymes.[3-5] The proposed reaction mechanism involves the formation of a hemimercaptal in which an internal hydride ion transfer takes place, aided by internal deprotonation of the hydroxy group by the amino group from the catalyst, as shown in eq 1. We



(1)

thought that such a reaction step might also be efficient if the alkylthio substituent were replaced by an alkylamino substituent, whose much greater resonance electron-donating ability should more efficiently stabilize the resonance electron-withdrawing carbonyl group being formed in the reaction. For this reason, we decided to study the reaction of *N,N,N'*-trimethylethylenediamine with phenylglyoxal hydrate, whose reaction with hydroxide ions has already been studied kinetically in this laboratory.[6] In order to interpret the results, we also studied the reactions of some simple tertiary and secondary amines.

Results

Kinetics. To learn the effect of tertiary amines on the rate of transformation of phenylglyoxal hydrate to mandelate, the kinetics were studied in 0.1000 *M* hydrochloric acid solutions to which 0.146–1.20 *M* trimethylamine had been added. The rate constants obtained are plotted as solid circles against the free amine concentration in Figure 1. The catalytic activity of secondary monoamines of varying basicity was studied by carrying out the reaction in pyrrolidine, morpholine, and 2-methoxy-*N*-methylethylamine buffer solutions. The results obtained with pyrrolidine are listed in Table I. The rate constants obtained using 2-methoxy-*N*-methylethylamine are plotted against the free amine concentration in Figure 1, using different symbols for the various concentrations of 2-methoxy-*N*-methylethylammonium chloride. A similar plot of the morpholine data is shown in Figure 2. The most effective amine catalyst was *N,N,N'*-trimethylethylenediamine, for which the results are listed in Table II.

Accidental contamination of a reaction solution with magnesium sulfate (used in drying some pyrrolidine) led to the observation that this salt is an effective catalyst for the reaction in the presence of pyrrolidine. Runs carried out with a small amount of magnesium sulfate and 0.1005 *M* pyrrolidinium chloride gave first-order rate constants that increased from 0.0015 to 0.0046 sec^{-1} as the free pyrrolidine concentration increased from 0.0068 to 0.153 *M*. The rate in the presence of 0.100 *M* pyrrolidine and no added pyrrolidinium salt was independent (k = 0.0041 ± 0.0001 sec^{-1}) of the amount of magnesium salt added over the range 3×10^{-6} to 3×10^{-4} *M*, probably because the solutions were so basic that the solubility product of magnesium hydroxide was exceeded in all cases. No major amount of catalysis by magnesium ions was noted for the basic rearrangement of phenylglyoxal hydrate in the absence of amine.

Reaction Products. A 3-ml aliquot of catalyst solution was added to both the reference and reaction cells, and 10 μl of phenylglyoxal hydrate solution was added to the latter. The initial absorbances of about 0.9 would drop to about 0.014 if the reaction consisted only of the formation of amides or salts of mandelic acid. The infinite absorbances obtained in the sodium hydroxide runs exceeded the theoretical values by less than 0.01, and the spectra at infinite time were very similar to that of sodium mandelate. In a run carried out on a 1-l. scale, acidification led to the isolation of mandelic acid. The infinite absorbance values obtained using trimethylamine buffers were 0.04–0.09 higher than the theoretical values. The final spectra were those that would have been expected if the formation of mandelic acid had been accompanied by 4–10% benzoylformic acid formation.

Runs using 7–20 $\times 10^{-4}$ *M* phenylglyoxal hydrate were carried out on a 1-l. scale using pyrrolidine, morpholine, and *N,N,N'*-trimethylethylenediamine buffers. After the excess amine was largely neutralized, extraction gave *N*-mandeloylpyrrolidine, *N*-mandeloylmorpholine, and *N*-(2-

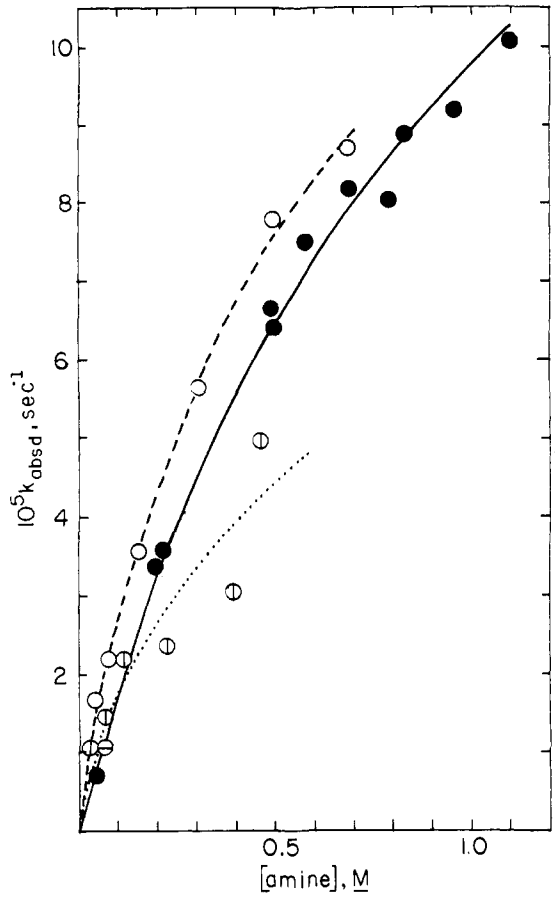


Figure 1. Plot of first-order rate constants for reaction of phenylglyoxal hydrate vs. amine concentrations. (●) Trimethylamine in the presence of 0.100 *M* trimethylammonium chloride. 2-Methoxy-*N*-methylethylamine in the presence of: (○) 0.0400 *M*, (⊕) 0.0801 *M*, and (⊖) 0.100 *M* 2-methoxy-*N*-methylethylammonium chloride.

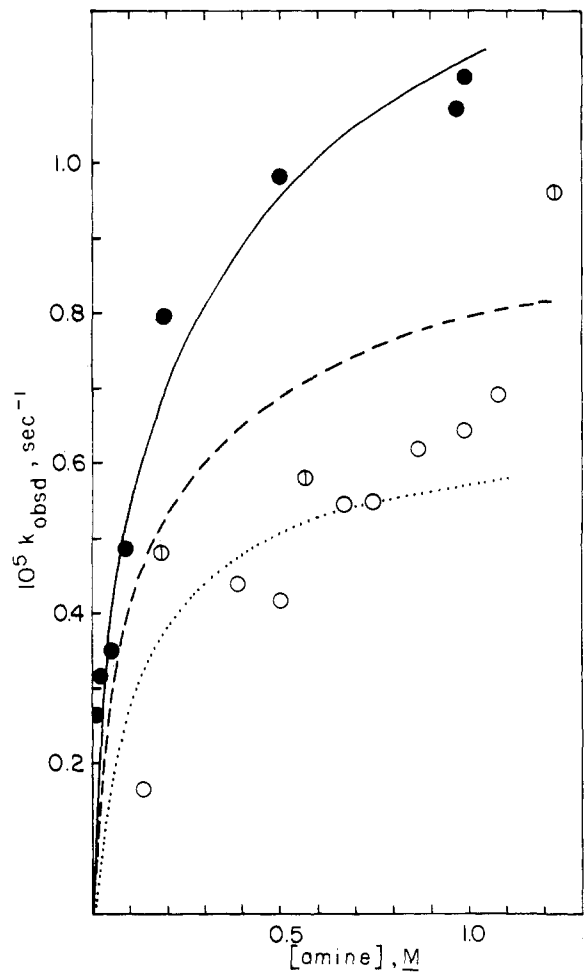


Figure 2. Plot of first-order rate constants for reaction of phenylglyoxal hydrate vs. morpholine concentration. In the presence of: (●) 0.0100 *M*; (⊕) 0.0200 *M*; (○) 0.0600 *M* morpholinium chloride.

Table I. Kinetics of the Reaction of Phenylglyoxal Hydrate in the Presence of Pyrrolidine Buffers[a]

$[(CH_2)_4NH]_t$,[b] *M*	$[HCl]_{added}$, *M*	[NaCl], *M*	10^5k, sec^{-1} Obsd	Calcd
0.1111	0.1008	0	3.8	3.8
0.1297	0.0198	0.0692	41.1	43.2
0.1402	0.1008	0	9.3	9.3
0.1552	0.0499	0.0442	27.5	25.4
0.1641	0.0599	0.0348	25.6	22.7
0.1922	0.0898	0.0069	18.3	18.0
0.2084	0.1008	0	16.8	17.5
0.2761	0.1008	0	22.4	23.0
0.4231	0.1008	0	28.5	30.0
0.5263	0.00996	0.0550	64.0	63.7
0.5399	0.0299	0.0421	51.5	51.6
0.5547	0.0499	0.0278	44.0	43.9
0.5667	0.1008	0	32.0	33.6
0.5791	0.0798	0.0037	36.2	36.8
0.6214	0.0827	0	37.0	36.9
0.6994	0.0827	0	37.6	38.1
1.028	0.0100	0.0384	52.6	54.9
1.052	0.0500	0.0129	46.4	43.7
1.069	0.0698	0	39.3	40.3
1.119	0.1008	0	40.7	37.1

[a] In aqueous solution at 35.0°. [b] Total concentration of pyrrolidine in all forms.

Table II. Kinetics of the Reaction of Phenylglyoxal Hydrate in the Presence of *N,N,N'*-Trimethylethylenediamine Buffers[a]

$[Me_2NC_2H_4NHMe]_t$,[b] *M*	$[HCl]_{added}$, *M*	[NaCl], *M*	10^5k, sec^{-1} Obsd	Calcd
0.0298	0.0200	0.0798	20.5	21.0
0.0300	0.0200	0.0798	19.9	21.2
0.0421	0.0403	0.0607	4.15	3.89
0.0436	0.0403	0.0610	6.37	6.96
0.0462	0.0403	0.0606	11.7	12.0
0.0499	0.0400	0.0600	19.3	19.1
0.0502	0.0403	0.0604	20.2	19.1
0.0523	0.0403	0.0609	21.5	22.5
0.0600	0.0403	0.0603	35.4	33.4
0.0601	0.0201	0.0795	56.5	57.8
0.0647	0.0403	0.0596	40.2	39.2
0.0716	0.0403	0.0605	50.8	50.4
0.0799	0.0399	0.0597	56.0	54.5
0.0901	0.0798	0.0201	18.7	16.7
0.0902	0.0798	0.0201	18.1	16.9
0.0904	0.0403	0.0598	63.2	62.1
0.0998	0.0602	0.0397	52.2	51.0
0.1072	0.0973	0.0026	15.2	15.2
0.1200	0.0798	0.0201	45.2	48.7
0.1262	0.0403	0.0600	82.9	80.8
0.1273	0.0972	0.0026	38.2	37.9
0.1400	0.1003	0	40.2	45.7
0.1492	0.0403	0.0602	88.3	86.8
0.1571	0.0972	0.0025	58.8	59.7

[a] In aqueous solution at 35.0°. [b] Total amine concentration.

dimethylaminoethyl)mandelamide, respectively. After acidification, another extraction gave mandelic acid in each case. No other products were isolated.

The infinite absorbance values obtained in the kinetic runs tended to be higher in the slower reactions. They exceeded the theoretical values by maxima of 0.04, 0.14, 0.3, and 0.5 in the runs using *N,N,N'*-trimethylethylenediam-

Table III. Acidity Constants in Water at 35°[a]

Acid	pK_a
$PhCOCH(OH)_2$	11.19
Pyrrolidinium ion	10.99
Morpholinium ions	8.27
$MeOCH_2CH_2NH_2Me^+$	9.44
$MeNHCH_2CH_2NMe_2 \cdot H^+$	9.43
$MeN^+H_2CH_2CH_2N^+HMe_2$	5.90
Me_3NH^+	9.64

[a] At zero ionic strength.

Table IV. Equilibrium Constant for Combination of Amines with Phenylglyoxal Hydrate[a]

Amine	K_c, M^{-1}
Pyrrolidine	104 ± 12^b
Morpholine	32 ± 1^b
2-Methoxy-*N*-methylethylamine	19 ± 4^b
N,N,N'-Trimethylethylenediamine	19 ± 2^c
Trimethylamine	$\sim 0.6^d$

[a] In water at 35.0°. [b] To give largely carbinolamine. [c] Obtained from kinetic measurements. [d] To give zwitterions. This value is almost undoubtedly in the range $0-2.0\ M^{-1}$.

ine, pyrrolidine, 2-methoxy-*N*-methylethylamine, and morpholine, respectively. Therefore, the rate constants obtained with the latter two amines are regarded as less reliable because of side reactions, especially in the slower runs.

Acidity Constants. Potentiometric determinations of acidity constants for phenylglyoxal hydrate and the protonated forms of the amines studied gave the p*K* values listed in Table III.

Carbinolamines. Equilibrium constants (K_c) for the formation of electrically neutral 1:1 adducts from phenylglyoxal and the amines studied were determined by measuring the decrease in the pH of amine buffers (as much as 0.4 pH unit) that accompanies the presence of increasing concentrations of phenylglyoxal hydrate.[7] The study of the reaction of formaldehyde with secondary amines by Sander and Jencks[8] and similar work show that the K_c values for secondary amines, which are listed in Table IV, probably refer largely to carbinolamine formation (eq 2).

$$PhCOCH(OH)_2 + HNR_2 \overset{K_c}{\rightleftharpoons} PhCOCH(OH)NR_2 + H_2O \quad (2)$$

The value for trimethylamine, which is so small as to be relatively unreliable, would have to refer to the formation of a hydrogen-bonded complex and/or a zwitterion as shown in eq 3

$$PhCOCH(OH)_2 + NMe_3 \overset{K_c}{\rightleftharpoons} PhCOC(O^-)HNMe_3^+ + H_2O \quad (3)$$

that is analogous to the one formed from trimethylamine and formaldehyde hydrate.[9] The fact that the rough value of K_c listed for trimethylamine in Table IV is 22% as large as its equilibrium constant for zwitterion formation from formaldehyde hydrate,[9] whereas the value of K_c listed for morpholine is only 4% as large as its equilibrium constant for carbinolamine formation from formaldehyde hydrate,[8] suggests that the actual value of K_c for trimethylamine may be smaller than that listed, or that much of the adduct may be a hydrogen-bonded complex rather than a zwitterion.

The K_c determination data gave no evidence for the formation of adducts involving two molecules of amine per molecule of phenylglyoxal hydrate, but this does not rule out the possible importance of such adducts at higher amine concentrations than those (<0.10 *M*) at which measurements were made. (The pH method for studying the combination of phenylglyoxal hydrate with amines is not very useful at high amine concentrations.)

From the reaction of morpholine with phenylglyoxal hydrate was isolated a stable crystalline solid whose elemental analysis and proton magnetic resonance spectrum were those expected from the carbinolamine. Pyrrolidine gave a somewhat unstable crystalline solid that decomposed slowly to an oil. The ^1H NMR spectrum of the solid agreed well and the elemental analysis fairly well with the carbinolamine structure. When excess pyrrolidine was used, an oily solid was obtained that may have consisted of about equal amounts of the carbinolamine and the aminal $[C_6H_5COCH(NC_4H_8)_2]$, but this was not established unequivocally. Reaction of phenylglyoxal hydrate with 2-methoxy-*N*-methylethylamine gave an oil whose ^1H NMR spectrum was plausible for the carbinolamine.

Discussion

The hydroxide catalyzed reaction is assumed to proceed by the mechanism given previously[6] which is shown in eq 4-7.

$$PhCOCH(OH)_2 + OH^- \overset{K_1}{\rightleftharpoons} PhCOCH(OH)O^- \quad (4)$$

$$PhCOCH(OH)O^- + OH^- \overset{K_2}{\rightleftharpoons} PhCOCH(O^-)_2 \quad (5)$$

$$PhCOCH(OH)O^- \xrightarrow{k_1} PhCH(OH)CO_2^- \quad (6)$$

$$PhCOCH(O^-)_2 \xrightarrow{k_2} PhCH(O^-)CO_2^- \xrightarrow{H_2O} PhCH(OH)CO_2^- \quad (7)$$

$$PhCOCH(OH)_2 + A \xrightarrow{k_3} \text{product} \quad (8)$$

$$PhCOCH(OH)O^- + A \xrightarrow{k_4} \text{product} \quad (9)$$

$$PhCOCH(OH)NR_2 + OH^- \overset{K_3}{\rightleftharpoons} PhCOCH(O^-)NR_2 + H_2O \quad (10)$$

$$PhCOCH(OH)NR_2 + R_2NH \overset{K_d}{\rightleftharpoons} PhCOCH(NR_2)_2 + H_2O \quad (11)$$

$$PhCOCH(OH)NR_2 + R_2NH \xrightarrow{k_5} \text{product} \quad (12)$$

When any amine (A) is added, the possibility of general base catalysis of the reaction of the hydrate (eq 8) or its conjugate base (eq 9) is introduced. If the amine is secondary, significant amounts of the reactant may be present as carbinolamine (eq 2), carbinolamine anion (eq 10), or aminal (eq 11), and an additional reaction pathway involving amine catalysis of decomposition of the carbinolamine (eq 12) is possible.

The rate constants are defined to include all the kinetically equivalent pathways for reaction. For example, k_3 covers all mechanisms in which the transition state comes from one molecule of amine and one molecule of phenylglyoxal hydrate without the gain or loss of protons (but perhaps with the gain or loss of solvent molecules). The values of k_3 are of major interest because, in the case of *N,N,N'*-trimethylethylenediamine, reaction by the mechanism we are seeking (the nitrogen equivalent of the mechanism shown in eq 1 for a sulfur case) will appear in the k_3 term. However, the values of the other constants must be determined in order to obtain k_3 values.

The effect of electrolyte concentrations on ionic activity coefficients was allowed for by the Davies equation.[10] Since some of the amine concentrations used were above 1 *M*, there should also be solvent effects on ionic activity coefficients. These were approximated by a procedure analogous to one used previously,[11] in which pK_w at zero ionic strength is assumed to increase linearly with the mole fraction of organic solute present (as it does for dioxane for mole fractions up to 0.3[12]) and by the same amount as for the same mole fraction of dioxane. To implement this assumption the Davies activity coefficient $\gamma_\pm$ is multiplied by

$\delta_{\pm}$, whose value may be obtained from MF, the mole fraction of added solute, by use of eq 13

$$\log \delta_{\pm} = 6.46\,\mathrm{MF} \tag{13}$$

which is based on data on aqueous solutions of dioxane.[12]

The added assumption that no significant fraction of reactant is ever present as the dianion[13] leads to the general eq 14 for k_{obsd}, the first-order rate constant for disappearance of reactant by the proposed scheme.

$$k_{obsd} = \frac{k_1K_1[OH^-] + K_1k_2K_2\left(\frac{[OH^-]}{\gamma_{\pm}\delta_{\pm}}\right)^2 + k_3[A] + K_1k_4[OH^-][A] + k_5K_c[A]^2}{1 + K_1[OH^-] + K_c[A] + K_cK_3[OH^-][A] + K_cK_d[A]^2 + \frac{K_cK_a[AH^+]}{K_{ach}}} \tag{14}$$

For runs carried out using sodium hydroxide, all but the first two terms in the numerator and the denominator disappear. Least-squares treatment[15] of the five k_{obsd} values determined in the present study and seven values determined previously, all at ionic strength 0.10, using the new K_1 value of 276 M^{-1}, gave values of $(2.63 \pm 0.15) \times 10^{-4}$ sec^{-1} and $(928 \pm 30) \times 10^{-4}$ M^{-1} sec^{-1} for k_1 and k_2K_2/γ_+^2, respectively, in reasonable agreement with the values obtained previously.

For the k_{obsd} values obtained using trimethylamine (Figure 1), the first four terms in the numerator and the first three in the denominator of eq 14 are relevant. A least-squares treatment[15] using the K_c value 0.6 M^{-1} obtained from potentiometric measurements (Table IV) gave k_3 and k_4 values of 8.8×10^{-5} and 17×10^{-5} M^{-1} sec^{-1}, respectively, and a standard deviation of 7.1% from the k_{obsd} values. Since the value of K_c is so small that its potentiometric determination is relatively unreliable, we also carried out least-squares treatments using K_c values of zero and 2.0 M^{-1} (estimated from the potentiometric measurements to be the maximum plausible value). With a K_c of zero, k_3 and k_4 were 6.8×10^{-5} M^{-1} sec^{-1} and zero, respectively, and the standard deviation was 9.8%. With a K_c of 2.0 M^{-1} sec^{-1}, k_3 and k_4 were 8.5×10^{-5} and 90×10^{-5} M^{-1} sec^{-1}, respectively, and the standard deviation was 6.9%. According to an F test,[16] the improvements in the standard deviation brought about by using a K_c value of 0.6 or 2.0 M^{-1} rather than zero were significant at the 90%, but not the 95%, confidence level. When no allowance was made for medium effects on ionic activity coefficients, standard deviations from the k_{obsd} values were 22% or more. We conclude that the treatment of the medium effect that we have used is a plausible one, that k_3 is quite probably in the range $(0.6\text{–}1) \times 10^{-4}$ M^{-1} sec^{-1}, and that k_4 cannot be evaluated reliably but is probably less than 10^{-3} M^{-1} sec^{-1}. The fit obtained with a K_c value of 0.6 is shown by the solid line in Figure 1.

All the terms in eq 14 are potentially significant for the secondary amines studied. For the monoamines, however, the basicity of the carbinolamines is so lowered, relative to that of the amines, by the benzoyl and hydroxyl substituents on the same carbon atom as the amino group that K_{ach}, the acidity constant of the protonated carbinolamine, is much larger than K_a, the acidity constant of the protonated amine. This makes the last term in the denominator negligible. Since K_3 is equal to K_w/K_{ac}, where values of K_{ac}, the acidity constant of the carbinolamine, are estimated in the Appendix, estimated values of K_3 are available. This leaves k_3, k_4, k_5, and K_d as unknowns for any secondary amine. Least-squares treatment[15] of the data on pyrrolidine gave the k_3 and k_4 values listed in Table V and k_5 and K_d values of $(9.0 \pm 1.2) \times 10^{-4}$ M^{-1} sec^{-1} and 2.7 ± 0.3 M^{-1}, respectively. The standard deviation of the k_{calcd} values, which are listed in Table I, from the k_{obsd} values was 5.2%. When either k_5 or K_d was left out of the treatment, the resulting standard deviation was 15% or more. The value of K_d is smaller than the equilibrium constant 14 M^{-1} for the formation of dimorpholinomethane from *N*-hydroxymethylmorpholine and morpholine at 25°,[17] probably because of steric hindrance by the benzoyl substituent. Although the least-squares treatment of the data used to determine K_c gave a value of zero for K_d, this treatment is not very sensitive to the value of K_d. With a K_d value of 2.7 M^{-1}, the pH data used to determine K_c may still be fit with a standard deviation of 0.01.

Table V. Values of k_3 and k_4 for Various Bases[a]

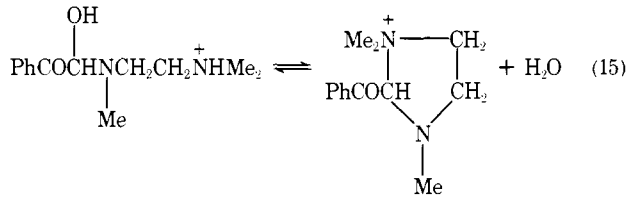
Base	$10^4 k_3$, M^{-1} sec^{-1}	$10^4 k_4$, M^{-1} sec^{-1}
Me_3N	0.8 ± 0.2[b]	5 ± 5[b]
Pyrrolidine	38 ± 5	105 ± 12
Morpholine	1.5 ± 0.1	21 ± 3
$MeOCH_2CH_2NHMe$	2.8 ± 0.6	50 ± 4
$Me_2NCH_2CH_2NHMe$	279 ± 15	
OH^-	726 ± 41[c]	928 ± 30[d]

[a] Unless otherwise noted, the ± figures are estimated standard deviations calculated by a computer program in which no account has been taken of uncertainties in the values of K_c, k_{obsd}, pK's, etc. [b] This allows for any plausible uncertainty in K_c. [c] This is the value of k_1K_1, which has the same meaning for hydroxide ions as k_3 has for other bases. [d] This is the value at ionic strength 0.1 of $k_2K_2/\gamma_{\pm}^2$, which has the same meaning for hydroxide ions as k_4 has for other bases.

The k_{obsd} values obtained using morpholine and 2-methoxy-*N*-methylethylamine buffers fit eq 14 (without the K_{ach} term) rather poorly. Parameters obtained by minimizing the sum of the squares of the fractional deviations led to standard deviations of at least 17% from the k_{obsd} values. In view of the tendency for the smaller rate constants obtained with these two amines to be less reliable in terms of fractional uncertainties, we obtained parameters by minimizing the sum of the squares of the deviations, i.e., $\Sigma(k_{obsd} - k_{calcd})^2$, and neglecting the most aberrant rate constant obtained using morpholine (the smallest one). The values of K_d and k_5 obtained were within their estimated standard deviations of zero. When these values were taken as zero, we obtained the values of k_3 and k_4 listed in Table V and standard deviations of 4.3×10^{-6} and 8.5×10^{-7} sec^{-1} from the k_{obsd} values obtained in the presence of 2-methoxy-*N*-methylethylamine and morpholine, respectively. The lines through the points for these two amines in Figures 1 and 2 were calculated from these values of k_3 and k_4. The discrepancies between the points and the lines probably arise largely from the side reaction(s) that produce(s) the rather large infinite absorbance values already referred to. The k_3 and k_4 for these two oxygenated amines are believed to be less reliable than those for the other amines. Since one source of uncertainty is an additional reaction and another is that no contribution of the k_5 pathway has been allowed for, it is likely that these k_3 and k_4 values are too large.

When eq 14 was applied to the k_{obsd} values obtained using *N,N,N'*-trimethylethylenediamine, it was necessary to treat K_c, whose direct experimental determination would have been greatly complicated by the dibasic nature of the amine, as a disposable parameter. When k_4, k_5, and K_d were neglected, values of 279×10^{-4} M^{-1} sec^{-1}, 19.3 M^{-1}, and $10^{-8.95}$ M were obtained for k_3, K_c, and K_{ach}, respectively, and the standard deviation from the k_{obsd} values was 6.1%. The k_{calcd} values are listed in Table II. When any of the constants k_4, k_5, and K_d were included in the regression

analysis, the standard deviation increased (because of a decrease in the number of degrees of freedom), the values of k_3, K_c, and K_{ach} were not changed significantly, and the values obtained for k_4, k_5, and K_d were smaller than their estimated standard deviations. In other words, the k_3 term is so large that the rate data may be correlated satisfactorily in terms of the reaction pathways governed by k_1, k_2, and k_3. The contribution of the k_4 and k_5 pathways is not large enough for meaningful values of these rate constants to be obtained. The validity of this interpretation of the results is supported by the plausibility of the values of K_c and K_{ach} obtained. Equilibrium constants for carbinolamine formation appear to be controlled largely by steric factors,[8] but polar effects may also play a significant role in some cases.[18] Hence, it is reasonable that K_c for *N,N,N'*-trimethylethylenediamine should have about the same value as K_c for 2-methoxy-*N*-methylethylamine (cf. Table IV), a secondary amine with about the same steric properties and basicity. K_{ach} is a measure of the basicity of $PhCOCH(OH)N\text{-}MeCH_2CH_2NMe_2$, a derivative of *N,N,N',N'*-tetramethylethylenediamine in which one of the methyl groups bears hydroxy and benzoyl substituents. A ρ^* value of 3.30 for the acidity of monoprotonated tertiary amines in which the substituent is attached directly to the nitrogen atom[19] and an attenuation factor of 2.8 for every added atom of separation between the substituent and the nitrogen atom lead to estimates that these substituents will decrease the basicities of the near and far amino groups by 3.65 and 0.17 pK units, respectively. On a per amino group basis, the pK_a of monoprotonated *N,N,N',N'*-tetramethylethylenediamine is 8.96 at 35°.[11] Hence pK_{ach} should be about 8.79 if the monoprotonated carbinolamine does not cyclize to an imidazolidinium ion, as shown in eq 15, to an appreciable extent.[20] The



(15)

difference between the observed and estimated values of K_{ach} can be covered exactly by an equilibrium constant of 0.45 for the reaction given in eq 15, but this difference is not clearly larger than the combined uncertainties in the two K_{ach} values.

Figure 3 is a Brønsted plot of the k_3 and k_4 values. The lines shown are the least-squares lines through the points for the three secondary amines pyrrolidine, morpholine, and 2-methoxy-*N*-methylethylamine. Considering the uncertainties in the rate constants for the latter two amines, the agreement with the lines is believed to be satisfactory. However, the points for trimethylamine lie considerably below the respective lines. This may arise in part from k_3 and k_4 for morpholine and 2-methoxy-*N*-methylethylamine being larger than the true values, a possibility we have already discussed. However, these k_3 and k_4 values would have to be lowered by implausibly large amounts to fall on straight lines that also pass through the points for trimethylamine and pyrrolidine. Furthermore, the resulting lines would correspond to rather implausible Brønsted β values of 1.0 or more. It therefore appears that trimethylamine is not reactive enough to fall on the Brønsted line described by relatively unhindered secondary amines. There are simple proton transfer reactions in which secondary and tertiary amines fall on separate Brønsted lines.[21] Hence the amines referred to may be increasing the rate of hydride transfer simply by deprotonating a hydroxy group. The transition

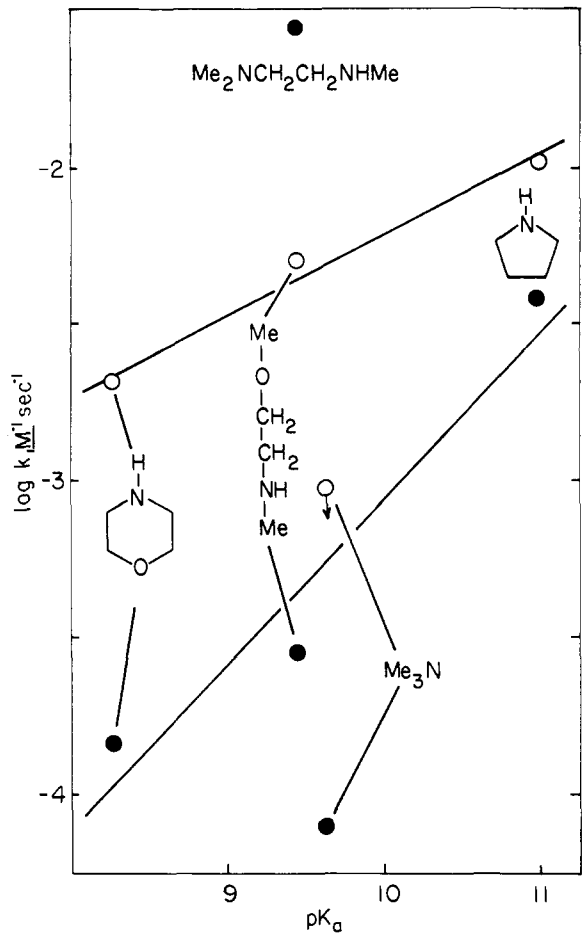
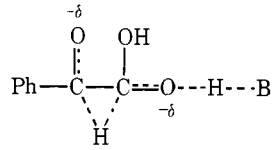


Figure 3. Brønsted plot for reactions of phenylglyoxal hydrate with amines: (●) k_3; (○) k_4. The lines are based on the points for the three secondary monoamines. The point with an arrow is an upper limit.

state in such a reaction would resemble **1** in the case of the k_3 reaction, but we have no convincing argument as to the



1

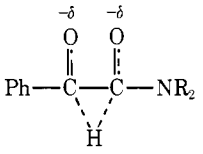
relative timing of the proton transfer and the hydride transfer. If the bases are acting simply as deprotonating agents, then the ratio of the equilibrium constant for the reaction governed by k_4 to that for the reaction governed by k_3 will be that shown in eq 16. Since a carboxylic acid, even one

$$\text{ratio} = \left(\frac{[PhCH(O^-)CO_2^-][PhCOCH(OH)_2]}{[PhCH(OH)O^-][PhCH(O^-)CO_2H]}\right)_{equil} \quad (16)$$

with an α-O^- substituent, will be a much stronger acid than phenylglyoxal hydrate, this ratio will be much larger than 1.0. Therefore k_4 would be the rate constant for a more exergonic reaction than k_3 so that the transition state should come earlier and the Brønsted β should be smaller for the k_4 than for the k_3 reaction. The plots in Figure 3 give β values of 0.26 and 0.52, respectively.

If the only way in which a secondary amine ever brought about the hydrogen transfer reaction in phenylglyoxal that we are studying were by simple deprotonation of phenylglyoxal hydrate and its conjugate base, the only product formed would be mandelate ions. Actually, mandelamide derivatives are significant products with all the secondary

amines we have studied. This makes particularly plausible the hypothesis that one reason that secondary amines are more reactive than tertiary amines is because they have mechanisms available to them (of the appropriate kinetic form) that are not available to tertiary amines. Thus, a mechanism in which the rate-controlling step is a hydride transfer in the conjugate base of the carbinolamine (transition state **2**) is kinetically indistinguishable from a rate-con-

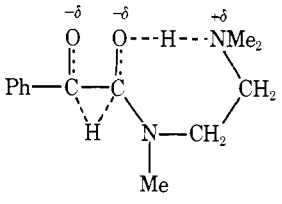


2

trolling attack of amine on the conjugate base of phenylglyoxal hydrate. Hence reaction via **2** is included in k_4, and any analogous rate-controlling hydride transfer in the carbinolamine itself is included in k_3.

The most striking characteristic of Figure 3 is that k_3 for *N,N,N'*-trimethylethylenediamine is almost 100 times as large as it should be to fall on the line described by the points for the other three secondary amines. The conclusion that trimethylethylenediamine is remarkably reactive does not arise from any incorrect partitioning of the k_{obsd} values into the various terms of the kinetic equation used. Even if the other secondary amines were assumed to react solely by the k_3 pathway, their k_3 values would be less than twice as large for the two oxygenated amines and less than four times as large for pyrrolidine (and the standard deviations from the k_{obsd} values would be implausibly large). Assuming that trimethylethylenediamine has a k_4 value as large as that found for 2-methoxy-*N*-methylethylamine lowers the value of k_3 by less than 0.5%. The assumption of any k_4 large enough to give significantly diminished k_3 values ruins the fit to the k_{obsd} values.

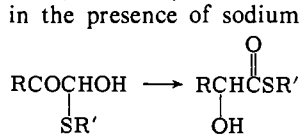
We propose that the large value of k_3 for *N,N,N'*-trimethylethylenediamine arises from a mechanism analogous to that proposed by Franzen for ω-dialkylaminoalkanethiols[3-5] (eq 1). That is, the carbinolamine undergoes an internally base catalyzed hydride transfer reaction via a transition state such as **3**. Reaction by this mechanism would



3

yield the substituted mandelamide. In a product isolation experiment, 91% of the product obtained was *N*-(2-dimethylaminoethyl)-*N*-methylmandelamide, and 9% was mandelic acid; these products accounted for only 47% of the reactant (perhaps because of inefficiency in extracting the highly water-soluble amide), but no other products were detected. This isolation experiment makes it clear that much and perhaps all of the anomalously large magnitude of k_3 arises from an amide-forming process.

Not long after finding that magnesium ions catalyze the reaction of phenylglyoxal hydrate in the presence of pyrrolidine, we learned that Hall and Poet had reported magnesium (and other metal) ion catalysis of reactions of the type shown in eq 17 in the presence of sodium acetate or *N*-



(17)

methylpyrrolidine.[22] Evidence was described for a mechanism in which base removes a proton from the carbon to which the R'S group is attached in a magnesium chelate derivative of the reactant; the resulting intermediate is then protonated at the carbon atom to which the R group is attached giving a magnesium chelate derivative of the product. Like Hall and Poet we observed about a 25-fold acceleration of the reaction rate by added magnesium ions. A mechanism of the type they proposed would be less favorable in our case because the α-SR substituent markedly increases the acidity of hydrogen atoms attached to the same carbon whereas the α-amino substituent does not.[23] However, we have not obtained enough evidence to put any possible mechanism on a secure basis.

Experimental Section

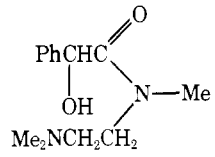
Reagents. Phenylglyoxal hydrate was recrystallized as described previously[6] to give material, mp 84–85°; that used in kinetic runs was then recrystallized from hexane to give white needles, mp 87–87.5°. Matheson trimethylamine gas was used without further purification. Pyrrolidine, morpholine, and *N,N,N'*-trimethylethylenediamine were all refluxed and fractionally distilled over sodium through a 4-ft column packed with glass helices. In addition, the *N,N,N'*-trimethylethylenediamine used in kinetic studies was purified by GLC on a 10-ft column of 2% potassium hydroxide and 10% Carbowax 20M on Chromosorb 60–80 W at 114°. None of these amines showed impurities upon GLC. Morpholine that had been refluxed over sodium only briefly or that had been allowed to stand too long after purification reacted with phenylglyoxal hydrate much more rapidly than pure morpholine did and gave unusually high infinite absorbances and strong infinite absorption around 320 nm in kinetic runs.

2-Methoxy-*N*-methylethylamine. A procedure analogous to that of Tipson was used to prepare 2-methoxyethyl *p*-toluenesulfonate:[24] ir (neat) 1130 (ether), 1440 and 1590 (aromatic C–C), 1150–1170 and 1340 cm^{-1} (sulfonate); ^1H NMR[25] (CD_3SOCD_3) δ 2.41 (s, 3, CH_3Ar), 3.20 (s, 3, CH_3O), 3.51 (t, 2, J = 5 Hz, CH_2OMe), 4.18 (t, 2, J = 5 Hz, CH_2CH_2OMe), 7.49 (d, 2, J = 7 Hz, ortho hydrogen), and 7.84 ppm (d, 2, J = 7 Hz, meta hydrogen). Then 115 g (0.5 mol) of this tosylate was added with stirring to 300 ml of refluxing methylamine over a period of 2 hr. After 24 hr of stirring and addition of 3 ml of water, 20 g of sodium hydroxide was added slowly, and the contents of the reaction flask was distilled into a receiver that was protected by a Dry Ice condenser. After the vapor reached 100°, 5 ml of water was added to the reaction flask and the distillation continued briefly using a mild vacuum. Enough sodium was added to the distillate to react with the water in it. Redistillation through a fractionating column with −20° coolant in the reflux condenser removed most of the methylamine. Then xylene was added as a distillation base yielding 34.8 g (78%) of 98% pure (by GLC) 2-methoxy-*N*-methylethylamine: bp 97–98° (lit.[26] bp 98–99°); ^1H NMR (CD_3SOCD_3) δ 1.83 (s, 1, NH), 2.25 (s, 3, CH_3N), 2.65 (t, 2, J = 6 Hz, NCH_2CH_2), 3.32 (s, 3, CH_2OCH_3), and 3.44 ppm (t, 2, J = 6 Hz, CH_2OMe); neutral equivalent (calcd 89.14) 88.85. The material used for pK_a determinations and kinetic runs was further purified by GLC at 85°.

***N*-Mandeloylpyrrolidine.** In a procedure similar to that used for preparing *N*-benzylmandelamide,[27] 7.63 g (50 mmol) of mandelic acid and 3.63 g (50 mmol) of pyrrolidine in 1000 ml of xylene were refluxed for 18 hr, using a Dean-Stark trap to remove the water formed. Concentration and cooling gave 9.3 g (90%) of straw-colored powder, mp 91–93.5°, in three crops. Recrystallization from 95:5 hexane–xylene using Norite gave white crystals of *N*-mandeloylpyrrolidine:[28] mp 93–94°; uv_{max} (EtOH) 252 nm (ε 181), 258 (232), and 263 (181); ^1H NMR[25] (CD_3COCD_3) δ 1.6–1.84 (m, 4, CCH_2C), 2.6–3.0, and 3.2–3.6 (m, 4, NCH_2C), 4.60 (d, 1, J = 7 Hz, OH), 5.02 (d, 1, J = 7 Hz, $CHOH$), and 7.27 ppm (s, 5, ArH).

***N*-Mandeloylmorpholine.** A procedure analogous to that used for *N*-mandeloylpyrrolidine gave *N*-mandeloylmorpholine:[28] mp 102.5–103.5°; uv_{max} (EtOH) 252 nm (ε 224), 258 (223), and 263 (162); ^1H NMR[25] (CD_3SOCD_3) δ 3.5 (m, 8, OC_4H_8N), 5.4 (d, 1, J = 7 Hz, OH), 5.8 (d, 1, J = 7 Hz, $CHOH$), and 7.46 ppm (s, 5, ArH).

N-(2-Dimethylaminoethyl)-N-methylmandelamide. A procedure analogous to that used for *N*-mandeloylpyrrolidine gave *N*-(2-dimethylaminoethyl)-*N*-methylmandelamide:[28] mp 78–79.5°; uv_{max} (EtOH) 251 nm (ε 99), 257 (114), 262 (91), and 267 (54); ^1H NMR[25] (CD_3SOCD_3 at 120°) δ 2.11 [s, 6, $N(CH_3)_2$], 2.17–2.38 (m, 2, CH_2NMe_2), 2.82 (s, 3, $CONCH_3$), 3.08–3.60 (m, 2, $CONCH_2$), 4.93 (s, 1, OH), 5.27 (s, 1, C*H*OH), and 7.23 ppm (s, 5, ArH). This 120° ^1H NMR spectrum is simpler than the spectrum at room temperature, where rotation around the CO–N bond is slow enough that two separate spectra for the two conformers are seen. The conformer whose dimethylamino protons absorbed at δ 2.1 and *N*-methylamide protons at 2.7 ppm was about twice as abundant as the one absorbing at δ 2.0 and 2.9 ppm, respectively. Since a methyl group cis to the carbonyl oxygen atom of an amide usually absorbs at a higher field than one trans,[29] the peaks at δ 2.7 and 2.1 presumably arise from conformer **4**. This is in agreement with the generalization that the more stable conformer of such an amide should be the one with the smaller of the two substituents on the amide nitrogen atom cis to the carbonyl oxygen atom.[29] It is noteworthy that the dimethylamino protons in the two conformers are easily distinguishable in the ^1H NMR spectrum in spite of being four atoms away (along a flexible chain) from the center of cis–trans isomerism.



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N-(α-Hydroxyphenacyl)pyrrolidine. An aqueous 0.1 *M* pyrrolidine–0.1 *M* pyrrolidinium chloride solution was added to 5 ml of 0.15 *M* aqueous phenylglyoxal hydrate solution with vigorous shaking until a precipitate began to form. The initially formed precipitate was removed and about 10 ml of additional amine solution added to the filtrate. The new precipitate was a rather unstable solid that became oily upon storage or in a vacuum desiccator: ^1H NMR[25] ($CDCl_3$) δ 8.23 (d, 2, *J* = 10 Hz, ortho hydrogen), 7.3–7.7 (m, 3, meta and para hydrogen), 5.66 (s, 1, C*H*OH), 3.8–4.4 (broad s, 1, OH), 2.6–3.0 (m, 4, NCH_2), and 1.70 ppm (m, 4, CCH_2C).

Anal. Calcd for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37; N, 6.83. Found: C, 71.24; H, 7.61; N, 6.37.

N-(α-Hydroxyphenacyl)morpholine. When the pyrrolidine in the procedure described in the preceding section was replaced by morpholine, a stable solid was obtained that could be recrystallized from 1:10 chloroform–hexane to give fine white crystals of *N*-(α-hydroxyphenacyl)morpholine:[28] mp 82–83.5°; ^1H NMR[25] ($CDCl_3$) δ 8.30 (d, 2, *J* = 10 Hz, ortho hydrogen), 7.2–7.8 (m, 3, meta and para hydrogen), 5.43 (s, 1, C*H*OH), 4.0–4.2 (broad s, 1, OH), 3.68 (t, 4, NCH_2), and 2.74 ppm (m, 4, OCH_2).

N-(α-Hydroxyphenacyl)-N-methyl-2-methoxyethylamine. The reaction of phenylglyoxal hydrate with 2-methoxy-*N*-methylethylamine gave an oil. When some of this oil was taken up in chloroform-*d*, the ^1H NMR[25] spectrum showed a narrow singlet at δ 5.48 and a broad one at 3.7 ppm, which were attributed to the NC*H*OH and OH protons, respectively, of the carbinolamine by analogy to the ^1H NMR spectra of the carbinolamines derived from pyrrolidine and morpholine. The CHC=O peak of phenylglyoxal hydrate at δ 5.48 was absent. There was a 0.70 ppm difference in chemical shifts between the ortho hydrogen doublet and the largest peak in the meta and para hydrogen multiplet. This difference is 0.74 and 0.68 ppm in the carbinolamines derived from pyrrolidine and morpholine, respectively. It is 0.57 ppm in phenylglyoxal hydrate.

Kinetics. The reaction rate was measured by following the disappearance of the absorption maximum of phenylglyoxal hydrate at 249.5 nm in aqueous solution at 35.0 ± 0.1° and ionic strengths near 0.10. Initial phenylglyoxal hydrate concentrations in the range 5–9 × 10^{-5} *M* were used unless otherwise noted. Satisfactory first-order rate constants were obtained from the computer program PROGAEXP,[30] which also gave the infinite absorbances.

In a typical run, 3.00 ml of a base solution was pipetted into several 1.00-cm quartz cells, one of which was used as the reference cell and the others as sample cells in a Cary spectrophotometer, Model 1605, with automatic sample changer. After thermal equilibrium at 35.0 ± 0.1° had been reached, 10.0 μl. of 0.024 *M* phenylglyoxal hydrate was added to each sample cell, and the changes in absorbance at 249.5 nm followed. The solutions were prepared and the reactions carried out under nitrogen. Sodium chloride was added to the solutions as needed to bring the ionic strength to 0.10.

Most of the rate constants listed are the average of duplicate determinations. All the runs using sodium hydroxide, *N,N,N'*-trimethylethylenediamine, and pyrrolidine were followed past 79% reaction except the slowest pyrrolidine reaction, which was followed to 65%. All the runs using trimethylamine and 2-methoxy-*N*-methylethylamine were followed past 64% reaction, except for the slowest runs for each amine, which were followed to 31% and 53%, respectively. All the runs using morpholine were followed past 30% reaction and the average run past 50%.

An implicit multifunctional nonlinear regression analysis,[31] based on the values of the various known equilibrium constants and the known concentrations of added reagents, was used to calculate the concentrations of the various species present in the kinetic solutions and to obtain the optimum values of the constants treated as parameters.

Products of Reactions of Phenylglyoxal Hydrate with Bases. The reaction of 9.0 × 10^{-4} *M* phenylglyoxal hydrate with 0.0100 *M* sodium hydroxide was carried out on a 1000-ml scale and followed kinetically. The rate constant obtained (9.38 × 10^{-4} sec^{-1}) is within 8% of the value that may be calculated from the k_1 and k_2K_2 values determined using about 8 × 10^{-5} *M* phenylglyoxal hydrate. The reaction mixture was concentrated, acidified with hydrochloric acid, and extracted with diethyl ether to give 0.05 g (40%) of mandelic acid: mp 115–118°; ^1H NMR spectrum identical with that of an authentic sample.

The reaction of 7.4 × 10^{-4} *M* phenylglyoxal hydrate in a 0.1599 *M* pyrrolidine–0.0948 *M* pyrrolidinium chloride buffer was carried out on a 1000-ml scale and found to have a rate constant of 25.8 × 10^{-5} sec^{-1} in good agreement with comparable runs using about 8 × 10^{-5} *M* phenylglyoxal hydrate. When the reaction was complete, the volume was reduced to 100 ml and the solution neutralized to pH 7 and extracted with four 50-ml portions of ether. The remaining solution was then acidified and extracted with four more 50-ml portions of ether. After the ether had been evaporated from the extracts, the residues were dissolved in acetone-d_6. Only *N*-mandeloylpyrrolidine could be seen in the ^1H NMR of the extract of the pH 7 solution and only mandelic acid in the ^1H NMR of the extract from the acidic solution. Integrated intensities gave a 31% yield of the acid and 35% of the amide, based on phenylglyoxal hydrate.

Similar treatment of a 1000-ml reaction mixture containing 2.0 × 10^{-3} *M* phenylglyoxal hydrate, 0.017 *M* morpholine, and 0.001 *M* morpholinium chloride gave 20% *N*-mandeloylmorpholine and 46% mandelic acid. No other products were detected.

A similar 1000-ml reaction of 2.0 × 10^{-3} *M* phenylglyoxal hydrate in the presence of 0.050 *M* *N,N,N'*-trimethylethylenediamine, 0.040 *M* *N,N,N'*-trimethylethylenediamine hydrochloride, and 0.060 *M* sodium chloride gave, after 4 days at 35°, a 4% yield of mandelic acid and 43% *N*-(2-dimethylaminoethyl)-*N*-methylmandelamide. No other products were detected.

Determination of Acidity Constants. Solutions of amines that were 0.10 *M* in sodium chloride were titrated at 35° with 0.100 *M* hydrochloric acid using a Radiometer Model 26 pH meter, G202B (high pH) glass electrode, K401 calomel reference electrode, and an automatic titration assembly. The stirring motor was stopped before reading the pH.

In the previous potentiometric titration of phenylglyoxal hydrate to determine K_1, its equilibrium constant for reaction with hydroxide ions, a high-pH electrode had not been used.[6] Hence the determination was repeated. Titrations of 0.10 *M* sodium chloride with 0.10 *M* sodium hydroxide at 35° gave pH values, which were taken to be $-\log a_{H^+}$ values, and were combined with the known hydroxide concentrations and activity coefficients from the Davies equation[10] to give a value of −13.63 for the logarithm of the autoprotolysis constant of water at zero ionic strength. Although the accepted value is −13.68,[32] we used the value determined by our experimental methods in calculating K_1. The value of K_1 that minimized the sum of the squares of $pH_{obsd} - pH_{calcd}$ in six titrations of 0.01–0.03 *M* phenylglyoxal hydrate with 0.100 *M* sodium hy-

droxide at 35° was 276 M^{-1}. This value is about 12% larger than that obtained previously and corresponds to a pK_a of 11.19 for phenylglyoxal hydrate at zero ionic strength. Data from potentiometric titrations of the amines studied were treated analogously to get the pK values listed in Table III.

Equilibrium Constants for Carbinolamine Formation. Solutions of 0.05–0.10 M phenylglyoxal hydrate that were 0.10 M in sodium chloride were titrated at 35° with buffers that were 0.05–0.10 M in free amine and 0.05–0.10 M in amine hydrochloride and that contained sodium chloride as needed to bring the ionic strength to 0.10. Ten titrations were carried out with pyrrolidine, eight with 2-methoxy-*N*-methylethylamine, and three with morpholine. At much higher concentrations of amine, small concentrations of phenylglyoxal hydrate had too small an effect on the pH to permit calculation of reliable K_c values, and larger concentrations gave precipitates of carbinolamine. Equilibrium constants were calculated as described in the Appendix.

Acknowledgment. We thank Dr. William H. Sachs for help with data treatment and the OSU Instruction and Research Computer Center for the grant of computer time.

Appendix

Calculation of K_c Values. On the basis of material balance, charge balance, and equilibrium relationships, three relationships (eq 18–20) between concentrations and equilibrium constants may be derived.

$$[A]_0 = [A] + [A][H^+]/K_a + [G]_0 + [G]([A]^2K_cK_d - 1 - K_1K_w/([H^+]\gamma_\pm^2)) \quad (18)$$

$$[G]_0 = [G](1 + [A]K_c + [A]^2K_cK_d + K_w(K_1 + [A]K_cK_3)/([H^+]\gamma_\pm^2)) \quad (19)$$

$$[H^+] = K_a(K_w/([H^+]\gamma_\pm^2) + [G]K_w(K_1 + [A]K_cK_3)/([H^+]\gamma_\pm^2) + [Cl^-] - [H^+])/[A] \quad (20)$$

In these equations, G is phenylglyoxal hydrate, the subscript zeros refer to the total concentrations of A or G in all states of protonation or combination, K_w is the autoprotolysis constant of water at zero ionic strength, and K_a is the acidity constant of the protonated amine. These three equations were combined in an implicit multifunctional nonlinear regression analysis that obtained the values of K_c and K_d that minimized the sum of the squares of the values of $pH_{obsd} - pH_{calcd}$.[31] When K_d was set at zero, the values of K_c obtained, which are listed in Table IV, fit the observed pH values with standard deviations of 0.005, 0.01, and 0.05 in the cases of morpholine, pyrrolidine, and 2-methoxy-*N*-methylethylamine, respectively. These standard deviations were not improved by allowing K_d to assume a nonzero value.

The values of K_3 used in eq 18–20 were estimated by use of linear free energy relationships. However, when the value zero was used instead, the same values of K_c were obtained. Hence the acidities of the carbinolamines are estimated to be negligible under the conditions used to determine the K_c values. However, these acidities are significant under some of the conditions used in kinetic runs. Therefore the estimates will be described in detail here. The pK_a values of 17 compounds of the type RR′CHOH in water at 25° [33-37] or p(K_a/2) values for *sym*-diols were fit to eq 21.

$$pK_a = pK_0 + \rho^*(\sigma^*_R + \sigma^*_{R'}) \quad (21)$$

Since the original value of σ^*_H [38] gave rather poor agreement in this correlation, as it does in many others,[38,39] it was treated as a parameter to be determined by the regression analysis. Several σ^*_X values were obtained from the generalization that σ^*_X is equal to $2.8\sigma^*_{CH_2X}$,[38] and a σ^* value of 1.54 for the benzoyl group was obtained from the pK_a of phenylglyoxal hydrate. The least-squares values −1.33, 15.93, and 0.16 for ρ^*, pK_0, and σ^*_H, respectively, fit the observed pK_a values with a standard deviation of 0.08. To obtain a pK_a for $PhCOCH(OH)NMe_2$; a σ^* for the dimethylamino group was needed. The inductive substituent constant σ^I_X was originally defined as $0.45\sigma^*_{CH_2X}$, but that was on the basis of $\sigma^*_{CH_3}$ being zero.[40] Now that σ^*_H is the reference constant and $\sigma^*_{CH_3}$ is given the value −0.04,[41] $\sigma^*_{CH_2X}$ is more reasonably defined as $(0.04 + \sigma^I_X)/0.45$. This and a $\sigma^I_{NMe_2}$ value of 0.06[41] give a $\sigma^*_{NMe_2}$ value of 0.62. From this value, the pK_a of phenylglyoxal hydrate, and the assumption that ρ^* is the same at 35° as at 25°, a value of 12.74 is obtained for pK_{ac} for $PhCOCH(OH)NMe_2$ at 35°. Since the acidic protons in carbinolamines are two atoms further from the substituents than the acidic protons in the corresponding secondary ammonium ions, the variations in pK_{ac} values were assumed to be $(1/2.8)^2$ as large as the variations in the pK_a values of the corresponding secondary ammonium ions. This gave pK_{ac} values of 12.80, 12.46, 12.61, and 12.61[42] for the carbinolamines derived from pyrrolidine, morpholine, 2-methoxy-*N*-methylethylamine, and *N,N,N′*-trimethylethylenediamine, respectively. The basicities of the carbinolamines derived from the monoamines were estimated similarly and found to be even more negligible than the acidities, not only in the experiments used to determine K_c but also in the kinetic experiments.

References and Notes

(1) (a) This investigation was supported in part by Public Health Service Grant GM 18593 from the National Institute of General Medical Sciences. Abstracted from the Ph.D. dissertation of C. D. Fischer, Jr., 1974. (b) Allied Chemical Fellow, 1972–1973.
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Geometry of the Adducts of 2,4-Hexadienes with *N*-Sulfinylarylsulfonamides. A Stereospecific but Nonconcerted Diels–Alder Reaction[1a]

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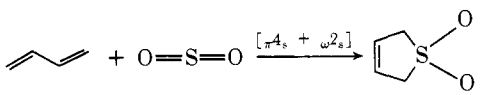
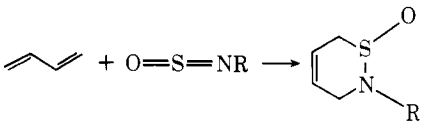
Abstract: The isomeric 2,4-hexadienes were allowed to react with *N*-sulfinyl-*p*-toluenesulfonamide, yielding 3,6-dihydro-3,6-dimethyl-2-(*p*-tolylsulfonyl)-2*H*-1,2-thiazine 1-oxides. The following correlations were observed: (*E,E*)-C_6H_{10} → **1** and **2** (diastereomeric suprafacial adducts); (*E,Z*)-C_6H_{10} → **3** (suprafacial adduct); (*Z,Z*)-C_6H_{10} → **4** (antarafacial adduct). The structures of **1–4** follow from oxidation to sultams (**5, 6**) and from NMR induced shift studies. An adduct with cyclohexadiene was demonstrated to be a diastereomeric mixture (**7**). Analogous adducts (**9, 10**) were obtained with *N,N'*-bis(*p*-tolylsulfonyl)sulfur diimide. The stereochemical results are best accommodated by a nonconcerted (two-step) dipolar mechanism of addition, as specifically required for **4** (which arises from an overall trans addition to the diene).

The stereochemistry of the cycloadditions and eliminations between sulfur dioxide and conjugated dienes (sulfolene reaction) has been quantitatively established; it is a linear cheletropic, suprafacial (cis), *concerted* process.[2] The



isoelectronic imines of sulfur dioxide might be expected to react analogously; however, in actuality, they afford six-membered dihydrothiazine oxides.[3] As part of a broad in-

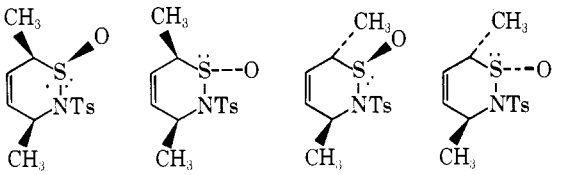


(R = aryl, arylsulfonyl, etc.)

vestigation into the mechanism of the sulfolene and related reactions, we have examined the stereochemistry of this latter cycloaddition. In this report, the reactions of the three isomeric 2,4-hexadienes (trans,trans, cis,trans, cis,cis) with *N*-sulfinyl-*p*-toluenesulfonamide have been found to produce, stereoselectively, all possible configurationally isomeric adducts. From correlations between reactants and products, it is possible to infer a *nonconcerted* mechanism for the thiazine oxide forming reaction, as will be shown.

Results

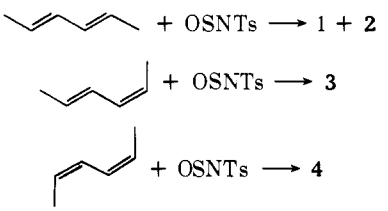
Cycloadditions with OSNTs. Taking into consideration the pyramidal hybridization of sulfur in sulfinamides,[4] there are only four possible diastereomers of the adduct between 2,4-hexadiene and *N*-sulfinyl-*p*-toluenesulfonamide (OSNTs). These are designated **1–4**.



1 **2** **3** **4**

Each of these structures (full name; 3,6-dihydro-3,6-dimethyl-2-(*p*-tolylsulfonyl-2*H*-1,2-thiazine 1-oxide) was obtained from one or another of the hexadienes according to Scheme I. From *trans,trans*-hexadiene and OSNTs, a major isomer (mp 110°) and a minor isomer (mp 115°)

Scheme I



were obtained. As will subsequently be shown, they have structures **1** and **2**, respectively. From *cis,trans*-hexadiene, a single product was obtained (mp 121°), for which structure **3** will be demonstrated. From *cis,cis*-hexadiene and OSNTs, a small amount of the remaining isomer (mp 100°) was obtained; it will be assigned structure **4**.

Structural Assignments (1–4). The relative configurations of the isomers ensues from two lines of evidence: (1) correlations between the corresponding sultams produced by oxidation, and (2) paramagnetic shifts induced in the NMR spectra of **1–4** by tris(dipivalomethanato)europium(III) [Eu(dpm)$_3$].

Of the three asymmetric centers in the molecules **1–4**, one may be selectively removed by oxidation of the sulfinyl