reactivity. The data presented herein will be discussed in a subsequent, more general article on the effect of structure on reactivity.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Structural Effects in the Reactivity of Primary Amines with Piperonal[1]

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The rate of the uncatalyzed, second-order reaction of piperonal with a series of primary aliphatic amines, RNH_2, has been measured at 0, 25 and 45°. The values of *k* do not parallel the basicity of RNH_2. However, a linear relation between log *k* and the free energies of dissociation of the corresponding addition compounds, $RNH_2 \cdot B(CH_3)_3$, is observed, showing that similar structural effects are present in the two reactions. Several other reactions show this correlation. Heats and entropies of activation have been calculated.

While the reactivity of aldehydes and ketones with semicarbazide has been the subject of several investigations,[2] the effect of the structure of the amine on the rate of carbonyl addition reactions has not been elucidated. The formation of the Schiff base from an aldehyde and a primary amine in alcoholic solution is a suitable example for such a study. In the absence of acid catalysts, it is a rapid, second-order reaction.[3] This paper describes the kinetics of the reaction of piperonal with a series of aliphatic primary amines in methanol, at three different temperatures.

The observed rate constants, *k*, are given in Table I. The basicity of the amine in water (or in methanol, which would be closely comparable)[4] is not a good index of the rate. Bell[5] has shown that the apparent basicities of amines in aqueous solution are markedly affected by solvation and that the dissociation constant in an aprotic solvent is preferred when the Brønsted catalysis law is to be applied. These solvent effects serve mainly to differentiate the three classes of amines, however, and probably are not the cause of a poor correlation between basicity and rate of reaction of a series of primary amines.

TABLE I

RATE OF SCHIFF BASE FORMATION FROM RNH_2 AND PIPERONAL

R	10^2 *k*, liters/mole-sec. 0.00°	24.97°	45.00°
Me	1.92	5.55	11.4
Et	0.952	2.88	6.00
n-Pr	1.04	3.15	6.40
i-Pr	0.267	0.895	1.98
n-Bu	1.15	3.37	6.83
i-Bu	1.13	3.16	6.23
s-Bu	0.292	0.940	2.00
t-Bu	0.0267	0.115	0.299

A correlation appears, however, when a different reference acid is used in estimating basicity. A linear relation is found between log *k* and the standard free energies of dissociation of the corresponding amine–boron trimethyl addition compounds.[6] These quantities (log k_0 and ΔF°_{100}) are plotted in Fig. 1. Similar linear plots are obtained with log k_{25} and log k_{45}. While the existence of such correlations probably is not general and would depend on the choice of substrates and of reference acids, here it indicates that changes in the various structural parameters produce similar effects on the rate of Schiff base formation and the extent of association of $RNH_2 \cdot B(CH_3)_3$. According to Brown and co-workers, many of these effects are steric in nature[6]; they have already shown, moreover, that hindered bases react slowly in displacement reactions.[7]

The same kind of correlation may be found in other cases where the reactivities of amines have been compared. Besides the well known cases where a series of basic catalysts obeys the Brønsted catalysis law, or a series of substituted anilines follows the Hammett equation,[8] there are several comparisons involving the amines of Table I. The data of Brady and Cropper[9] for the reaction of amines with 2,4-dinitrochlorobenzene, and the data of Arnett, Miller and Day[10] for the aminolysis of methyl acetate are shown in Fig. 2. The transannular interaction between a carbonyl group and a nitrogen atom in a nine-membered ring has been measured by the shift in the carbonyl frequency in the infrared.[11] Because of the essential similarity of this interaction to the first step of Schiff base formation and because the effects of methyl, isopropyl and *t*-butyl groups on the nitrogen atom were reported,[11] the shift in carbonyl frequency is

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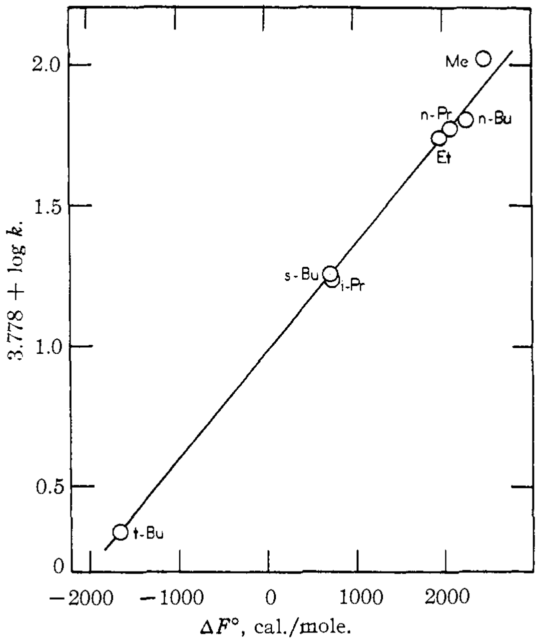

Fig. 1.—Linear free energy relation between rate of Schiff base formation and dissociation of trimethylboron complex for primary amines.

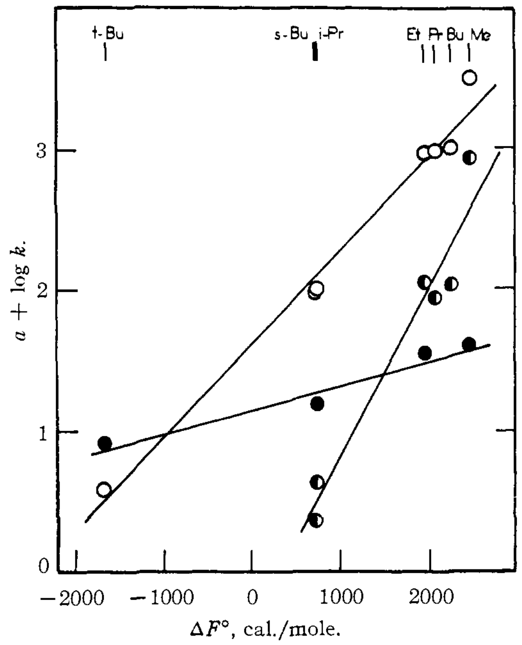

Fig. 2.—Correlation of amine reactivities with free energies of dissociation of trimethylboron complexes: ○, reaction with 2,4-dinitrochlorobenzene, $a = 2$; ◐, reaction with methyl acetate, $a = 7.556$; ●, transannular interaction, $a = 0$.

plotted as k in Fig. 2, although there is no reason to expect this quantity to be a linear function of free energy.

Hansson[12] has recently shown that the reactivity of amines can be correlated by the equation $\log k/k_0 = r(S_a + S_c) + t$. The same result would be obtained by extending the Swain–Scott equation[13] to a greater variety of amines than originally given. Since the substituent (nucleophilic) constants in either case would be proportional to the abscissas of Fig. 1 or 2, the rate constants reported in this paper would fit these equations. It is of still more interest to us, however, to interpret our results according to Taft,[14] in an effort to separate the steric from the inductive effects quantitatively. It will first be necessary to do further work with amines incorporating a wider range of inductive effects. The importance of both inductive and steric effects in the reactions of amines is clearly shown in the amine-catalyzed ionization of nitroethane.[15]

The heats and entropies of activation calculated from the rate constants are given in Table II. The values of about 7 kcal./mole obtained for the activation energy may be compared with 5.7 kcal./mole for the formation of an aromatic Schiff base[3b] and 2 kcal./mole for the reaction of acetone with semicarbazide.[2] Conant and Bartlett[2] discussed the latter, rather low value.

Although many of the variations are within experimental error (note the difference in both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the two temperature ranges), some conclusions may be drawn from Table II. The α-substituted amines, *i*-Pr, *s*-Bu and *t*-Bu, show elevated heats of activation. In *t*-$BuNH_2$, this is partly offset by the parallel increase in the entropy term so often observed. There appears to be an entropy effect of −2.2 cal./deg. which lowers k for *i*-$BuNH_2$ relative to $MeNH_2$.

TABLE II

APPARENT HEATS AND RELATIVE ENTROPIES OF ACTIVATION

R	$\Delta H^{\ddagger}$, kcal./mole 0–25°	25–45°	Av.	$\Delta S^{\ddagger}$, cal./deg.-mole 0–25°	25–45°	Av.
Me	6.9	6.8	6.8	(0)	(0)	(0)
Et	7.2	6.9	7.1	−0.3	−0.8	−0.6
n-Pr	7.2	6.7	7.0	− .4	−1.1	− .8
i-Pr	7.8	7.5	7.7	− .4	−1.3	− .9
n-Bu	7.0	6.7	6.8	− .7	−1.4	−1.1
i-Bu	6.7	6.4	6.6	−1.9	−2.4	−2.2
s-Bu	7.6	7.1	7.4	−1.2	−2.4	−1.8
t-Bu	9.4	9.0	9.2	+1.0	+0.3	+0.7

Although $\Delta H^{\ddagger}$ is related only distantly to ΔH for the gas-phase dissociation of $RNH_2{\cdot}B(CH_3)_3$, these two quantities also appear subject to the same structural effects; following Brown and Horowitz,[16] the equation $\Delta H = 32.2 - 2.03\Delta H^{\ddagger}$ was obtained and is plotted in Fig. 3.

The equilibrium constant for Schiff base formation was measured by analysis of reaction mixtures containing water (5–20 moles/l.). At the same time, the effect of water on reaction rate was observed. Since K is only slightly increased by 20 M H_2O while k is more than doubled, water accelerates the reverse as well as the forward reaction (Table III). A parallel between rate and equi-

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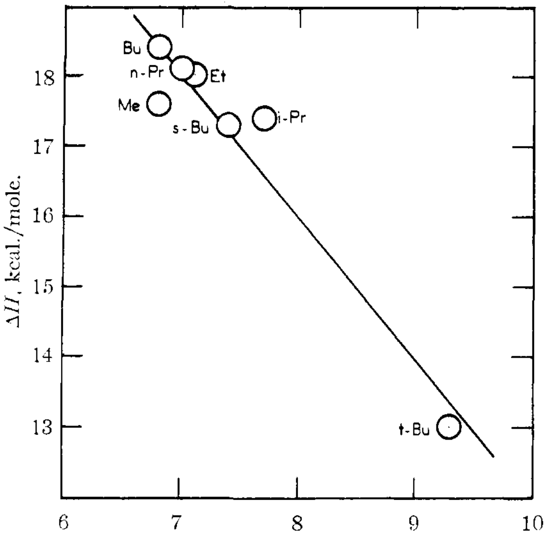

Fig. 3.—ΔH for $RNH_2{\cdot}B(CH_3)_3$ dissociation *vs.* $\Delta H^{\ddagger}$ for reaction of RNH_2 with piperonal.

librium is seen in *n*-$BuNH_2$, *s*-$BuNH_2$ and *t*-$BuNH_2$.

TABLE III

RATE AND EQUILIBRIUM CONSTANTS IN THE PRESENCE OF ADDED WATER

Amine	$[H_2O]$, moles/l.	$k_2 \times 10^2$, l./mole-sec.	$K \times 10^3$
n-$BuNH_2$	0	3.36	. .
	5.1	3.96	3.18
	10.0	4.78	3.23
	20.0	8.5	3.41
s-$BuNH_2$	20.0	. .	2.16
t-$BuNH_2$	20.1	. .	0.110

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Experimental

Materials.—Piperonal was recrystallized twice from 70% ethanol. *sec*-Butylamine, prepared according to Marvel and Noyes,[17] and commercial samples of the other liquid amines were fractionated. Methyl- and ethylamine hydrochlorides were recrystallized from methanol–chloroform; the free amines were generated by dropping concentrated potassium hydroxide solution onto the hydrochlorides and absorbing the vapors in methanol. The solvent for the kinetic runs was reagent grade methanol.

Amine Titration.—Analyses were carried out by a refinement and extension of the method of Crowell and Peck,[3a] in which *n*-butylamine is titrated in the presence of piperonylidene *n*-butylamine using standard methanolic HCl and brom cresol green indicator. A small empirical correction to compensate for the presence of the Schiff base was carefully determined by titrating, under standard conditions, known quantities of Schiff base in solutions containing various amounts of amine hydrochloride. For example, in the titration of *sec*-butylamine with 0.020 *N* acid, the correction *V* in ml. per 10-ml. sample is given by $V = (5 + 500A)S$, where *A* and *S* are amine hydrochloride (*i.e.*, free amine before titration) and Schiff base concentration, respectively.

Use of a reference indicator solution in all titrations was essential, for the color changes near the end-point are gradual, and the correction values depend on the precise color chosen. Corrections were determined directly for the Schiff bases of ethylamine and the four butylamines. These compounds were prepared by the method of Campbell and co-workers,[18] and vacuum distilled. Since the equation given above for the *sec*-butyl system represented all those tested, except *t*-butyl, within 15%, it was also applied to the methyl, *n*-propyl and *i*-propyl systems. Piperonylidene-*t*-butylamine appeared too basic for brom cresol green; brom cresol purple served in this one case.

Rate Measurements in Absolute Methanol.—Reaction mixtures were made up by pipetting standard amine solution into a weighed amount of piperonal in solution in a 100-ml. volumetric flask and diluting to the mark. A 10-ml. aliquot was withdrawn at once and delivered into 30 ml. of methanol, containing indicator, and titrated immediately with 0.02 *N* methanolic HCl. Eight more analyses were made in the course of a run. Typical results are shown in Table IV. Each value of ***k*** given in Table I is an average of at least three runs. The average deviation from the mean ***k*** was usually 0.5% and never more than 1%. The value for *n*-butylamine was also checked by method B[3a], in which the Schiff base concentration was followed spectrophotometrically: ***k*** = 0.0325 l./mole-sec. at 25°.

TABLE IV

REACTION OF *s*-BUTYLAMINE WITH PIPERONAL[a] AT 24.97°

Time, min.	HCl,[b] ml.	Corr.,[c] ml.	Amine concn., *M*	*k*, l./mole-min.
0	8.90	0.01	0.01827	. . .
3.05	8.54	.02	.01751	0.589
7.85	8.04	.03	.01646	.571
13.70	7.50	.04	.01533	.566
20.65	6.92	.06	.01409	.574
29.10	6.33	.07	.01285	.572
38.20	5.76	.08	.01166	.575
48.95	5.24	.09	.01059	.565
59.10	4.82	.09	.00970	.560

[a] Initial concn. 0.02414 *M*. [b] 0.02060 *M*; 10-ml. samples. [c] Predetermined correction for effect of Schiff base on end-point.

Studies in Methanol–Water Solutions.—The rate of formation of piperonylidene-*n*-butylamine was measured at 24.97° in 5, 10 and 20 *M* solutions of water in methanol. The final aliquot was titrated 12 hours after the others. Fading of the end-point, caused by hydrolysis of the Schiff base, was minimized by titrating only 5-ml. aliquots and diluting them with ice-cold methanol. The reaction showed kinetics in excellent agreement with the course predicted for a second-order forward reaction opposed by a first-order reverse reaction.[19] The values of *k* in Table III were calculated by this equation.

Equilibrium constants for formation of the Schiff bases of *n*-, *s*- and *t*-butylamines were measured at 24.97°. The Schiff bases, freshly distilled, were analyzed by hydrolyzing them in excess standard aqueous HCl and back-titrating with aqueous NaOH, using methyl red indicator. Solutions 0.04 *M* in Schiff base and up to 20 *M* in water were titrated after 9 and 29 hours.

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