

absorption in the 5.0–6.0- $\mu$  region. All attempts at crystallization from a variety of solvents resulted in decomposition with the appearance of a band at 5.95  $\mu$ . Analysis of the material directly from the reaction mixture after drying at 55° for 48 hr. *in vacuo* gave the following result.

*Anal.* Calcd. for C<sub>19</sub>H<sub>14</sub>N<sub>4</sub>O<sub>5</sub>: C, 57.9; H, 3.56. Found: C, 57.9; H, 3.50.

This material could be converted to IVd by heating with aqueous bicarbonate for an additional 120 hr.

*Reaction of 1-Benzoyl-2-phenylpyrazolo[1,2-a]pyrazole with Hydrochloric Acid.* Two hundred milligrams of IVa was treated with 6 ml. of concentrated hydrochloric acid. The resulting solution was heated under reflux for 10 hr. during which time 0.039 g. of benzoic acid (identified by infrared and melting point)

sublimed into the condenser. On cooling the solution, an additional 0.012 g. of benzoic acid (61% over-all) was obtained. The filtrate was evaporated *in vacuo* to yield 0.241 g. of a brown hygroscopic solid. This was treated with picric acid to give what appeared to be the *hydropicrate* of 2-phenylpyrazolo[1,2-a]pyrazole, yield 0.230 g. (82%), as a yellow solid, m.p. 174–178°. This material was unstable in solution and was analyzed directly.

*Anal.* Calcd. for C<sub>18</sub>H<sub>13</sub>N<sub>5</sub>O<sub>7</sub>: C, 52.55; H, 3.19; N, 17.02. Found: C, 52.54; H, 3.19; N, 16.80.

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## The Reaction of Aliphatic Diamines with Phenyl Acetate

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The reactions of the aliphatic primary amines *n*-propylamine and *n*-butylamine, the diamines NH<sub>2</sub>(CH<sub>2</sub>)<sub>*n*</sub>NH<sub>2</sub>, and their conjugate acids NH<sub>2</sub>(CH<sub>2</sub>)<sub>*n*</sub>NH<sub>3</sub><sup>+</sup> (where *n* = 2–6), with phenyl acetate are kinetically first order in amine and first order in ester. The lack of detectable termolecular terms provides evidence that intermolecular general base and general acid catalysis is not significant in the aminolysis of phenyl acetate by alkyl amines. The positive deviations of the log *k<sub>r</sub>* values for the diamines from a Brønsted plot for the reaction of simple amines with phenyl acetate suggest that some contribution from intramolecular general base and general acid catalysis might occur or alternatively that the diamines form a separate Brønsted series. The reactions of 2-dimethylaminoethylhydrazine and 3-dimethylamino-propylhydrazine with phenyl acetate were also found to be first order in nucleophile and first order in ester. This result is in marked contrast to the importance of general base and/or general acid assistance in the reaction of hydrazine and *N*-methylhydrazine with phenyl acetate. The rate constants for the reaction of dimethylaminoalkylhydrazines with phenyl acetate are about 10<sup>3</sup> greater than predicted from a Brønsted plot and the dependence of the rate constants on the mole fraction of the dimethylamino group in the free-base form suggests a very significant intramolecular general base catalysis.

Previous reports of investigations of the aminolysis, ammonolysis, hydrazinolysis, etc., of phenyl acetate (PA) have shown these reactions to be subject to general base and general acid catalysis. Bruice and Mayahi<sup>3</sup>

found the ammonolysis of PA to follow the rate expression (30°, H<sub>2</sub>O,  $\mu$  = 1.0 *M*)

$$\frac{+d(P)}{dt} = [0.245(\text{NH}_3) + 0.722(\text{NH}_3)^2](\text{PA}) = [k_n(\text{NH}_3) + k_{gb}(\text{NH}_3)^2](\text{PA}) \quad (1)$$

where *k<sub>n</sub>* and *k<sub>gb</sub>* represent rate constants for second-order nucleophilic attack of ammonia and third-order general base assisted nucleophilic attack of ammonia, respectively. Jencks and Carriuolo<sup>4a</sup> reported the following rate laws for the aminolysis of PA by several simple aliphatic amines (25°, H<sub>2</sub>O,  $\mu$  = 1.0 *M*).<sup>4b</sup>

$$\frac{+d(P)}{dt} = [4.5(n\text{-BuNH}_2) + 5.0(n\text{-BuNH}_2)^2 + 1900(\text{OH}^-)(n\text{-BuNH}_2)](\text{PA}) \quad (2)$$

$$\frac{+d(P)}{dt} = [4.5(\text{Me}_2\text{NH}) + 14.0(\text{Me}_2\text{NH})^2 + 2430(\text{OH}^-)(\text{Me}_2\text{NH})](\text{PA}) \quad (3)$$

In addition it was found by Jencks and Carriuolo<sup>4a</sup> that the hydroxylaminolysis of PA exhibited general acid as well as general base catalysis, *viz.*

$$\frac{-d(\text{PA})}{dt} = [0.70(\text{NH}_2\text{OH}) + 6.0(\text{NH}_2\text{OH})^2 + 1.7(\text{NH}_2\text{OH})(\text{NH}_3^+\text{OH})](\text{PA}) = [k_n(\text{NH}_2\text{OH}) + k_{gb}(\text{NH}_2\text{OH})^2 + k_{ga}(\text{NH}_2\text{OH})(\text{NH}_3^+\text{OH})](\text{PA}) \quad (4)$$

where *k<sub>ga</sub>* is the rate constant for the termolecular

(3) T. C. Bruice and M. F. Mayahi, *J. Am. Chem. Soc.*, **82**, 3067 (1960).

(4) (a) W. P. Jencks and J. Carriuolo, *ibid.*, **82**, 675 (1960). (b) We were unable to detect a *k<sub>gb</sub>* term for either *n*-butyl- or *n*-propylamine reacting with PA (see Results).

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general acid assisted nucleophilic attack of hydroxylamine on the ester bond. Similarly Bruice and Benkovic<sup>5</sup> have found the hydrazinolysis of PA to be subject to both general acid and general base catalysis (18°, H<sub>2</sub>O,  $\mu = 1.0 M$ ). Support for the supposition that the termolecular terms do represent general base

$$\frac{-d(\text{PA})}{dt} = [0.245(\text{H}_2\text{NNH}_2) + 10.75(\text{H}_2\text{NNH}_2)^2 + 2.62(\text{H}_2\text{NNH}_2)(\text{H}_2\text{NNH}_3^+)](\text{PA}) \quad (5)$$

and general acid catalyzed reactions stems from: (1) the deuterium solvent kinetic isotope effects associated with these terms; (b) the fact that product analysis, when carried out, has shown the ester to have undergone an aminolysis type reaction; (c) the catalyst species may be replaced by other general acid and general base pairs<sup>6</sup>; and (d) the efficiency of catalysis follows the expectation of the Brønsted relationship.<sup>7</sup>

The efficiency of general catalytic processes are of great interest because of their most probable involvement in enzymic ester hydrolysis.<sup>8-10</sup> One of the tenets of most active-site hypotheses is that the bringing together of the ester with the catalytic and nucleophilic groups at the active site is responsible for much of the efficiency of enzyme catalysis. Numerous model enzyme experiments have tended to uphold this hypothesis. Bruice and Benkovic,<sup>11</sup> in comparing the rate constants for the reaction of trimethylamine with substituted phenyl acetates to the rate constants for the intramolecular attack of the dimethylamino group on the phenyl ester bonds of  $\gamma$ -(N,N-dimethylamino)butyrates and  $\delta$ -(N,N-dimethylamino)valerates, found the rate enhancement on going from bimolecular to intramolecular processes to be between 1 and  $5 \times 10^3$ . This increase in rate was furthermore associated only with the  $\Delta S^*$  term ( $\Delta H^*$  and  $\rho$  were the same for both intramolecular and bimolecular reactions indicating no change in mechanisms). The cost in negative free energy of activation on bringing the amine and substrate together to form the transition state would then appear to be about 4-5 kcal. mole<sup>-1</sup> (at 25°). An additional expenditure of 4-5 kcal. mole<sup>-1</sup> in negative free energy should then occur on bringing the catalytic species into the transition state in the termolecular general base and general acid catalyzed reactions. This has been shown to be the case<sup>5</sup> in the hydrazinolysis of phenyl acetates. The ability of the very improbable termolecular processes to occur is of course related to the fact that, due to their catalytic nature, the potential energy barrier is lowered and the resultant compensatory changes in  $\Delta H^*$  and  $T\Delta S^*$  tend to make the values of  $\Delta F^*$  for  $k_n$ ,  $k_{gb}$ , and  $k_{ga}$  comparable (eq. 1 to 5).<sup>5</sup>

As shown, we can greatly increase the numerical value of the rate constant by conversion of a bimolecular nucleophilic displacement into an intramolecular reaction. One would anticipate, *a priori*, that a similar

contrivance might be employed to increase the numerical value of the rate constant by converting a termolecular general acid and/or general base catalyzed nucleophilic displacement reaction into a lower order process. The present study was designed to ascertain what type of rate enhancements, if any, are obtained when the nucleophilic amine and the general acid and general base catalytic species, respectively, are contained within a single molecule. On the basis of the report by Jencks and Carrioulo<sup>4a</sup> that the rate constants  $k_n$  and  $k_{gb}$  are comparable for the reaction of aliphatic amines such as *n*-butylamine, with PA we have examined the kinetics of reaction of a series of diamines with PA. Also, on the basis of the similar finding by Bruice and Benkovic<sup>5</sup> for the hydrazinolysis of PA we have examined the kinetics of reaction of 2-dimethylaminoethyl- and 3-dimethylaminopropylhydrazine with PA. In the diamines it was anticipated that the second amino group, either free or as its conjugate acid, would behave as an intramolecular general base or general acid species, respectively. In the N,N-dimethylaminoalkylhydrazines it was hoped that the dimethylamino group would act as a general base catalyst in assisting the nucleophilic attack of the hydrazine group on the ester bond.

## Experimental

**Materials.** The  $\alpha,\omega$ -diaminoalkanes were obtained from the Aldrich Chemical Co., Inc.; *n*-propylamine, *n*-butylamine, and N-methylhydrazine were Eastman White Label. The amines were converted to their hydrochlorides and recrystallized several times from aqueous ethanol and stored in a vacuum desiccator over P<sub>2</sub>O<sub>5</sub> before use.

**2-Dimethylaminoethylhydrazine** was obtained by the method of Biel, *et al.*,<sup>12</sup> as a colorless oil, b.p. 94-96° at 62.5 mm.,  $n_D^{25}$  1.4592 (63% yield); lit. 75-79° at 7.3 mm.,  $n_D^{25}$  1.4541.

*Anal.* Calcd. for C<sub>4</sub>H<sub>13</sub>N<sub>3</sub>: C, 46.56; H, 12.70; N, 40.73. Found: C, 46.35; H, 12.72; N, 41.02.

**3-Dimethylaminopropylhydrazine** was prepared in the same manner and also obtained as a colorless oil, b.p. 112-115° at 64 mm.,  $n_D^{25}$  1.4602 (57% yield).

*Anal.* Calcd. for C<sub>5</sub>H<sub>15</sub>N<sub>3</sub>: C, 51.28; H, 12.82; N, 35.89. Found: C, 51.26; H, 13.21; N, 35.54.

The hydrazines were converted to their crystalline dihydrochlorides, recrystallized from ethanol-ether, and stored over P<sub>2</sub>O<sub>5</sub> *in vacuo* before use. In the preparation of the hydrazine hydrochlorides, the ethanol employed was dried over Mg and distilled under N<sub>2</sub>. All recrystallizations were carried out under N<sub>2</sub>.

$pK_a'$  determinations were performed potentiometrically employing the apparatus previously described by Bruice and Bradbury<sup>13</sup> using the treatment of data described by Noyes<sup>14</sup> and correcting for hydroxide ion concentration as prescribed by Britton.<sup>15</sup> The apparatus and procedure were first tested by a determination of the thermodynamic  $pK_a$  values of 1,3-diaminopropane (found, 8.51 and 10.45; lit.<sup>16</sup> 8.51 and 10.49).

(12) J. H. Biel, W. K. Hoya, and H. A. Leiser, *ibid.*, 81, 2527 (1959).

(13) T. C. Bruice and W. C. Bradbury, *J. Org. Chem.*, 28, 3403 (1963).

(14) A. A. Noyes, *Z. physik. Chem. (Leipzig)*, 11, 495 (1893).

(15) H. T. S. Britton, "Hydrogen Ions," Chapman and Hall, London, 1955, p. 219.

(5) T. C. Bruice and S. J. Benkovic, *J. Am. Chem. Soc.*, 86, 418 (1964).

(6) T. C. Bruice and J. J. Bruno, *ibid.*, 83, 1124 (1961).

(7) L. R. Fedor and T. C. Bruice, *ibid.*, 86, 4117 (1964).

(8) T. Spencer and J. M. Sturtevant, *ibid.*, 81, 1874 (1959).

(9) T. C. Bruice, *Proc. Natl. Acad. Sci. U. S. A.*, 47, 1924 (1961).

(10) M. L. Bender, Abstracts, 6th International Congress of Biochemistry, New York, N. Y., 1964.

(11) T. C. Bruice and S. J. Benkovic, *J. Am. Chem. Soc.*, 85, 1 (1963).

The determined values of  $pK_a'$  (at about  $10^{-3} M$ ;  $\mu = 1.0 M$  with KCl) employed in the kinetic calculations are recorded in Table II.

**Kinetics.** The kinetic procedure employed has been previously described.<sup>7</sup> Water used was glass distilled under  $N_2$  and stored under  $N_2$ . In making up solutions, water was added under  $N_2$  pressure. Standard solutions were further saturated with  $N_2$  and then transferred to the spectrophotometric cuvettes. Any air in the cuvettes was displaced with  $N_2$ .

## Results

Reactions were carried out at  $25^\circ$  in water at a constant ionic strength of  $1.0 M$  (with KCl) under  $N_2$ . Constant pH was maintained by employing the amine and its conjugate acid as both reactant and buffer. The concentration of buffer was maintained in great excess over PA so that pseudo-first-order conditions were obtained.

The only simple monoamine investigated in detail was *n*-propylamine. The aminolysis of PA by *n*-propylamine was found to be first order to at least three half-lives. Under the pseudo-first-order conditions employed, the rate expression of eq. 6 was found to pertain so that values of  $(k_1 + k_{OH'})$  were determined from the slope of plots of  $(k_{obsd} - k_{hyd'})$  vs. *n*-PrNH<sub>2</sub> concentration at constant pH values. Plots of  $(k_1 + k_{OH'})$  vs.  $K_w/a_H$  then provided  $k_{OH}$  as the slope and  $k_1$  as intercept.

$$\frac{-d(\text{PA})}{dt} = [k_1(n\text{-PrNH}_2) + k_{OH}(n\text{-PrNH}_2)(\text{OH}^-) + k_{hyd}(\text{OH}^-)](\text{PA})$$

At constant pH

$$k_{obsd} = (k_1 + k_{OH'})B_T \left[ \frac{K_a'}{K_a' + a_H} \right] + k_{hyd}' \quad (6)$$

In eq. 6  $B_T = [n\text{-PrNH}_2 + n\text{-PrNH}_3^+]$ ,  $K_a'$  is the acid dissociation constant of  $n\text{-PrNH}_3^+$ , and  $a_H$  is the hydrogen ion activity as determined by the glass electrode. In Figure 1 are plotted the determined pseudo-first-order rate constants ( $k_{obsd}$ ) vs.  $B_T$  at constant pH for *n*-propylamine. Also included in Figure 1 is a similar plot for *n*-BuNH<sub>2</sub>. The absolute linearity of the plots of Figure 1 substantiates that these aminolysis reactions are not second order in amine. Jencks<sup>4a</sup> reported the reaction of *n*-BuNH<sub>2</sub> with PA to be subject to general base catalysis wherein the value of  $k_n \cong k_{ga}$  (eq. 2). By replotting the data provided by Jencks and Carriuolo it can be shown that the curvature in the plots of  $k_{obsd}$  vs.  $B_T$  fall within ca. 5% experimental error in the values of  $k_{obsd}$ .

Under the pseudo-first-order conditions employed, the reaction of the diamines with PA were found to follow the rate law of eq. 7.

$$\begin{aligned} \frac{-d(\text{PA})}{dt} &= [k_1(\text{NH}_2(\text{CH}_2)_n\text{NH}_2) + k_2(\text{NH}_2(\text{CH}_2)_n\text{NH}_3^+) + k_3(\text{OH}^-)(\text{NH}_2(\text{CH}_2)_n\text{NH}_2) + k_{hyd}(\text{OH}^-)](\text{PA}) \\ k_{obsd} &= k_1(\text{NH}_2(\text{CH}_2)_n(\text{NH}_2) + k_2(\text{NH}_2(\text{CH}_2)_n(\text{NH}_3^+) + k_3(\text{OH}^-)(\text{NH}_2(\text{CH}_2)_n(\text{NH}_2) + (\text{OH}^-) \quad (7) \end{aligned}$$

(16) C. R. Bertsch, W. C. Fernelius, and B. P. Block, *J. Phys. Chem.*, **62**, 444 (1958).

$$\frac{k_{obsd}}{B_T} = \left[ \frac{k_1 K_1 a_H + k_2 K_1 K_2 + k_3 K_1 K_2 K_w a_H^{-1}}{K_1 K_2 + K_1 a_H + a_H^2} \right]$$

where  $K_1$  and  $K_2$  are the first and second acid dissociation constants and  $B_T$  was the total concentration of

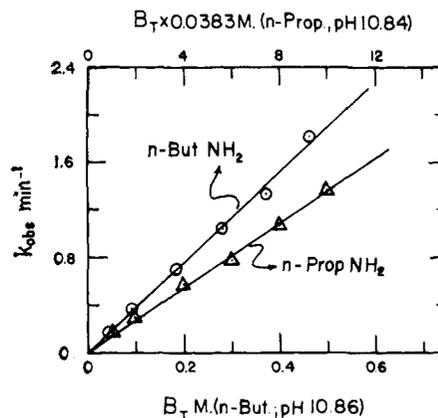


Figure 1. Plots of the pseudo-first-order rate constants for the aminolysis of phenyl acetates by *n*-butylamine and *n*-propylamine. The linearity of the plots establishes the reactions to be first order in amine.

amine in all its ionic species. All the diamines gave very good pseudo-first-order kinetics with PA to at least three half-lives. Only in the case of 1,2-diaminoethane and 1,3-diaminopropane were the rate constants for specific base catalysis evaluated. By operating at lower pH values the  $k_3$  term can be made kinetically unimportant so that eq. 7 becomes eq. 8.

$$\frac{k_{obsd}}{B_T} (K_1 K_2 + K_1 a_H + a_H^2) = k_1 K_1 a_H + k_2 K_1 K_2 \quad (8)$$

Plots of the left-hand side of eq. 8 vs.  $a_H$  give  $k_1 K_1$  as the slope and  $k_2 K_1 K_2$  as the intercept ( $a_H = 0$ ). Knowing all other variables and constants, values of  $k_3$  were obtained from eq. 7 by approximation. In Table I the experimentally determined apparent second-order rate constants are compared to the calculated constants employing eq. 7 and the determined  $K_1$ ,  $K_2$ ,  $k_1$ ,  $k_2$ , and  $k_3$  constants (these constants are tabulated in Table II). In the case of the remaining diamines of  $n = 4, 5$ , and  $6$  a full analysis was not attempted. The apparent second-order rate constants ( $k_{obsd}/B_T$ ) could adequately be determined by working at as low pH values as the  $pK_a'$  values would allow, effectively eliminating any contribution from specific base aminolysis, and using eq. 8 graphically to find  $k_1$  and  $k_2$ . The values of  $k_1$  and  $k_2$  are included in Table II. The values of  $K_1$  and  $K_2$  employed in the calculation of the rate constants were determined potentiometrically (see Experimental) at  $B_T = ca. 10^{-3} M$ . The range of concentrations of  $B_T$  employed in the kinetic studies included concentrations greater than  $10^{-3} M$ . Since the pH of solutions of diamines changes on dilution (concentration dependence of  $pK_a'$ ) and the effect becomes more pronounced as the amino groups become more separated, the values of  $k_1$  and  $k_2$  for 1,4-diaminobutane, 1,5-diaminopentane, and 1,6-diaminohexane are probably no better than  $\pm 10$  to  $15\%$ , though the calculated and found values of Table I are in general closer than this.

**Table I.** Comparison of Experimental Values of the Apparent Second-Order Rate Constants ( $k_{\text{obsd}}/B_T$ ) with Values Calculated from Equation 7 Employing the Constants Tabulated in Table II

pH	$-(k_{\text{obsd}}/B_T)$ , l. mole <sup>-1</sup> min. <sup>-1</sup>	
	Found	Calcd.
	<b>NH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub></b>	
7.89	0.020	0.021
9.33	0.185	0.227
9.78	0.552	0.513
10.19	0.913	0.939
10.52	1.43	1.38
10.70	1.71	1.68
10.85	1.98	1.97
	<b>NH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>NH<sub>2</sub></b>	
8.17	0.0371	0.0374
9.29	0.512	0.531
9.83	2.39	2.44
10.15	4.88	5.06
10.20	5.93	5.60
10.38	8.70	7.58
10.70	14.9	14.15
10.73	15.4	14.60
11.02	22.6	22.6
11.30	33.5	35.0
	<b>NH<sub>2</sub>(CH<sub>2</sub>)<sub>4</sub>NH<sub>2</sub></b>	
8.76	0.0987	0.0920
9.02	0.166	0.166
9.15	0.208	0.225
10.35	2.88	2.77
10.57	3.71	3.87
	<b>NH<sub>2</sub>(CH<sub>2</sub>)<sub>5</sub>NH<sub>2</sub></b>	
9.19	0.304	0.304
9.32	0.412	0.411
9.45	0.555	0.555
9.55	0.710	0.701
	<b>NH<sub>2</sub>(CH<sub>2</sub>)<sub>6</sub>NH<sub>2</sub></b>	
9.29	0.333	0.335
9.47	0.496	0.501
9.60	0.661	0.667

second dissociation constant  $K_2$ , via the rate expression

$$-\frac{d(\text{PA})}{dt} = \left[ \left[ \frac{k_1 K_2}{K_2 + a_{\text{H}}} \right] B_T + k_{\text{hyd}}(\text{OH}^-) \right] (\text{PA}) \quad (10)$$

The values of  $k_1$  were determined via plots of  $k_{\text{obsd}}/B_T$  vs. pH which possessed the requisite sigmoid shape. The instability of hydrazine solutions in the presence of air and base is well known.<sup>17</sup> The aminoalkylhydrazines employed in these studies were found to be very unstable especially at the more alkaline pH values employed and reproducible kinetics could not be obtained without the rigid exclusion of air from the reaction solutions. Excellent first-order kinetics were not obtained with the hydrazines. The reactions proceeded at a greater initial rate, slowing somewhat to proceed with a constant rate. The pseudo-first-order rate constants were calculated from the slopes of  $\log a/(a-x)$  vs.  $t$  plots using the points after the first 25% reaction. Slightly lower rate constants were obtained if  $t_{1/2}$  were taken when  $\log a/(a-x) = 0.3$ . Plots of  $k_{\text{obsd}}$  vs.  $B_T$  were linear but the second-order rate constants are probably no better than  $\pm 20\%$ . The determined constants are included in Table II.

### Discussion

All the primary amines investigated in this study were found to react with PA via second-order kinetics (eq. 11) where  $k'$  represents a pH-sensitive apparent

$$k_{\text{obsd}} = k' B_T \quad (11)$$

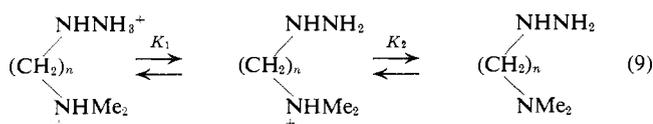
second-order rate constant. Therefore, intermolecular general base and general acid catalysis would appear to

**Table II.** The Kinetic Expressions and Associated Rate Constants Determined for the Reaction of a Series of Nitrogen Bases with Phenyl Acetate [at 25° in water, ionic strength 1.0 M (with KCl)]

	Base	pK	Reaction kinetics	Rate constants <sup>a</sup>	pH range	No. of		Concn. range of total base ( $B_T$ ), M
						pH values at which $k_{\text{obsd}}$	No. $k_{\text{obsd}}$ detd.	
(1)	(CH <sub>3</sub> ) <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub> NHNH <sub>2</sub>	9.23 <sup>b</sup>	$k(\text{B})(\text{E})$	0.885	8.71–10.38	5	23	0.02–0.155
(2)	(CH <sub>3</sub> ) <sub>2</sub> N(CH <sub>2</sub> ) <sub>3</sub> NHNH <sub>2</sub> (6.83) <sup>c</sup>	9.83 <sup>c</sup>	$k(\text{B})(\text{E})$	1.33	9.37–10.65	5	22	0.056–0.44
(3)	NH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> NH <sub>3</sub> <sup>+</sup>	7.53 <sup>c</sup>	$k(\text{B})(\text{E})$	$2.23 \times 10^{-2}$	6.98–10.85	7	33	0.0246–0.453
	NH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>	10.18 <sup>c</sup>	$k(\text{B})(\text{E})$	1.68				
(4)	NH <sub>2</sub> (CH <sub>2</sub> ) <sub>3</sub> NH <sub>3</sub> <sup>+</sup>	10.18 <sup>c</sup>	$k(\text{B})(\text{OH}^-)(\text{E})$	1000	8.17–11.26	10	47	0.006–0.485
	NH <sub>2</sub> (CH <sub>2</sub> ) <sub>3</sub> NH <sub>2</sub>	9.18 <sup>c</sup>	$k(\text{B})(\text{E})$	0.35				
	NH <sub>2</sub> (CH <sub>2</sub> ) <sub>3</sub> NH <sub>2</sub>	10.62 <sup>c</sup>	$k(\text{B})(\text{E})$	19.9				
(5)	NH <sub>2</sub> (CH <sub>2</sub> ) <sub>4</sub> NH <sub>3</sub> <sup>+</sup>	10.62 <sup>c</sup>	$k(\text{B})(\text{OH}^-)(\text{E})$	$1.13 \times 10^4$	8.81–9.30	5	17	0.01–0.48
	NH <sub>2</sub> (CH <sub>2</sub> ) <sub>4</sub> NH <sub>2</sub>	9.94 <sup>c</sup>	$k(\text{B})(\text{E})$	1.4				
(6)	NH <sub>2</sub> (CH <sub>2</sub> ) <sub>5</sub> NH <sub>3</sub> <sup>+</sup>	10.77 <sup>c</sup>	$k(\text{B})(\text{E})$	9.24	9.17–9.57	4	21	0.05–0.5
	NH <sub>2</sub> (CH <sub>2</sub> ) <sub>5</sub> NH <sub>2</sub>	10.40 <sup>c</sup>	$k(\text{B})(\text{E})$	4.88				
(7)	NH <sub>2</sub> (CH <sub>2</sub> ) <sub>6</sub> NH <sub>3</sub> <sup>+</sup>	10.81 <sup>c</sup>	$k(\text{B})(\text{E})$	14.9	9.32–10.28	3	26	0.05–0.5
	NH <sub>2</sub> (CH <sub>2</sub> ) <sub>6</sub> NH <sub>2</sub>	10.59 <sup>c</sup>	$k(\text{B})(\text{E})$	6.84				
(8)	NH <sub>2</sub> (CH <sub>2</sub> ) <sub>4</sub> NH <sub>2</sub>	10.85 <sup>c</sup>	$k(\text{B})(\text{E})$	6.80	9.84–10.84	5	23	0.05–0.5
	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>	10.84 <sup>b</sup>	$k(\text{B})(\text{E})$	4.15				
	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>	10.84 <sup>b</sup>	$k(\text{B})(\text{E})(\text{OH}^-)$	$3.48 \times 10^8$				

<sup>a</sup> In units of min. and M. <sup>b</sup> By half-neutralization. <sup>c</sup> By potentiometric titration (see Experimental).

In the concentration range employed, the reaction of PA with 2-dimethylaminoethylhydrazine and 3-dimethylaminopropylhydrazine was dependent on the



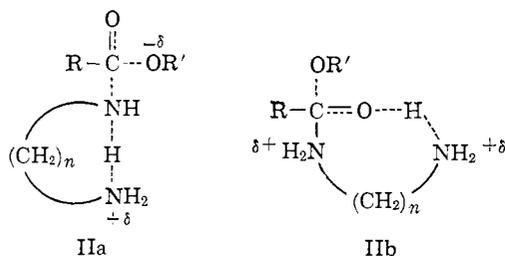
be of no significance in the reaction of simple mono- and di-primary aliphatic amines with PA.<sup>4b</sup> The lack of termolecular terms in the reaction of 2-dimethylaminoethylhydrazine and 3-dimethylaminopropylhydrazine with PA is surprising since from the rate expression for the reaction of hydrazine with PA

(17) E. C. Gilbert, *J. Am. Chem. Soc.*, **51**, 2744 (1929).



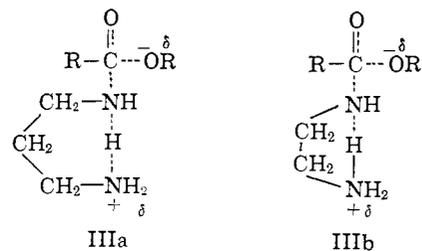
that alkyl hydrazines have still less of an  $\alpha$ -effect.<sup>18</sup> Therefore, hindrance of the nucleophilicity of the hydrazine group by the protonated dimethylamino group (as in Ib) may be in effect but of course cannot explain the rate enhancement. We suggest that the  $10^3$ -fold rate acceleration for the rate constant is best explained *via* an intramolecular general base catalysis of the hydrazinolysis reactions as depicted in Ia. The resultant effect is that the hydrazine group exhibits the nucleophilicity of an amine with a  $pK_a$  over three units greater (*i.e.*, the dimethylamino group has imparted its basicity to the hydrazine without also imparting its large steric hindrance). In support of an intramolecular general base catalyzed mechanism (Ia) is the finding that the dimethylaminoalkylhydrazines exhibit only second-order kinetics with PA while methylhydrazine<sup>18</sup> reacts with PA *via* third-order general base catalysis. The intramolecular process of Ia would be second order over-all and it would appear that the second-order, intramolecular, general base catalysis has swamped out the third-order, intermolecular, general base catalyzed reaction.

Most of the diamines, as either the free base or mono acid forms, exhibit rate constants (for the free base  $k_2/2$ ) greater than predicted from the Brønsted plot which is based on the rate constants for primary and secondary monoamines. The positive deviations amount, however, to less than an order of magnitude. It is quite possible that the positive deviations do occur because of intramolecular general acid and general base catalysis as in IIa,b but, if so, the catalytic



processes are not of great kinetic significance. The largest rate enhancement in the diamines is seen to be

for  $\text{NH}_2(\text{CH}_2)_3\text{NH}_2$  (12-fold) while the rate constant for  $\text{NH}_2(\text{CH}_2)_2\text{NH}_2$  fits the Brønsted plot for the monoamines. This may reflect the more favorable structure of IIIa as compared to IIIb. The value of the rate



constant for  $\text{NH}_2(\text{CH}_2)_6\text{NH}_2$  is not known with great accuracy and may be greater than that indicated in Figure 2. Care must be taken in drawing conclusions about the relative rates for the diamines, since their positive deviations from the Brønsted plot are in most instances comparable. In fact a reasonably good Brønsted plot may be drawn to correlate the rate data for the diamines and their monoprotonated species. It might be reasonably concluded that the diamines and their monoprotonated species belong to different Brønsted series than the monoamines. It is known that nitrogen bases of different types (amines, pyridines, imidazoles, etc.) may fall into distinct Brønsted series of approximately parallel slopes and small separation.<sup>19</sup> This alternate explanation for the greater reactivity of the diamines and their conjugate acids is strengthened by our finding that PA does not exhibit susceptibility to general catalysis by primary *n*-alkylamines (a result not in accord with the findings of Jencks and Carriuolo<sup>4a</sup>). Additional support for the intramolecular catalysis proposed for the dimethylaminoalkylhydrazines is the great susceptibility of PA to general base catalyzed hydrazinolysis.<sup>5</sup>

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