Correlation of the Nucleophilic Reactivity of Aliphatic Amines

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Received June 18, 1964

Data for the reaction of 39 amines with 15 substrates were correlated by the Swain–Scott equation, but not by the Taft equation. The n-values of the amines were lowered by electron-attracting groups and by alkyl branching (F-strain).

Because the Taft equation[1] successfully correlated the base strengths of aliphatic amines,[2] it was natural

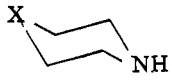
$$\log \frac{k}{k_0} = \sigma^*\rho^*$$

to see if it would correlate their reactivities as well. If not, other correlations would be sought.

Results

Literature data on the reactivities of aliphatic amines were collected and are presented in Table I. Because the data refer mostly to alkyl-substituted amines, it was appropriate to measure the reactivities of some polar-substituted amines (Table II). Also, because the literature data for ethyl chloroformate had a large experimental error, some rate constants were measured for dimethylcarbamyl chloride (Table III), another acyl chloride, which is easier to study.

Taft plots of the rate data showed no over-all correlation with σ^*, for example, 2,4-dinitrochlorobenzene (Fig. 1). There is some trend of lower reactivity with increased branching. The points for 4-substituted piperidines describe a rough line for one set of secondary



amines where steric effects are constant. (The scatter of the points from linearity probably can be attributed to the fact that the rate constants were determined in ethanol and the σ^*-values in water.[3]) The least-squares slope of the Taft-type plot gives $\rho^* = -1.4$, electron-attracting substituents slowing the rate as expected. This suggests that increased alkyl branching (electron-donating groups) lowers the rate constants by F-strain.[4]

To achieve a more quantitative correlation, attention was given to the Swain–Scott equation,[5] following,

$$\log k_{\text{amine-substrate}} - \log \frac{k_1}{(H_2O)} = sn$$

where k_1 is the first-order hydrolysis rate constant of the substrate. No aliphatic amine reactivities were described.[6] Values of $k_1 = 2.87 \times 10^{-7}$ sec.$^{-1}$, $s = 0.96$ for glycidol,[7,8] and $k_1 = 9.85 \times 10^{-7}$ sec.$^{-1}$, $s = 1.00$, for epichlorohydrin[7,8] were used. Standard n-values for eight amines were then calculated analytically from the known[9] rates of their reactions with these two epoxides, using the Swain–Scott equation. These n-values were plotted against extensive recorded data for ethylene oxide, propylene oxide, chloro acetate ion, isocyanic acid (at 18°), 2,4-dinitrochlorobenzene, methyl bromide, ethyl bromide, and allyl bromide. Reasonably linear plots were obtained in each case (Fig. 2). Then, subsidiary n-values obtained graphically from 2,4-dinitrochlorobenzene, as secondary standard, were plotted against less complete data for carbon dioxide, isocyanic acid at 60°, ethyl chloroformate, methyl isothiocyanate, piperonal, and dimethylcarbamyl chloride to give further straight lines (Fig. 3).

Three points of all those plotted were omitted from the least-squares calculations of the slopes. Diethylamine reacted with ethylene oxide and isocyanic acid much faster than expected. Ammonia reacted faster than expected with ethylene oxide. Therefore, very small substrates or very large amines are likely to show deviations.

Discussion

Evaluation of the Swain–Scott Correlation.—The approximate linearity of the plots in Fig. 2 and 3 shows that the nucleophilic reactivity of aliphatic amines toward varied substrates can be correlated by a two-parameter equation. The correlation is not exact, as indicated by the scatter in some of the plots and by the omission of three points as noted above. Nevertheless, the Swain–Scott equation correlates the data quite well and should be useful.

Differential solvation of the amines or their transition states does not appear to be significant since data from a wide variety of solvents can be correlated.

The n-values of the most reactive amines are quite high compared with those of most nucleophiles. Many of the amine values fall in the range 4–5, which is about the reactivity of thiocyanate or iodide ions. As already noted, polar substituents or alkyl branching lower the values.

The s-Values.—The rates of reaction of 2,4-dinitrochlorobenzene and ethyl chloroformate are most dependent on nucleophilicity of the amine (s-values 2.7 and 2.4). These halides react by the addition–elimination mechanism.[10,11] Dimethylcarbamyl chloride is

(1) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 556.

(2) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957).

(3) (a) H. H. Jaffe, *Chem. Rev.*, **53**, 229 (1953); (b) H. C. Brown, D. H. McDaniel, and O. Haefliger in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1955, p. 577; (c) H. K. Hall, Jr., *J. Phys. Chem.*, **60**, 63 (1956); (d) C. D. Ritchie and E. S. Lewis, *J. Am. Chem. Soc.*, **84**, 591 (1962).

(4) H. C. Brown, *J. Chem. Soc.*, 1248 (1956).

(5) C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, **75**, 141 (1953).

(6) A linear free-energy plot for acetylation and 2,4-dinitrophenylation of aliphatic amino acid anions was given by D. M. Brouwer, M. J. van der Vlugt, and E. Havinga [*Proc. Koninkl. Ned. Akad. Wetenschap.*, **61**, 141 (1958)].

(7) J. N. Bronsted, M. L. Kilpatrick, and M. Kilpatrick, *J. Am. Chem. Soc.*, **51**, 428 (1929).

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(9) J. Hansson, "The Reaction Between Alkylene Oxides and Amines," Lindstedt's, Lund., 1955; *Chem. Abstr.*, **52**, 849 (1958).

(10) J. F. Bunnett, *Quart. Rev.*, **12**, 1 (1960).

(11) H. K. Hall, Jr., and C. H. Lueck, *J. Org. Chem.*, **28**, 2818 (1963).

TABLE I

RATE CONSTANTS[a] AND n- AND s-VALUES FOR THE REACTIONS OF ALIPHATIC AMINES

	Substrate, temp., factor[b]																
	In water										In methanol		In ethanol		In benzene		
Amine	Glycidol,[c] 20°, 10^{-5}	Epichlorohydrin,[c] 20°, 10^{-5}	Ethylene oxide,[c] 20°, 10^{-5}	Propylene oxide,[c] 20°, 10^{-5}	Chloroacetate ion,[d] 25°, 10^{-6}	Carbon dioxide,[e] 18°, 10^{-2}	Isocyanic dioxide,[f] 18°, 1	Isocyanic acid,[g] 60°, 10^{2}	Ethyl chloroformate,[h] 20°, 1	Methyl isothiocyanate,[i] 20°, 10^{-2}	Piperonal,[j] 25°, 10^{-2}	2,4-Dinitrochlorobenzene,[k-m] 25°, 10^{-4}	Dimethylcarbamyl 25°, 10^{-3}	Methyl bromide,[n] 100°, 10^{-6}	Ethyl bromide,[n] 100°, 10^{-6}	Allyl bromide,[n] 100°, 10^{-6}
Trimethylamine (1)	467	1180	1050	443	583									790	17.6	570
	6.20	*5.82*														
	6.01 av.															
Pyrrolidine (2)												460	330			
												5.67				
Dimethylamine (3)	120	867	300	267	417	253	3650	77.8				350		1000	25.5	513
	5.58	*5.68*														
	5.63 av.															
Piperazine (4)												274				
												5.59				
Piperidine (5)		700				297	2020		14,000			191	82			
		5.59														
Ethyldimethylamine (6)				132												
				5.44												
n-Butyldimethylamine (7)				117												
				5.38												
n-Propyldimethylamine (8)				109												
				5.36												
Hexamethylenimine (9)												100				
												5.43				
Hydrazine (10)						124	1160					59.8				
												5.34	85			
Morpholine (11)									150			41.7	39			
												5.29				
Methylamine (12)	63.3	234	70.0	61.7	115	98.3	763	23.4		5.49	5.55	31.6	37	532	8.17	138
	5.30	*5.11*														
	5.21 av.															
4-Trifluoromethylpiperidine (13)												28.3	27			
β-Hydroxyethyldimethylamine (14)				78.3								*5.22*				
				5.20												
N-Carbethoxypiperazine (15)									400			14.8	19			
												5.11				
3-Trifluoromethylpiperidine (16)												9.65	20			
												5.05				
n-Butylamine (17)										3.07	3.37	9.5	7.7			64.8
												5.04				
Isobutylamine (18)											3.16	6.8				46.0
												4.99				
n-Propylamine (19)				45.0						2.35	3.15	9.6		253	3.07	63.0
				4.95												

Ethylamine (20)		153	48.3	40.0	70	59.2	481	16.9		3.73	2.88	9.2		323	3.57	63.3
		4.93														
Allylamine (21)						43.8	265			2.33		4.38				
												4.92				
Benzylamine (22)						43.8	220		110	1.60		4.52				
												4.92				
Isopropyldimethylamine (23)				35.8												
				4.85												
Diethylmethylamine (24)				31.5												
				4.80												
Di-*n*-butylamine (25)												1.8				
												4.77				
Diethylamine (26)		100	40	35	50	110	1670	37.8				1.9		282	3.03	
		4.75														
Di-β-hydroxyethylamine (27)			29.2													
			4.75													
Di-*n*-propylamine (28)					33.3							1.6		172	1.68	48.5
												4.75				
sec-Butyldimethylamine (29)				25.7												
				4.71												
Isopropylamine (30)								9.37		2.25	0.895	1.0				21.0
												4.68				
sec-Butylamine (31)									18		0.94	0.91		84.9		20.7
												4.66				
Diisobutylamine (32)												0.63				
												4.60				
2-Methylpiperidine (33)									50			0.22				
												4.43				
t-Butylamine (34)				10.0		7.28	51.6	2.12	0.75	0.370	0.115	0.038		30.4		5.23
												4.15				
Ammonia (35)	6.17	30.0	7.66	7.67	6.33	1.75	17.9	0.915				0.04		91.2	2.07	23.0
	4.24	*4.22*														
	4.23 av.															
Triethylamine (36)	4.5	21.7		6.52	7.50									89.5	0.50	12.6
	4.10	*4.08*														
	4.09 av.															
t-Butyldimethylamine (37)				5.17												
				4.02												
Diisopropylamine (38)												0.009				
												3.92				
Tri-β-hydroxyethylamine (39)			2.42													
			3.85													
s^o			1.19	0.99	1.08	1.40	1.54	1.28	2.37	0.99	1.61	2.68	1.96	0.57	0.78	0.89
Intercept[o]			−9.21	−8.24	−9.56	−3.33	−5.16	−3.21	−9.61	−6.47	−9.60	−16.54	11.73	−6.36	−9.24	−8.48

[a] All rate constants (upper numbers) are M^{-1} sec.$^{-1}$; *n*-values (lower italic numbers) are dimensionless and are listed under the rate constants from which they are derived. [b] Multiply number in table by this factor to obtain the reported rate constant. [c] See ref. 9. [d] T. S. Moore, D. B. Somervell, and J. N. Derry, *J. Chem. Soc.*, **101**, 2459 (1912). [e] C. Faurholt and co-workers, described in footnote *f*. [f] M. B. Jensen, *Acta Chem. Scand.*, **13**, 289 (1959). [g] P. Johncock, G. F. Kohnstam, and D. Speight, *J. Chem. Soc.*, 2544 (1958). [h] H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5439 (1957). [i] R. Zahradnik, *Collection Czech. Chem. Commun.*, **24**, 3422 (1959). [j] R. L. Hill and T. I. Crowell, *J. Am. Chem. Soc.*, **78**, 2284 (1956). [k] J. J. Blanksma and H. H. Schreinemachers, *Rec. trav. chim.*, **52**, 428 (1933). [l] See ref. 13. [m] Present work. [n] N. Menshutkin, *Ber.*, **30**, 2775 (1897); *Z. Phys. Chem.*, **17**, 228 (1895). [o] From the equation, $\log k_2 = sn +$ intercept, where k_2 is in l. mole^{-1} sec.$^{-1}$.

TABLE II

BIMOLECULAR RATE CONSTANTS FOR THE REACTION OF AMINES WITH 2,4-DINITROCHLOROBENZENE IN ABSOLUTE ETHANOL AT 25.0°

Amine	$k_2 \times 10^4$, M^{-1} sec.$^{-1}$
Pyrrolidine	460
Piperazine	274
Piperidine	195
Hexamethylenimine	100
Hydrazine	59.8
Morpholine	41.7
Methylamine	31.6
4-Trifluoromethylpiperidine	28.3
N-Carbethoxypiperazine	14.8
n-Butylamine	10.0
3-Trifluoromethylpiperidine	9.67

still strongly dependent, with $s = 2.0$. The s-values for the reactions of the carbonyl compounds, piperonal, isocyanic acid, and carbon dioxide fall in the range 1.6–1.3. The SN2 reactions of epoxides and alkyl halides are least sensitive, the s-values ranging from 1.2–0.6.

Experimental

Materials.—Most of the amines were standard commercial samples, purified by drying over potassium hydroxide and distillation in a spinning-band column from sodium (except for N-carbethoxypiperazine, which was fractionally distilled with no alkali treatment). Purity by v.p.c. was >97.5% in all cases. 2,4-Dinitrochlorobenzene was an Eastman Kodak Co. product, recrystallized from benzene–hexane, m.p. 49.2–51.6°. Ethanol was a Pharmco product containing 0.15% water by Karl Fischer

TABLE III

BIMOLECULAR RATE CONSTANTS FOR THE REACTION OF AMINES WITH DIMETHYLCARBAMYL CHLORIDE IN ABSOLUTE ETHANOL AT 25.0°

$(\text{Acyl chloride})_0$	Amine	$(\text{Amine})_0$	k_2, M^{-1} sec.$^{-1}$
0.00362	Pyrrolidine	0.0463	0.37
0.0072	Pyrrolidine	0.0250	0.34
0.00688	Pyrrolidine	0.0249	0.31
0.0362	Pyrrolidine	0.0500	0.30
			0.33 ± 0.03
0.0054	Hydrazine hydrate	0.0886	0.10
0.0127	Hydrazine hydrate	0.0452	0.083
0.00181	Hydrazine hydrate	0.234	0.079
0.00290	Hydrazine hydrate	0.119	0.077
			0.085 ± 0.008
0.0072	Piperidine	0.0518	0.10
0.0366	Piperidine	0.0493	0.089
0.0342	Piperidine	0.0493	0.079
0.0072	Piperidine	0.100	0.077
0.0145	Piperidine	0.050	0.077
0.0072	Piperidine	0.1048	0.066
			0.082 ± 0.009
0.0380	Morpholine	0.104	0.044
0.0409	Morpholine	0.104	0.040
0.0109	Morpholine	0.200	0.034
			0.039 ± 0.004
0.0174	Methylamine	0.108	0.039
0.0167	Methylamine	0.108	0.037
0.0074	Methylamine	0.108	0.037
0.0387	Methylamine	0.0477	0.035
			0.037 ± 0.001
0.0109	N-Phenylpiperazine	0.150	0.035
0.0181	N-Phenylpiperazine	0.075	0.035
0.0109	N-Phenylpiperazine	0.0989	0.026
			0.032 ± 0.004
0.0127	3-Azabicyclo[3.2.2]nonane	0.100	0.033
0.0072	3-Azabicyclo[3.2.2]nonane	0.200	0.026
			0.030 ± 0.003
0.0181	4-Trifluoromethylpiperidine	0.100	0.027
0.0072	4-Trifluoromethylpiperidine	0.200	0.027
			0.027 ± 0
0.0253	3-Trifluoromethylpiperidine	0.100	0.021
0.0127	3-Trifluoromethylpiperidine	0.104	0.020
0.0145	3-Trifluoromethylpiperidine	0.20	0.019
			0.020 ± 0.001
0.3387	N-Carbethoxypiperazine	0.150	0.020
0.0109	N-Carbethoxypiperazine	0.30	0.018
			0.019 ± 0.001
0.0181	*n*-Butylamine	0.150	0.0081
0.0145	*n*-Butylamine	0.300	0.0073
			0.0077 ± 0.0004
	Sodium ethoxide	0.238	0.030
	None	...	No detectable reaction

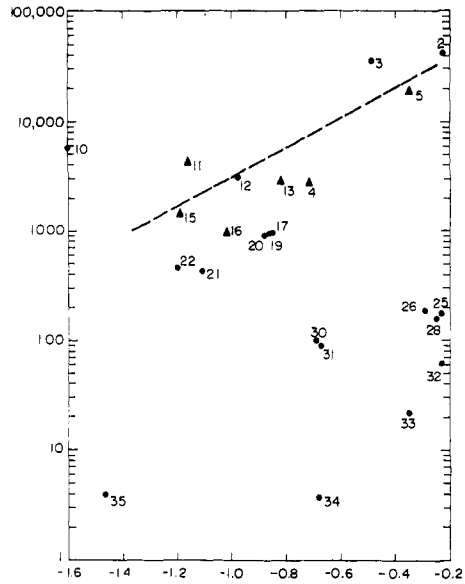

Fig. 1.—Correlation of 2,4-dinitrochlorobenzene reactions with $-\Sigma\sigma^*$ value of amine. Dotted line is drawn through the triangles representing data for 4-substituted piperidines: ordinate, log $10^4 k_2$; abscissa, $-\Sigma\sigma^*$ value of amine.

titration. Dimethylcarbamyl chloride (Monsanto Chemical Co.) was redistilled, b.p. 25° (0.8 mm.). Some difficulty was encountered in the preparations of 3- and 4-trifluoromethylpiperidines from sodium salts of the nipecotic acids,[12] probably owing to inadequate agitation of the reaction mixture. They were prepared by an alternate route.

4-Trifluoromethylpiperidine.—4-Trifluoromethylpyridine, b.p. 107.0–108.2°, 99+% pure by v.p.c., was prepared by the method of Raasch[12] in 65.3% yield. A solution of 59.0 g. (0.40 mole) of this compound in 200 ml. of tetrahydrofuran was hydrogenated over 0.30 g. of ruthenium dioxide at 115° and 1700 lb. Hydrogen, 0.85 mole (71%), was absorbed. The dark solution was dried over potassium carbonate, filtered, and distilled in a spinning-band column to give 47.6 g. (77.5%) of 4-trifluoromethylpiperidine, b.p. 133–135° (lit.[12] b.p. 133°), 99+% pure by v.p.c.

3-Trifluoromethylpiperidine.—3-Trifluoromethylpyridine, b.p. 116.3°, 99+% pure by v.p.c., was prepared in 65.5% yield exactly as for the 4-isomer. Hydrogenation exactly as before gave a 68.9% yield of 3-trifluoromethylpiperidine, b.p. 128–130° (lit.[12] b.p. 128–130°), 99+% pure by v.p.c.

Kinetic Methods.—The reactions of amines with 2,4-dinitrochlorobenzene were carried out as described by Brady and Cropper.[13] In a typical experiment, separate 0.0986 *M* solutions of piperidine and 2,4-dinitrochlorobenzene in absolute ethanol were made up. At zero time 25.0 ml. of the latter was pipetted with swirling into 50.0 ml. of the former in a flask held at 25.0°. Five aliquots, 10.0 ml., were removed at 3-min. intervals and pipetted immediately into beakers containing 10.0 ml. of 0.100 *N* hydrochloric acid, 20 ml. of water, and 20 ml. of absolute ethanol. The orange solutions were then quickly titrated potentiometrically with 0.100 *N* sodium hydroxide solution, the end point falling at an apparent pH of 6.5–7.0. Piperazine was the only amine requiring interpretation of the alkali titration curve. The break in the curve, which occurred at "pH" 6–8, is considered to correspond only to the conversion of the piperazine dication to the monocation. Also, 2,4-dinitrophenylation of only one end of the piperazine molecule is considered to occur. Calculations were carried out as described.[13,14]

For the dimethylcarbamyl chloride reactions, the kinetics were followed by a differential calorimetric method.[15] Some of the differential calorimetric experiments were made using a 15-fold excess or more of amine over dimethylcarbamyl chloride. In such cases the first-order rate constant for disappearance of

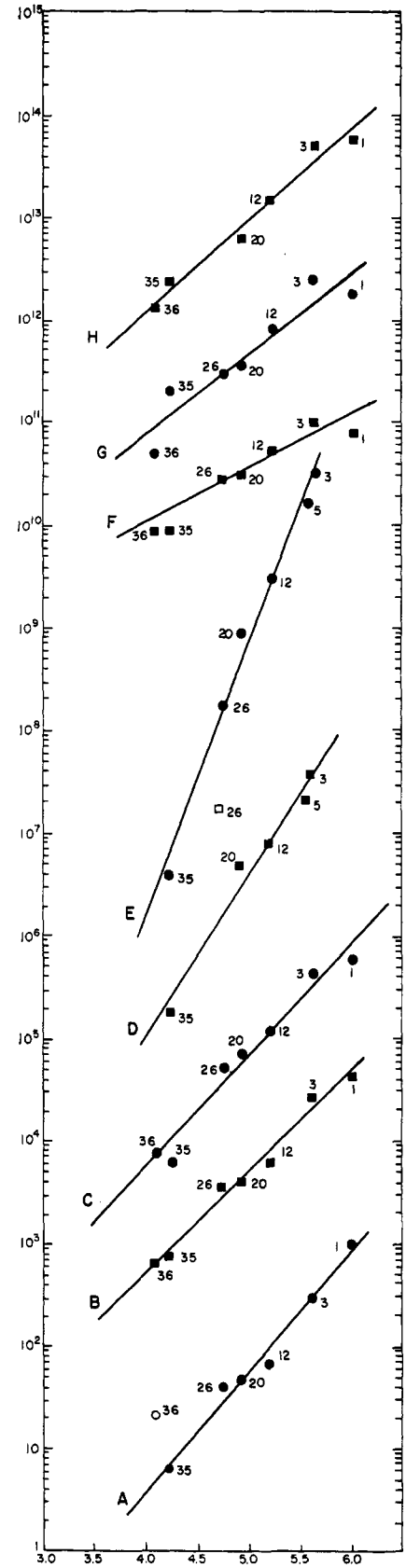

Fig. 2.—Correlation of reactions of ethylene oxide (A), propylene oxide (B), chloro acetate ion (C), isocyanic acid at 18° (D), 2,4-dinitrochlorobenzene (E), methyl bromide (F), ethyl bromide (G), and allyl bromide (H): ordinate, log k_2 (in arbitrary units); abscissa, standard *n*-value.

acyl chloride was determined by the method of Swinbourne,[16] which does not require a knowledge of the total area under the

(12) M. S. Raasch, *J. Org. Chem.*, **27**, 1406 (1962).

(13) O. L. Brady and F. R. Cropper, *J. Chem. Soc.*, 507 (1950).

(14) See J. C. Robb, *Nature*, **172**, 1055 (1953), for definitions of rate constants in the 2A + B case.

(15) C. H. Lueck, L. F. Beste, and H. K. Hall, Jr., *J. Phys. Chem.*, **67**, 972 (1963).

(16) E. S. Swinbourne, *J. Chem. Soc.*, 2371 (1960).

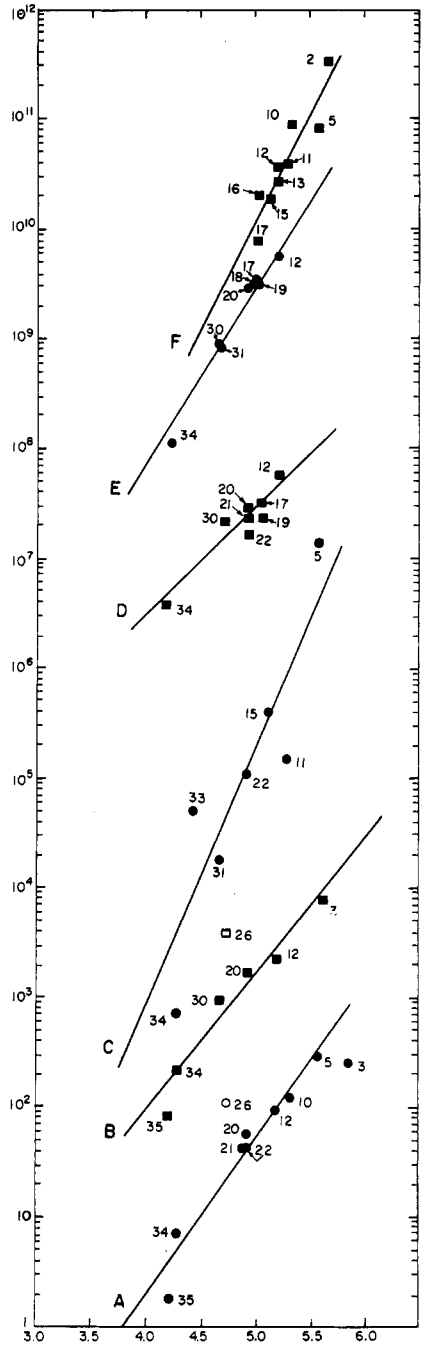

Fig. 3.—Correlation of reactions of carbon dioxide (A), isocyanic acid at 60° (B), ethyl chloroformate (C), methyl isothiocyanate (D), piperonal (E), and dimethylcarbamyl chloride (F): ordinate, log k_2 (in arbitrary units); abscissa, subsidiary n-value.

temperature–time curve. The first-order rate constant was then divided by the amine concentration to give the second-order rate constant.[14]

When the amine and dimethylcarbamyl chloride were used at more nearly equal equivalent concentrations, second-order kinetics was obeyed, and the approach of the temperature–time curve to the base line was very gradual. To determine the required total area, the area under the curve (to ~95% completion of reaction) was directly determined by computer integration and the area of the small additional part beyond the range of actual measurement was calculated as follows. Briefly, if the initial equivalent concentrations are appreciably different, one compound was in large excess over the other in the cell at >90% reaction, and heat was formed according to first-order kinetics. Since the reaction was quite slow at this stage, the heat was evolved practically as quickly as it was formed. Therefore, a semilogarithmic plot of ΔT_t, the observed temperature difference, in the region ~85–95% completion of reaction against time was linear, and a formal first-order rate constant, k_F, could be calculated from it. Finally, the area under a first-order temperature–time plot is

$$A_{\text{additional}} = \frac{\Delta T_f}{k_F}$$

Here ΔT_f is the reading at which our experimental observations ended, the area beyond which we wish to calculate. Values of $A_{\text{additional}}$ greater than 2% of the directly determined area significantly affected the linearity of the rate plot and the value of k_2. If the initial normalities were too nearly equal, first-order behavior did not begin past 90% reaction, and the method did not apply.

To establish the method as suitable for determining second-order kinetics, the rate of saponification of benzyl acetate in acetone–water (1:2 w./w.) at 35.0° was measured. The kinetic plots were linear to over 75% completion of reaction and the rate constants agreed well with each other (Table IV). Tommila[17] reported an extensive set of measurements of the rate constant for this reaction at various per cents of acetone and temperatures. Interpolation of his results gave a rate constant of 0.19 M^{-1} sec.$^{-1}$ for the conditions used in this study, in good agreement with the value of 0.20 ± 0.02 M^{-1} sec.$^{-1}$ obtained by the calorimetric method. Of incidental interest was the remarkably large cooling effect noted on introduction of the benzyl acetate into the reaction mixture. It was necessary to heat the pipet containing benzyl acetate to 55–65° to keep the recorder pen from leaving the chart. Tommila and co-workers have already stressed the importance of ester solvation in determining saponification rates.

TABLE IV

RATES OF SAPONIFICATION OF BENZYL ACETATE IN ACETONE–WATER (1:2 W./W.) AT 35.0°

(Benzyl acetate)$_0$	(Sodium hydroxide)$_0$	k_2, M^{-1} sec.$^{-1}$
0.0385	0.0518	0.21
0.0291	0.0518	0.18
0.0253	0.102	0.23
0.0294	0.102	0.18
		0.20 ± 0.02

No reaction of dimethylcarbamyl chloride with absolute ethanol alone was observed at 25.0° in a 15-min. reaction period. The low rate constant of 0.030 M^{-1} sec.$^{-1}$ obtained for sodium ethoxide in ethanol shows that ethoxide ion produced by ethanolysis of the amine could not contribute to the observed rates.

pK_a Values.—These were determined by potentiometric titration at constant temperature. The pK_a values at 30.0° were 9.48 for 4-trifluoromethylpiperidine ($-\Sigma\sigma^* = -0.82$) and 8.83 for 3-trifluoromethylpiperidine ($-\Sigma\sigma^* = -1.02$). At 25.0° a pK_a value of 8.53 for N-phenylpiperazine was obtained.

Acknowledgment.—The author is deeply indebted to Dr. M. S. Raasch for samples of 3- and 4-trifluoromethylpiperidine, to Miss Nancy Goyne, Mrs. Janet W. Willoughby, and Mr. John Bair for excellent technical assistance, and to Dr. L. F. Beste for helpful discussion.

(17) E. Tommila, *Suomen Kemistilehti*, **25**, 37 (1952).