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Sterically Hindered Phenolic Buffers. Application to Determination of Rates of Amidation of Ethyl Chloroformate¹

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A series of phenolsulfonic acids of varying pK_a was prepared for use as buffers. Bulky groups *ortho* to the hydroxyl group rendered the latter inert to acylation by ethyl chloroformate in water. The buffers were used to control pH in kinetic studies of the amidation of ethyl chloroformate. By working in sufficiently acidic solutions, the amidation reaction was slowed to measurable range. Semi-quantitative bimolecular rate constants were obtained. They were very high (10^4 l. mole⁻¹ sec.⁻¹ for piperidine) and were markedly decreased by steric hindrance in the amine.

Carbonyl chlorides react too rapidly with aliphatic amines for the rates of the reactions to be studied by conventional means. In order to slow the reaction to measurable speed, it appeared necessary to work under buffered conditions whereby only a minute amount of free, reactive amine is present. This can only be done in water solution, where a knowledge of pH and the pK_a value of the amine permit calculation of the free amine concentration. Although, in general, acyl chlorides hydrolyze so rapidly in water solution that a kinetic examination of any competing reaction cannot be made, ethyl chloroformate hydrolyzes rather slowly (half-life 51 min. at 20.1°).² This halide, therefore, was suitable for a study of amidation rates.

Sterically Hindered Buffers.—The choice of buffers presented some difficulties. Carboxylate buffers (acetate, tricarballoylate and citrate) and phenoxide buffers (*p*-phenolsulfonate) reacted quickly with ethyl chloroformate. Phosphate buffers, while they did not react with ethyl chloroformate, gave rise to drifting second-order amidation rate constants. Di-*o*-substituted phenols were found not to react with ethyl chloroformate provided that the substituents were sufficiently bulky. Since the amidation rate studies were to be carried out at various pH values, a series of di-*o*-substituted phenolsulfonic acids ranging in pK_a value from 2 to 9 was studied.³ We are aware of only one other use of sterically hindered buffers.⁴

The rate of hydrolysis of ethyl chloroformate was determined in the presence of each of the buffers. Data are given in Table I. It can be seen that Br, Cl, NO₂, SO₃⁻ and the benzo-ring in a 1-naphthol are suitably bulky *o*-substituents but CH₃ is too small.

Rates of Amidation of Ethyl Chloroformate.—The data obtained through the use of hindered

buffers on the rates of amidation of ethyl chloroformate are given in Table II. Although the

TABLE I
RATES OF HYDROLYSIS OF ETHYL CHLOROFORMATE^a IN THE PRESENCE OF HINDERED BUFFERS^b

Buffer	pK_a	$k_1 \times 10^4$, sec. ⁻¹	pH of reacn. soln.
Sodium 2,6-dinitrophenol-4-sulfonate (I)	<3.5	2.82	2.75
Disodium 2,4-dinitronaphthol-7-sulfonate (II)	<3.5	2.49	2.50
Tripotassium 6-nitrophenol-2,4-disulfonate (III)	5.2	2.51	5.15
Sodium 2-nitro-6-methylphenol-4-sulfonate (IV)	6.8	24.2	6.40
Sodium 2,4-dichlorophenol-6-sulfonate (V)	7.7	2.75	7.70
Potassium 2,6-dimethylphenol-4-sulfonate (VI)	9.5	>100	9.20
Dipotassium 4-chlorophenol-2,6-disulfonate (VII)	9.0	3.46 ^c	9.01
NaClO ₄ , 0.047 M	...	2.15	..
NaClO ₄ , 0.25 M	...	2.28	..
KNO ₃ , 0.28 M	...	2.43	..

^a 1×10^{-3} to 2×10^{-3} M. ^b 0.08 to 0.10 M. ^c Possible incursion of hydrolysis by hydroxyl ion.

TABLE II
RATES OF AMIDATION OF ETHYL CHLOROFORMATE^a IN PRESENCE OF HINDERED BUFFERS^b IN WATER AT 20.1°

Amine	pK_a	Total amine concn. $\times 10^3$, M	Buffer	pH	Corrected $k_1 \times 10^4$, sec. ⁻¹	k_2 , l. mole ⁻¹ sec. ⁻¹
Piperidine	11.20	7.99	III	5.40	19.1	1.5×10^4
		5.62	III	5.75	27.6	1.4×10^4
Morpholine	8.30	5.02	III	5.15	62.6	1.8×10^3
		5.30	III	4.75	18.4	1.2×10^3
Neopentylamine	10.16	7.61	V	7.20	62.9	75
		7.43	V	6.80	45.4	140
Benzylamine	9.29	3.63	V	6.70	103	110
<i>t</i> -Butylamine	10.40	7.79	VII	9.25	33.3	0.65
		6.36	VII	9.00	21.6	0.88
2-Methylpiperidine	11.15	7.36	VII	8.25	39.5	43
		4.89	VII	7.80	12.7	58
<i>s</i> -Butylamine	10.51	8.24	V	7.60	18.0	20
		8.26	V	8.00	33.4	15
1-Carboethoxy-piperazine	8.23	5.35	III	4.50	22.0	2.2×10^3
		1.70	III	4.75	36.2	6.5×10^3
1-Tosylpiperazine	7.39	1.94	III	4.50	61.5	2.4×10^3
		2.00	III	4.81	91.5	2.0×10^3
<i>cis</i> -2,6-Dimethyl-piperidine	10.92	5.17	VII	8.75	44.5 ^c	
		5.58	VII	8.40	32.4 ^c	
		2.64	VII	7.90	10.9 ^c	

^a $1-2 \times 10^3$ M. ^b 0.08-0.10 M. ^c Initial values; pro-found downward drift.

(5) The rate in the presence of *cis*-2,6-dimethylpiperidine was higher than first order in ethyl chloroformate.

(1) For the preceding article in this series on acyl chloride reactivities, see H. K. Hall, Jr., and D. W. Morgan, *J. Org. Chem.*, **21**, 249 (1956).

(2) (a) H. Böhme and W. Schürhoff, *Chem. Ber.*, **84**, 28 (1951); (b) H. K. Hall, Jr., *THIS JOURNAL*, **77**, 5993 (1955).

(3) The choice of these compounds was based on their predicted pK_a values. The latter were predicted by assuming additivity of the effects of single substituents on the ionization constant of phenol. See (a) J. M. Vandenberg, C. Henrich and S. C. Vandenberg, *Anal. Chem.*, **26**, 726 (1954); (b) H. Zollinger, W. Bücher and C. Wittwer, *Helv. Chim. Acta*, **36**, 1711 (1953).

(4) J. G. Pritchard and F. A. Long (*THIS JOURNAL*, **78**, 6010 (1956)) recently have used hindered pyridine bases in a study of the hydrolysis of epoxides.

halide disappeared according to reasonably good first-order kinetics in all but one reaction,⁶ the calculated second-order "constants" are only roughly constant. Some deviations from strict constancy are to be expected. The pK_a value of the amines might be in error by as much as 0.15 unit and the pH measurement by another 0.15 unit, since it was not possible to maintain strictly constant pH throughout a run. Complete mixing of the halide may not have occurred instantaneously. Salt effects on the rate constant also may enter. These errors, if additive, easily could lead to an error in concentration of free amine, and therefore of k_2 , of a factor of two.

Some additional kinetics experiments were performed by the method of intermittent titration, maintaining pH as constant as possible manually. The unavoidable fluctuation in pH , and hence in amine concentration, make this method very approximate. However, the second-order rate constants were in the same range as those obtained above, so the hindered buffers do not affect the rates significantly. Because of its convenience, this latter method was used to determine the rates of amidation of several additional amines.

The final estimates of the amidation rate constants are summarized in Table III. Although their approximate nature is clear, they represent the only information on rates of reaction of an acyl chloride with aliphatic amines.

TABLE III

k_2 , l. mole ⁻¹ sec. ⁻¹	Amine
10 ⁴	Piperidine, pyrrolidine, hexamethyleneimine
10 ²	Morpholine, thiamorpholine, 1-carbethoxypiperazine, 1-benzoylpiperazine, 1-tosylpiperazine, <i>n</i> -butylamine, benzylamine, neopentylamine, 2-methylpiperidine
10	<i>s</i> -Butylamine
1	<i>t</i> -Butylamine

Two conclusions can be drawn from the rate constants summarized in Table III. First, the rate constants are exceptionally high. This is doubtless caused by the high nucleophilicity of the amines and by the ease of displacement of halide from a carbonyl group.⁶ Second, the reaction is markedly subject to steric hindrance. It is of interest that neopentylamine does not exhibit a conspicuous degree of hindrance. A single methyl group in the 2-position of piperidine is effective, while introduction of a second methyl group, as in *cis*-2,6-dimethylpiperidine, brings about a change from first order to higher order in acid chloride. At present, no plausible mechanism for the latter reaction suggests itself.

Further progress in determining rapid amidation rates should be possible by the application of flow techniques.⁷

Applications of Hindered Buffers.—Although the present application of these buffers was not entirely satisfactory, other types of reaction are often encountered in which they may be applied

more successfully. Many simple pH -dependent reactions require extrapolation of the rate constants to zero buffer concentration because of buffer reactivity. In such cases, the use of the hindered buffers should prove advantageous.

Experimental

Buffers.—III and V, obtained from Eastman Kodak Co., were used as received. Buffer II, a crude yellow solid obtained from the Brothers Chemical Co., was purified by crystallization of the disodium salt.

Buffer IV: *o*-Cresol was sulfonated with SO₃ in liquid SO₂.⁸ The crude sulfonic acid was nitrated in glacial acetic acid and was poured into aqueous sodium chloride. Two recrystallizations from water gave pure material. The potassium salt was poorly soluble in water.

Anal. Calcd. for C₇H₆NSO₆Na: C, 32.9; H, 2.4. Found: C, 32.9, 32.9; H, 2.5, 2.3.

Buffer (I): The procedure was that of King⁹ modified in that efficient stirring was provided by a Lightnin 1/32 h.p. motor with a stainless steel stirrer. This maintained the reaction mixture as a brown creamy suspension and permitted temperature maintenance at 20–30°.

Buffer VI: This was prepared by sulfonation of 2,6-dimethylphenol with SO₃ in SO₂.

Buffer VII: A mixture of 662 g. of 4-chlorophenol, 660 ml. of 96% sulfuric acid and 1850 ml. of fuming sulfuric acid (25% SO₃) was heated for 5 hr. on the steam-bath. It was cooled, diluted with 1200 ml. of ice-water mixture and drained overnight on sintered glass filters to give 2177 g. of white material. The disulfonic acid, 1945 g., was dissolved in 500 ml. of water and neutralized with 783 g. of potassium hydroxide in 700 ml. of water. The salt crystallized from the hot solution. After chilling in ice and filtering, the precipitate was washed with absolute ethanol and ether to give, after drying *in vacuo*, 1552 g. (82.7%) of white crystals. Two recrystallizations from water gave an analytical sample.

Anal. Calcd. for C₆H₄O₇S₂ClK₂: C, 19.75; H, 0.82. Found: C, 19.89, 19.84; H, 0.87, 0.83.

Potassium 2-bromo-6-nitrophenol-4-sulfonate,¹⁰ pK_a 3.4, was too insoluble in water for kinetics experiments. The sodium salt, prepared by ion exchange, coated the silver electrodes and caused erratic readings.

Attempts to prepare a hindered buffer of pK_a 6–7 failed. Since the pK_a of IV was in this range, it appeared that corresponding phenols with bulky alkyl groups instead of methyl would be suitable. Sulfonation of *o*-isopropyl-, *o*-cyclohexyl- and *o*-*t*-butylphenols followed by nitration failed to give crystalline buffers.

The pK_a values of the phenols were taken as the pH at half-neutralization in a titration of a 100-mg. sample in 50 ml. of water with 0.5 *N* sodium hydroxide, using a Gilmont 1-ml. pipet.

Amines.—Liquid amines, mostly Eastman Kodak Co. White Label, were dried over potassium hydroxide and distilled in a spinning band column.

The pK_a values for the amines used only in intermittent titration runs were: pyrrolidine, 11.22; *N*-benzoylpiperazine, 7.73; hexamethyleneimine, 11.20; *n*-butylamine, 10.54; thiamorpholine, 9.00.

Ethyl Chloroformate.—Eastman Kodak Co. White Label material was redistilled, b.p. 93.5°.

Kinetics Experiments.—The concentration cell method of Swain and Ross¹¹ was used. A typical run will be described in detail. Tripotassium 6-nitrophenol-2,4-disulfonate, 20.68 g., was weighed into a 500-ml. volumetric flask and made up to the mark with CO₂-free distilled water. The solution was divided into two equal portions by use of a 250-ml. volumetric flask. The two portions were poured into two special 500-ml. round-bottom single-neck 29/26 flasks. These flasks were fitted with three extra necks each. One neck carried a salt bridge which connected the two flasks. This was a piece of 8 mm. tubing containing a sodium perchlorate (5%)–agar (3%) gel. The second neck

(6) Cf. S. L. Bafna and V. Gold, *J. Chem. Soc.*, 1406 (1953); V. Gold and E. G. Jefferson, *ibid.*, 1409 (1953); P. D. Bartlett, R. H. Jones and D. C. Dittmer, *THIS JOURNAL*, **79**, 2153, 2159 (1957).

(7) See, for example, L. Pearson, B. R. W. Pinsent and F. J. W. Roughton, *Disc. Faraday Soc.*, **17**, 141 (1954), and other papers in this volume.

(8) L. Leiserson, R. W. Bost and R. LeBaron, *Ind. Eng. Chem.*, **40**, 508 (1948).

(9) R. King, *J. Chem. Soc.*, **119**, 2112 (1921).

(10) E. Sakellarios, *Ber.*, **55B**, 2846 (1922).

(11) C. G. Swain and S. D. Ross, *THIS JOURNAL*, **68**, 658 (1946).

of each flask held a silver-silver chloride electrode. This was a length of 22-gage silver wire, wrapped around an 8 mm. glass rod, which had been coated by using it as the anode while electrolyzing *ca.* 0.5 *N* hydrochloric acid for 10 minutes using two dry cells in series. Through the third neck of the titration flask was placed the tip of a Gilmont 1-ml. micropipet-buret containing 0.5304 *N* HCl. The third neck of the reaction flask was used to introduce the acyl halide. The standard taper central neck carried a blade-type stirrer driven by an electric motor of adjustable speed. Piperidine, 4.9226 g., was weighed into a 50-ml. volumetric flask and made up to the mark with CO₂-free distilled water; 20 ml. of this solution was added by pipet to both the reaction and the titration flask. Glass and calomel electrodes were placed in one flask and the pH was lowered to 5.40 by the addition of 19.270 ml. of 1.87 *N* nitric acid from a Koch 5-ml. automatic microburet. The process was repeated on the other flask. The glass and calomel electrodes were replaced by the salt bridge and silver-silver chloride electrodes (the latter were damaged if introduced into the solution containing piperidine prior to neutralization). The electrodes were connected to a Leeds and Northrup type K-2 potentiometer, set at zero. This in turn led to a Leeds and Northrup type 2430-d galvanometer. Stirring was begun. Several drops of ethyl chloroformate were placed in a 2-ml. weight buret and the weight was determined. To the reaction flask were added two drops of the chloroformate, and the weight buret was set aside for subsequent weighing. The time at which the galvanometer needle crossed zero was noted, after which just sufficient standard hydrochloric acid was added from the pipet to bring the needle back. The process was repeated until the volume added was 2.000 ml. (68.2% of the calculated amount). The final pH was 5.22. Reactions were, in general, not carried to completion because the electrodes did not last indefinitely. For some of the faster reactions, the quantities of chloride ion formed after 10 half-lives were found to be in good agreement with the theoretical values.

Precipitation of amine salts of the buffers was noted in several instances. V formed precipitates with cyclohexylamine and benzylamine, though, in the latter case, at least one kinetic run could be made at a lower buffer concentration.

Intermittent titration runs were performed in the same flasks. The amine, 2-3 g., was weighed into 250 ml. of

water and was brought to the proper pH by 2 *N* hydrochloric acid. With stirring, the ethyl chloroformate was added. With the pH meter locked in the "on" position, the pH could be held fairly constant by the progressive addition of 0.5 *N* sodium hydroxide solution from a Gilmont 1-ml. pipet.

Calculations.—First-order rate constants were calculated as previously described.^{2b} If necessary, they were extrapolated to zero time. They were corrected for hydrolysis by subtracting 2.28×10^{-4} sec.⁻¹^{2b} from the observed rate constant. The corrected constant was then divided by the concentration of free amine to give the second-order rate constant.

The rate constants obtained by the method of intermittent titration exceeded those obtained by the concentration cell method by factors of 2-3. This is attributed to a higher concentration of alkali, and hence of amine, in the vicinity of the pipet tip.

Product Isolation.—It was deemed unnecessary in general to isolate the products. The reaction is firmly established as one of preparative value.¹² Since *cis*-2,6-dimethylpiperidine gave unusual kinetics behavior, however, it was necessary to verify that amidation was actually occurring.

To a solution of 200 g. of VII and 34.0 g. of *cis*-2,6-dimethylpiperidine in 3.5 l. of water at 25° was added 5.0 ml. of ethyl chloroformate with stirring. After two days at room temperature, the mixture was acidified with a solution of 40 ml. of concentrated sulfuric acid in 150 ml. of water and was continuously extracted overnight with methylene chloride. The organic extract was dried over magnesium sulfate, the solvent was distilled and the residue was distilled in a small Claisen flask to give 1.00 g. (11.7%) of 1-carbethoxy-*cis*-2,6-dimethylpiperidine, b.p. 123° (34 mm.), *n*_D²⁰ 1.4552.

Anal. Calcd. for C₁₀H₁₉O₂N: C, 64.82; H, 10.33. Found: C, 65.33, 65.14; H, 9.95, 10.00.

Therefore, at least part of the observed reaction consists of amidation.

(12) (a) T. S. Moore, M. Boyle and V. M. Thorn, *J. Chem. Soc.*, 39 (1929); (b) K. R. Jacobi, *Ber.*, **66**, 113 (1933); (c) H. W. Stewart, N. Q. Quinones, E. G. Lee and J. J. Denton, *J. Org. Chem.*, **18**, 1878 (1953).

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Correlation of the Base Strengths of Amines¹

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The base strengths of primary, secondary and tertiary non-aromatic amines were plotted against the Taft σ^* -values. Each class of amine lay on a different line. This indicates that solvation of the ammonium ion through the N⁺-H bonds plays an important role in determining base strength. All the *tertiary* amines gave an excellent correlation with the sum of the σ^* -values, irrespective of their degree of steric hindrance. This suggests that B-strain is not a factor determining the pK_a value. For *secondary* and *primary* amines, only those amines with a low degree of steric hindrance gave a linear plot against σ^* -values. This is also incompatible with the B-strain theory (for the primary amines), but in good agreement with the solvation theory if solvation of the ammonium ion is regarded as subject to hindrance. These correlations permit the prediction of the pK_a values of new amines.

Introduction

The Taft equation² $\log k/k_0 = \sigma^* \rho^*$ has enjoyed outstanding success in correlating rate and equilibrium data for many reactions of aliphatic com-

pounds. No correlation of the σ^* -values with the pK_a values of amines has been reported, however. This omission is striking in view of the excellent correlation which exists between the former and the pK_a values for carboxylic acids. The only report on this topic is that of Hansson,³ who showed that the pK_a values of a limited group of tertiary amines could be correlated with structural parameters similar to those of Taft. In the present communication, we describe an extension of this

(1) This is the third in a series of papers on base strengths. For paper II, see *THIS JOURNAL*, **78**, 2570 (1956).

(2) In this equation k and k_0 are the rate or equilibrium constants for the substituted and the reference compound, respectively, σ^* is a constant which expresses the polar effect of the substituent, and ρ^* is a constant measuring the susceptibility of the reaction in question to polar effects. The treatment is summarized by R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, ed., John Wiley and Sons, Inc., New York, N. Y., 1956.

(3) J. Hansson, *Svensk Kem. Tidskrift*, **67**, 256 (1955); "A Kinetic Study of the Addition of Amines to Propylene Oxide," Lund, 1955.