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Kinetic Studies of Bimolecular Nucleophilic Substitution. I. Rates of S_N2 Reactions of Phenacyl Bromide with Sodium Phenoxides and Sodium Carboxylates in 50% Aqueous Acetone

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The rates of the bimolecular nucleophilic substitution (S_N2 reactions) of phenacyl bromide with sodium para-substituted phenoxides, sodium para-substituted benzoates, and sodium aliphatic carboxylates have been measured in 50% aqueous acetone at 10—70°C. Linear free-energy relationships between the nucleophilic reactivities and basicites (expressed in terms of the pK_a's of the conjugate acids) have been observed in the reactions of para-substituted aromatic nucleophiles, whereas no linear relationships have been seen in the reactions of aliphatic carboxylates except in the cases of sodium acetate, sodium formate, and sodium monochloracetate. An equation, $\log k_2 = \alpha pK_a + \text{const.}$, has been applied to these reaction series and to the 30 literally-known series of S_N2 reactions. The correlation coefficients have then been calculated as a measure of the precision of these linear relationships. Hammett's ρ values for the reactions of para-substituted aromatic nucleophiles have also been calculated, and the several factors which affect the linear relationships have been discussed.

Although bimolecular nucleophilic substitution, or S_N2 reactions, have received intensive attention for more than three-quarters of a century, relatively few data$^{1-13,20)}$ are available for any systematic investigation of the correlation between the S_N2 nucleophilic reactivity and base dissociation constants; observation of substituted dialkylaniline,$^{1-4,11)}$ substituted pyridines,$^{7,13)}$ phosphines,$^{6)}$ phenoxides,$^{10,12,20)}$ thiophenoxides,$^{8)}$ and carboxylates$^{5)}$ has shown that the basicity of the nucleophiles paralleled the S_N2 reactivity only in the narrow range of structural variation.

We have measured the rates of the S_N2 reaction of phenacyl bromide with various carboxylates and phenoxides in order to provide additional examples of linear relationships between the nucleophilicity and the basicity. The title bromide was chosen as a substrate because of its ease of bimolecular nucleopheilic substitutions due to the carbonyl group adjacent to the reaction center, although the reaction of the phenacyl system might not be typical of one-step S_N2 reactions but might, rather, be considered somewhat close to a carbonyl-carbon attack by a nucleophile.$^{14)}$ As nucleophiles with known pK_a values of the conjugate acids, various sodium para-substituted benzoates and sodium para-substituted phenoxides and several aliphatic carboxylates were used.

Results and Discussion

The S_N2 reactions were conducted on phenacyl bromide in 50 vol% aqueous acetone over the temperature range of 50—80°C for various sodium carboxylates and over that of 0—50°C for sodium phenoxides. A clear-cut second-order behavior was observed in each reaction. The rate constants and the activation parameters are shown in Tables 1, 2, and 3.

The correlation between the basicity and the nucleophilicity for these nucleophiles is represented graphically in Figs. 1 and 2 by plotting the logarithms of the rate constant at 30°C for the phenoxides, or at 70°C for the carboxylates, against the pK_a values$^{15)}$ of the corresponding conjugate acids in

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14) For a summary, see C. A. Bunton, "Nucleophilic Substitution at a Saturated Carbon Atom," Elsevier Publishing Co., Amsterdam (1963), pp. 35—38.
15) For the pK_a values for the phenols, *cf.* A. I. K_a Biggs and R. A. Robinson, *J. Chem. Soc.*, **1961**, 388. For the pK_a values for the carboxylic acids, *cf.* Landolt-Börnstein, "Physikalisch-chemische Tabellen," Julius Springer, Berlin, Hauptband II, 1120 (1923).

Table 1. Rate constants[b] and activation parameters for the S_N2 reactions of phenacyl bromide with sodium *p*-substituted phenoxides in 50% aqueous acetone[a]

p-Substituent Temp., °C	H	*p*-NO_2	*p*-CH_3	*p*-Br
9.82	2.67×10^{-2}	—	—	—
10.0	—	—	4.95×10^{-2}	—
20.0	—	—	1.24×10^{-1}	2.25×10^{-2}
25.0	1.07×10^{-1}	—	—	—
30.0	1.67×10^{-1}	1.65×10^{-3}	2.43×10^{-1}	5.73×10^{-2}
40.0	—	3.97×10^{-3}	—	1.31×10^{-1}
50.0	6.77×10^{-1} [c]	1.10×10^{-2}	9.80×10^{-1} [c]	3.03×10^{-1} [c]
$\Delta H^{\neq}$ (50.0°)	13.4 ± 0.66	17.8 ± 0.79	13.0 ± 0.60	15.5 ± 0.21
$\Delta S^{\neq}$ (50.0°)	-18.1 ± 2.3	-12.8 ± 2.5	-18.6 ± 2.1	-13.4 ± 0.68
$\mathrm{p}K_a$[15]	10.0	7.15	10.26	9.36

a) Initial concentrations of phenacyl bromide and nucleopiles were respectively 0.023—0.0514 M and 0.0602—0.114 N.

b) $\mathrm{sec}^{-1}\mathrm{M}^{-1}$

c) Extrapolated from data at other temperatures.

Table 2. Rate constants[b] and activation parameters for the S_N2 reactions of phenacyl bromide with sodium *p*-substituted benzoates in 50% aqueous acetone[a]

p-Substituent Temp., °C	*p*-NO_2	*p*-Cl	H	*p*-CH_3
50.0	1.15×10^{-3} [c]	2.78×10^{-3} [c]	3.35×10^{-3} [c]	4.01×10^{-3}
60.0	2.87×10^{-3}	7.00×10^{-3}	8.07×10^{-3}	8.78×10^{-3}
70.0	6.86×10^{-3}	1.22×10^{-2}	1.70×10^{-2}	2.27×10^{-2}
80.0	1.44×10^{-2}	3.20×10^{-2}	3.67×10^{-2}	—
$\Delta H^{\neq}$ (50.0°)	18.3 ± 0.39	17.2 ± 0.97	17.3 ± 0.35	18.3 ± 0.97
$\Delta S^{\neq}$ (50.0°)	-15.6 ± 1.1	-17.3 ± 2.8	-16.6 ± 1.0	-13.4 ± 2.9
$\mathrm{p}K_a$[15]	3.40	4.03	4.18	4.37

a) Initial concentrations of phenacyl bromide and the nucleophiles were respectively 0.100—0.110 M and 0.125—0.130 N.

b) $\mathrm{sec}^{-1}\mathrm{M}^{-1}$

c) Extrapolated from data at other temperatures.

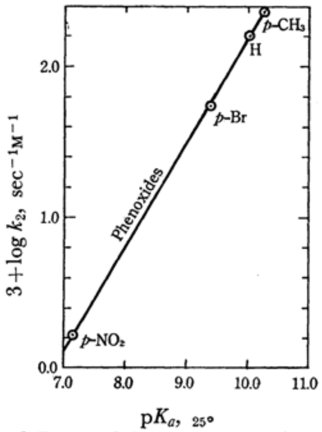
Table 3. Rate constants[b] and activation parameters for the S_N2 reactions of phenacyl bromide with sodium salts of various aliphatic carboxylic acids in 50% aqueous acetone[a]

Sodium carboxylate Temp., °C	Chloro-acetate	Formate	Acetate	Propionate	*n*-Butyrate	Caproate
50.0	7.07×10^{-4} [c]	1.10×10^{-3} [c]	1.86×10^{-3}	2.82×10^{-3} [c]	3.62×10^{-3} [c]	5.05×10^{-3}
60.0	1.78×10^{-3}	2.82×10^{-3}	4.77×10^{-3}	6.75×10^{-3}	8.80×10^{-3}	1.42×10^{-2}
70.0	4.10×10^{-3}	6.12×10^{-3}	1.17×10^{-2}	1.59×10^{-2}	1.97×10^{-2}	3.45×10^{-2}
80.0	8.82×10^{-3}	1.31×10^{-2}	—	3.38×10^{-2}	4.08×10^{-2}	—
$\Delta H^{\neq}$ (50.0°)	18.1 ± 0.06	18.0 ± 0.19	19.2 ± 0.16	18.3 ± 0.24	17.3 ± 0.14	19.5 ± 0.44
$\Delta S^{\neq}$ (50.0°)	-17.2 ± 0.18	-18.4 ± 0.6	-11.8 ± 0.5	-14.0 ± 0.7	-16.2 ± 0.4	-8.78 ± 1.3
$\mathrm{p}K_a$[15]	2.81	3.67	4.73	4.89	4.83	4.86

a) Initial concentraions of phenacyl bromide and the nucleophiles were respectively 0.100 M and 0.130—0.135 N.

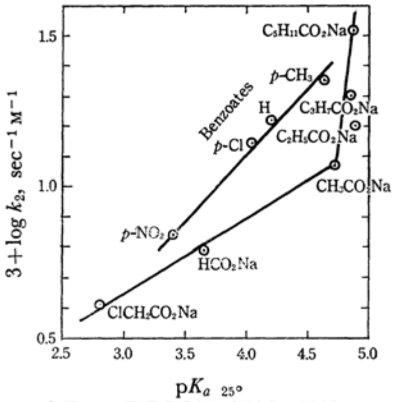
b) $\mathrm{sec}^{-1}\mathrm{M}^{-1}$

c) Extrapolated from data at other temperatures.



(Phenacyl Br + PhONa 30°C, 50% aq. acetone)

Fig. 1. Correlation between nucleophilicity and basicity for sodium phenoxides in the S_N2 reaction of phenacyl bromide.



(Phenacyl Br + RCOONa 70°C, 50% aq. acetone)

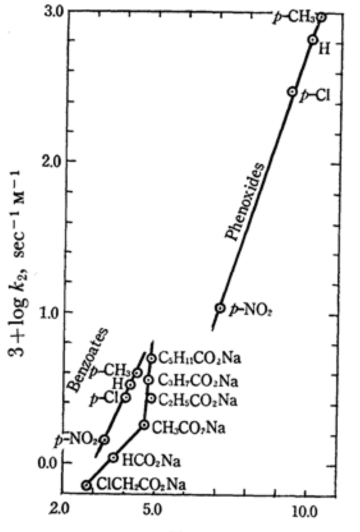
Fig. 2. Correlation between basicity and nucleophility for sodium carboxylates in the S_N2 reaction of phenacyl bromide.

water. Linear correlations were observed between the rate constants and the pK_a values for para-substituted phenoxides and for para-substituted benzoates, whereas a refracted linear relation was exhibited by a series of aliphatic carboxylates, as is shown in Fig. 2. In order to compare the nucleophilic reactivity of these nucleophiles at the same temperature, the correlation at 50°C is presented in Fig. 3 by using extrapolated rate constants.

The equation (an extended[16] Brϕnsted equation):

$$\log k_2 = \alpha \mathrm{p}K_a + \text{constant} \quad (1)$$

where α is a substrate constant, has been applied to these reaction series, and also to the literally-



(Phenacyl Br + Base 50°C, 50% aq. acetone)

Fig. 3. Correlation between nucleophilicity and basicity for various ionic nucleophiles in the S_N2 reaction phenacyl bromide.

known S_N2 reactions. Table 4 gives the α values, along with their correlation coefficients.[18] Among the 33 reaction series, three series, *i. e.*, S_N2 reactions with tertiary and secondary aliphatic phosphines and the aliphatic carboxylates, have α values greater than 1. It has been stated by several investigators[16] that a higher α value implies a greater degree of bond formation in the S_N2 transition state containing those nucleophiles. However, the abnormally high values of α for these three reaction series with aliphatic nucleophiles present a problem which must be explained by another factor apart from the above-mentioned bond-formation.

The correlation coefficient, r,[18] has been used as a measure of the precision for these linear correlations (Table 4). The r's for the S_N2 reactions of phenacyl bromide with para-substituted phenoxides and with para-substituted benzoates are greater than 0.95, indicating a satisfactory linear correlation, whereas the lower value (0.605) for the aliphatic carboxylates indicates that the correlation for these nucleophiles is not adequately presented by Eq. (1). Among the 23 examples listed in Table 4, 9 reaction series, including the two for phenacyl bromide, are found to have correlation coefficients greater than 0.95; the correlation coefficients for the 7 reaction series with phenoxides, benzoates, dimethylanilines and substituted pyridines have values between 0.90—0.95. These data reconfirm the well-known generalization that a more quantitative linear free-energy relationship may be expected within a narrower structural

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[16] See J. F. Bunnett, "Nucleophilicity," in Annual Reviews of Physical Chemistry, Annual Reviews Inc., Palo Alto, California, Vol. 14 (1963), pp. 271—290.

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[18] H. H. Jaffé, *Chem. Revs.*, **53**, 234, 253 (1953).

TABLE 4. VALUES OF THE BRØNSTED COEFFICIENT α AND HAMMETT'S ρ VALUES FOR S_N2 REACTIONS OF SOME NUCLEOPHILES

Compound	Nucleophile type and number	Reaction temp. °C	Solvent	α	$r^{a)}$	$\rho^{b)}$	$r^{a)}$	Rate data Ref.	pK_a data Ref.
CH_3I	$RC_6H_4N(C_2H_5)_2$, 7	35	90% aq. acetone	0.562	0.990	−2.87	−0.983	1 and 2	17 a
	$RC_6H_4N(CH_3)_2$, 9	35	90% aq. acetone	0.666	0.987	−2.11	−0.759	4	4
	$RC_6H_4N(CH_3)_2$, 5	100	$C_6H_5NO_2$	0.558	0.978	−2.44	−0.995	3	17 a
	$RC_6H_4N(CH_3)_2$, 4	80	$C_6H_5NO_2$	0.590	0.962	−2.31	−0.995	11	17 b
	Pyridine (4-R, H), 3	60	CH_3NO_2	0.295	—	—	—	7	7
	Pyridine (2,6-Me_2, 2,4,6-Me_3), 2	60	CH_3NO_2	0.435	—	—	—	7	7
C_2H_5I	$RC_6H_5N(CH_3)_2$, 6	80	$C_6H_5NO_2$	0.770	0.939	−2.97	−0.962	11	17 b
	RR′R″P, 8	35	Acetone	1.66	0.799	—	—	6	6
	RR′PH, 3	35	Acetone	1.34	—	—	—	6	6
	C_6H_5RR′P, 3	35	Acetone	0.332	—	—	—	6	6
n-C_3H_7Br	Pyridine (4-Me, H), 2	60	CH_3NO_2	0.341	—	—	—	7	7
CH_2=$CHCH_2Br$	Pyridine (3-R, 3,4-RR′, 4-R), 14	60	CH_3NO_2	0.358	—	—	—	7	7
	Pyridine (2-R, 2,3- 2,4-, 2,5-RR′), 5	60	CH_3NO_2	0.498	0.738	—	—	7	7
(n-$C_3H_7)_2CHBr$	p-RC_6H_4ONa, 3	60	C_2H_5OH	0.317	—	−1.18	—	12	15
$C_6H_5CH_2CH_2Br$	p-RC_6H_4ONa, 6	60	C_2H_5OH	0.471	0.918	−1.45	−0.991	12	15
$C_6H_5CH_2Br$	Pyridine (4-Me, H), 2	60	CH_3NO_2	0.325	—	—	—	7	7
	RC_6H_4SLi, 7	20	CH_3OH	0.198	0.937	−0.571	−0.971	8	8
p-$CH_3OC_6H_4CH_2Br$	RC_6H_4SLi, 7	20	CH_3OH	0.149	0.891	−0.439	−0.947	8	8
p-$CH_3C_6H_4CH_2Br$	RC_6H_4SLi, 7	20	CH_3OH	0.204	0.922	−0.584	−0.948	8	8
p-$BrC_6H_4CH_2Br$	RC_6H_4SLi, 7	20	CH_3OH	0.257	0.950	−0.745	−0.989	8	8
p-$NO_2C_6H_4CH_2Br$	RC_6H_4SLi, 7	20	CH_3OH	0.364	0.935	−1.07	−0.987	8	8
$HO(CH_2)_3Br$	RC_6H_4ONa, 6	61	H_2O	0.214	0.999	−0.579	−0.962	10	10
$C_2H_5O_3SCH_3$	Pyridine (3-, 4-Me, 3,5-Me_2), 4	61	H_2O	0.0996	0.967	—	—	13	13
	Pyridine (2-Me, H), 2	61	H_2O	0.120	—	—	—	13	13
	Pyridine (2,6-Me_2, 2,4,6-Me_3), 2	61	H_2O	0.111	—	—	—	13	13
	Imidazoles, 5	35	H_2O	0.273	0.877	—	—	13	13
NaO_2CCH_2Cl	RCO_2Na, 25	45	H_2O	0.229	0.929	—	—	5	5
	$R(CO_2Na)_2$, 6	45	H_2O	0.0934	0.756	—	—	5	5
NaO_2CCH_2Br	RCO_2Na, 7	25	H_2O	0.243	0.914	—	—	5	5
m-$NO_2C_6H_4COCH_2Br$	$RC_6H_4CSNH_2$, 6	30	C_2H_5OH	—	—	−0.960	−0.984	19	—
$C_6H_5COCH_2Br$	$RC_6H_4CSNH_2$, 10	30	C_2H_5OH	—	—	−0.912	−0.986	19	—
	n-$C_nH_{2n+1}CO_2Na$ ($n=1-5$), 4	70	50% aq. acetone	1.641	0.603	—	—	Present results	15
	RCO_2Na, 3	70	50% aq. acetone	0.237	—	—	—	Present results	15
	$RC_6H_4CO_2Na$, 4	70	50% aq. acetone	0.523	0.998	−0.533	−0.999	Present results	15
	RC_6H_4ONa, 4	30	50% aq. acetone	0.700	1.000	−2.368	−0.989	Present results	15
CH_3OSO_3Na	RC_6H_4ONa, 12	100	H_2O	0.301	0.992	−0.682	−0.993	20	15

a) r=the correlation coefficient.[18]

b) Brown's σ values were used (D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958)). For the σ values which are not cited in the Brown's table, Jaffé's σ values[18] were used.

change in the reaction components.

The Hammett equation is also applied to the reaction series with meta- and para-substituted aromatic nucleophiles. The correlation coefficients, r, of this linear relationship, listed in Table 4 along with the ρ values,[19] generally have greater values than those for the extended Brϕnsted equation, Eq. (1), of the various nucleophiles, indicating the better fit of the Hammett equation. This may also be anticipated on the basis the generalization mentioned above.

Most of the reaction series listed in Table 4 have been measured at an arbitray temperature in a selected organic solvent, whereas the pK_a values have been measured in most cases in an aqueous solution at room temperature; this is a widely-used way of presenting the correlations between the nucleophilicity and the basicity. However, for the purpose of a strict comparison of the nucleophlicity and the basicity, the following factors, which also affect the linear relationships, remained to be reexamined in the future: (a) the dilution effect for ionic nucleophilies; (b) the solvent effect on the S_N2 rates and the pK_a values, and (c) the temperature dependence of the S_N2 reaction rates and the pK_a values.

A reexamination of (a) may disclose a linear relationship which is theoretically sounder, since the rate for an ionic nucleophile would be enhanced at the higher dilution and, under such conditions, the ionic nucleophile may show a more intrinsic S_N2 reactivity.[21] As for (b), it is considered that a more or less different correlation might be expected if the measurements for both the S_N2 rate constant and the pK_a values are carried out in the same solvent. The method of making a reasonable choice of a standard solvent, hydroxylic or non-hydroxylic,[22] for the nucleophilicity scale is allso open to reinvestigation. Obviously, (c) presents the question of a standard temperature for the examination of these correlations. In this connection, the so-called isokinetic relationship[23] for these S_N2 reaction rates should be examined.

Experimental

Materials. Phenacyl bromide (mp 50.5—52.0°C) was prepared in the usual manner.[24] The sodium phenoxides and sodium carboxylates were prepared from sodium ethoxide and the respective conjugate acids. The ethanolic solution of the slight excess of the acid (or the phenol) was mixed with the ethanolic sodium ethoxide. The sodium salt was filtered, washed with ethanol, and then dried *in vacuo* to a constant weight in a tarred flask at 100—110°C. The reagent-grade acids (or phenols) were used as received.

Kinetic Measurements. The S_N2 reactions at 30°C were followed by pipetting 1.000-cc aliquots into 5.00 cc of 5% aqueous nitric acid and by then titrating the bromide ion by the Volhard method. For the reactions at 40—80°C, the sealed ampoule technique was used. Each ampoule contained 1.000 cc of an aliquot of the reaction mixture. Infinity titers were determined for at least ninety half-lives and gave reproducible results. All the rate data were treated graphically by a plot of $\log b(a-x)/a(b-x)$ against the time; the results are shown in Tables 1, 2, and 3. In each case the retion was followed to at least 80% completion, and a smooth linear relationship was obtained.

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[19] Two reaction series for the nucleophiles with unknown pK_a values are included (J. Okamiya, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **86**, 315 (1965)).

[20] G. H. Green and J. Kenyon, *J. Chem. Soc.*, **1950**, 1589.

[21] For the dilution effect, see E. A. Moelwyn-Hughes, "The Kinetics of Reactions in Solution," The Oxford Univ. Press, 2nd Ed. (1947), p. 128.

[22] For the nucleophilicity in the aprotic solvents, see A. J. Parker, *Quat. Revs.*, **16**, 163 (1962).

[23] J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1950).

[24] R. M. Cowper and L. H. Davidson in "Organic Syntheses," Coll. Vol. II, p. 480 (1943).