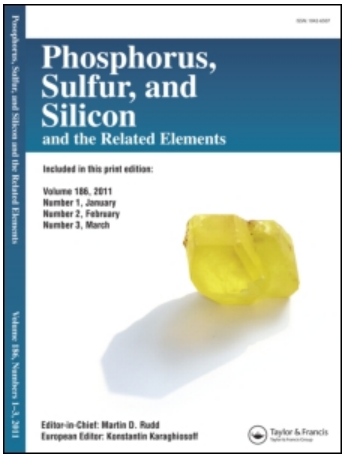


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

pKa VALUES OF 2- AND 2,6-DISUBSTITUTED PYRIDINE DERIVATIVES CONTAINING SULFENYL AND SULFINYL GROUPS AND σ* AND E_s VALUES OF SEVERAL SULFENYL AND SULFINYL GROUPS

Naomichi Furukawa[a]; Keiko Iida[a]; Tsutomu Kawai[a]; Satoshi Ogawa[a]; Shigeru Oae[ab]
[a] Department of Chemistry, University of Tsukuba, Ibaraki, Japan [b] Okayama University of Sciences, Okayama

To cite this Article Furukawa, Naomichi , Iida, Keiko , Kawai, Tsutomu , Ogawa, Satoshi and Oae, Shigeru(1984) 'pKa VALUES OF 2- AND 2,6-DISUBSTITUTED PYRIDINE DERIVATIVES CONTAINING SULFENYL AND SULFINYL GROUPS AND σ* AND E_s VALUES OF SEVERAL SULFENYL AND SULFINYL GROUPS', Phosphorus, Sulfur, and Silicon and the Related Elements, 19: 2, 239 — 253
To link to this Article: DOI: 10.1080/03086648408077585
URL: http://dx.doi.org/10.1080/03086648408077585

Phosphorus and Sulfur, 1984, Vol. 19, pp. 239–253
0308-664X/84/1902-0239/$18.50/0

pKa VALUES OF 2- AND 2,6-DISUBSTITUTED PYRIDINE DERIVATIVES CONTAINING SULFENYL AND SULFINYL GROUPS AND σ* AND E_s VALUES OF SEVERAL SULFENYL AND SULFINYL GROUPS

NAOMICHI FURUKAWA,* KEIKO IIDA, TSUTOMU KAWAI, SATOSHI OGAWA AND SHIGERU OAE†

Department of Chemistry, University of Tsukuba, Sakura-mura, Niihari-gun, Ibaraki 305, Japan

(*Received September 23, 1983*)

pKa Values of pyridine derivatives having sulfenyl and sulfinyl groups attached to either 2- or 2,6-positions in the pyridine nuclei were measured affording the following values; 2-SCH_3 (3.64), 2-$S(O)CH_3$ (0.17), 2-CH_2SCH_3 (5.40), 2-$CH_2S(O)CH_3$ (3.10), 2-CH_2OCH_3 (4.35), 2,6-$(SCH_3)_2$ (2.37), 2,6-$(CH_2SCH_3)_2$ (4.10), 2,6-$(CH_2S(O)CH_3)_2$ (1.53), 2,6-$(CH_2OCH_3)_2$ (3.50). These pKa values together with several other 2-substituted pyridines: 2-X-C_5H_4N in which X is Cl, Br, I, CN, $CO_2C_2H_5$, CH_3, H, OCH_3, were plotted against Taft σ* values to afford a good straight line giving $\rho^* = -4.5$. From fitting the above pKa values on this line, the σ* values of these groups were determined. Furthermore, E_s values of $CH_3S(O)$-, CH_3SCH_2-, $CH_3S(O)CH_2$-, CH_3OCH_2-groups were determined and the application of the σ* values was tested by measuring both acid and alkaline hydrolyses rates of the corresponding *p*-nitrophenyl acetates, the modified Taft method.

The additivity of these σ* values in the 2,6-positions in the pyridine nuclei was examined. The cation-transfer experiments were undertaken by using 2,6-bis(methylsulfinylmethyl)pyridine as mediator.

Recently, some simple sulfoxides containing pyridine nuclei, e.g., methyl 2-pyridyl sulfoxide, have been found to work as effective phase-transfer catalysts (PTC) which can promote the nucleophilic substitutions or alkylation reactions of active methylene compounds.[1] In such PTC reactions as liquid–liquid or liquid–solid binary phase systems, these sulfoxides may be able to dissolve nucleophiles into the organic phase by chelation of the metal cations by both the pyridyl nitrogen atom and the sulfinyl oxygen atom attached to the α-position of the pyridine nuclei.[2] On the other hand, neither the corresponding sulfide nor the sulfone work as effective PTC catalysts.[1b] In order to estimate the strength of the chelating ability of these sulfoxides, it is essential to know their pKa values since the pKa value indicates the affinity to the proton and hence would represent to some extent a measure of their chelating ability toward the alkali or alkaline-earth metal cations having small ionic radii.[3]

The pKa values of 2-, 3-, and 4-CH_3-substituted pyridines have been determined by Albert[4] and Charton,[5] whereas those of sulfinyl derivatives have never been reported in the literature. This paper describes the pKa values of several 2- and 2,6-disubstituted pyridine derivatives bearing sulfenyl, sulfinyl, and ether groups

† Present address; Okayama University of Sciences, Ridai-cho, Okayama.

together with the Taft-Hammett σ^* and E_s values of these functional groups such as $CH_3S(O)$, CH_3SCH_2, $CH_3S(O)CH_2$, and CH_3OCH_2 which were determined by measuring their pKa values.

RESULTS AND DISCUSSION

pKa Values of 2- and 2,6-Disubstituted Pyridines

We have found that 2- and 2,6-disubstituted pyridines bearing sulfinyl group work as better catalysts in comparison with the 4-substituted derivatives. Therefore, in order to investigate in detail the physical properties of these sulfur compounds, several pyridine derivatives bearing 2- and 2,6-disubstituted sulfur functional groups were prepared and subjected to measurement of their pKa values.

The pKa values were determined by the standard method from UV spectra of the aqueous hydrochloric acid solutions at 25°C and were calculated by the equation (1):

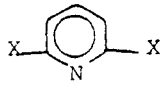
$$\mathrm{pKa} = \mathrm{pH} - \log\frac{A_{\mathrm{HL}} - A}{A - A_{\mathrm{L}}} \tag{1}$$

where A represents UV absorbance, HL and L represent protonated and free pyridine, respectively. The pKa values thus obtained along with the literature values as shown in brackets are listed in Table I.

TABLE I

pKa Values of pyridine derivatives containing sulfur substituents

1a 2-SCH_3
b 3-SCH_3
c 4-SCH_3
d 2-$S(O)CH_3$
e 3-$S(O)CH_3$
f 2-CH_2SCH_3
g 2-$CH_2S(O)CH_3$
h 2-CH_2OCH_3
i 2-OCH_3
j 3-OCH_3



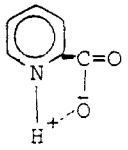
2a 2,6-SCH_3
b 2,6-CH_2SCH_3
c 2,6-$CH_2S(O)CH_3$
d 2,6-CH_2OCH_3

	X	pKa[a]
1a	2-SCH_3	3.64 (3,59)[b]
1b	3-SCH_3	4.48 (4.42)[b]
1c	4-SCH_3	5.95 (5.94)[b]
1d	2-$S(O)CH_3$	0.17[c]
1e	3-$S(O)CH_3$	3.03
1f	2-CH_2SCH_3	5.40
1g	2-$CH_2S(O)CH_3$	3.10
1h	2-CH_2OCH_3	4.35
2a	2,6-SCH_3	2.37
2b	2,6-CH_2SCH_3	4.10
2c	2,6-$CH_2S(O)CH_3$	1.53
2d	2,6-CH_2OCH_3	3.50

[a] Measured at 20°C. Errors are ±0.05.
[b] Reference 5.
[c] Error is ±0.1.

As shown in Table I, the pKa values of **1a–c** are 3.64, 4.48, and 5.95 which are in accordance with those of the values reported in the literatures.[4] Therefore, the pKa values of compounds **1** and **2** thus calculated are correct within experimental errors (± 0.05). Further, the pKa value of 2-methyl-sulfinyl pyridine is small (0.17) which is the limit of measurement of the present UV method and that of 2,6-dimethyl-sulfinylpyridine is too small to be measured.

pKa values of 2-, 3-, and 4-carboxypyridines (pKa_2) as shown in the literature are 5.37, 4.73, and 4.89,[6] respectively. This higher pKa value of 2-carboxypyridine than that of the 3- or 4-derivative is attributable to the formation of an intramolecular hydrogen bond between the carboxyl group and the nitrogen atom in the pyridine ring:



Hydrogen bonding is expected to be observed in the case of methyl 2-pyridyl sulfoxide. However, the pKa value of 2-pyridyl sulfoxide was lower than that of the corresponding 3-pyridyl derivative. This result seems to indicate that the inductive and field effects of the sulfinyl group at the 2-position of the pyridine ring are too strong to allow chelation of the proton intramolecularly by both the sulfinyl oxygen and nitrogen atoms. On the other hand, in order to estimate the strength of the inductive effect of several sulfur functional groups used in this experiment, the pKa values of several 2-substituted pyridines in the literature[6b] were plotted against their Taft σ^* values to afford a good straight line with $\rho^* = -4.5$ as shown in Table II and Figure 1. Charton reported that the Hammett plot of thirteen 2-substituted pyridines vs. σ_I values gives a straight line affording $\rho = -10.3$ ($r = 0.992$) which agrees well with our results.

The pKa values of methyl 2-pyridyl sulfide (**1a**) and methyl 2-pyridyl sulfoxide (**1d**) obtained in the present experiment were also plotted against their σ^* values

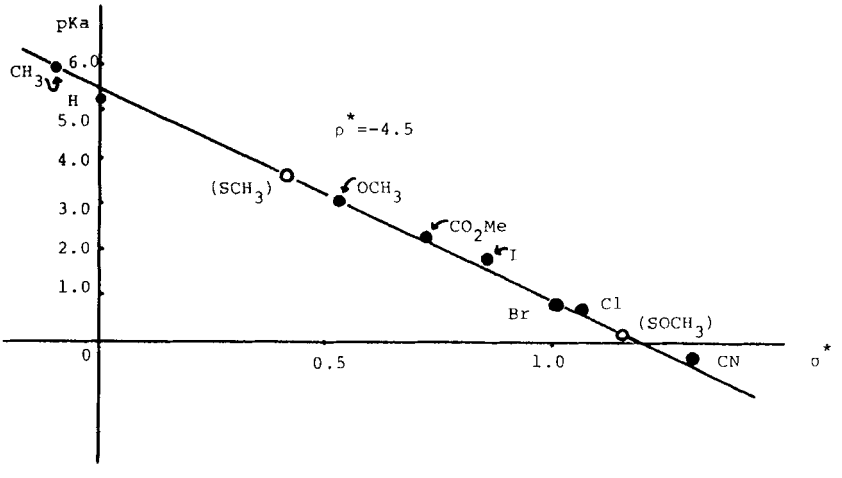


FIGURE 1 Taft-Hammett equation of 2-substituted pyridines.

TABLE II

pKa of 2-substituted pyridines and σ* values of 2-substituted pyridines

X	σ*	pKa
CH_3	−0.100	5.94
H	0.0	5.25
OCH_3	+0.52	3.06
$C_2H_5O_2C$	+0.71	2.21
I	+0.85	1.82
Br	+1.00	0.90
Cl	+1.05	0.72
CN	+1.30	−0.26
SCH_3	+0.41[a]	3.64
$S(O)CH_3$	+1.15[a]	0.17
CH_2SCH_3	0.01[a]	5.40
$CH_2S(O)CH_3$	0.51[a]	3.10
CH_2OCH_3	0.23[a]	4.35

[a] Obtained by plotting the pka by the Taft equation.

calculated from the corresponding σ_m values [$\sigma_m(SCH_3) = 0.15$,[7] $\sigma_m(S(O)CH_3) = 0.52$][7] by using the Taft equation, $\sigma_I = 0.45\sigma^*$,[8] assumed that σ_m is roughly equal to σ_I, and resulted in a nice fit to the above straight line as observed in Figure 1. In addition, the pKa values of other pyridine sulfides and sulfoxides can be plotted on this straight line, thus tentatively affording the σ* values of the following substituents, $CH_3S(O)$-, CH_3SCH_2-, $CH_3S(O)CH_2$- and CH_3OCH_2-, respectively. The σ* values of these substituents thus obtained are listed in Table II.

Acid and Alkaline Catalyzed Hydrolyses of p-Nitrophenyl Acetates

We attempted to evaluate whether the σ* values of the substituents determined as described above can be applied to another reaction system, e.g., by employing both acid and alkaline hydrolyses of the esters (3) ($XCH_2CO_2C_6H_4NO_2$-*p*), Taft's system.

If we assume that both acid and alkaline hydrolyses of *p*-nitrophenyl acetates take place mechanistically as substituted ethyl acetates, namely, if one can neglect the electronic effects due to the α-substituents in the acid-catalyzed hydrolysis of these esters (3), and E_s values are roughly equal in both hydrolyses, then the σ* and E_s values of these substituents could be determined by Eq. (2). In Eq. 2 k represents the rate constant for hydrolysis of substituted esters, and k_0 represents the rate constant for hydrolysis of *p*-nitrophenyl acetate. A and B indicate acid and base catalyzed hydrolyses, respectively.

$$\log(k/k_0)_B = \sigma^*\rho^* + E_s$$

$$\log(k/k_0)_A = E_s$$

$$\rho^* = \frac{1}{\sigma^*}\left[\log(k/k_0)_B - \log(k/k_0)_A\right] \qquad (2)$$

Accordingly, *p*-nitrophenyl acetates, $XCH_2CO_2C_6H_4NO_2$-*p* **3** (X:CH_3, H, CH_3S, $CH_3S(O)$, CH_3SCH_2, $CH_3S(O)CH_2$) were prepared by treating the corresponding carboxylic acid chloride with *p*-nitrophenol in the presence of triethylamine as a base. The E_s values of the following substituents, CH_3, Cl, CH_3S, are known; therefore, one can test whether the above equation can be applied to determine the E_s values of the unknown substituents. Indeed, Fife, *et al.*, reported that a plot of the logarithms of second-order rate constants for acid-catalyzed hydrolysis of the esters, $X'CO_2C_6H_4NO_2$-*p* (X' = CH_3, C_2H_5, *n*-C_3H_7, *t*-C_4H_9) vs. E_s, afforded a nice straight line with $\delta^* = 0.59$.[10] Initially, the acid-catalyzed hydrolysis of *p*-nitrophenyl esters **3a–g** at 35°C and at various HCl concentrations (1.52–5.00*M*, ionic strength was held constant at 4.80*M* with LiCl) were carried out and the k_{obs} values obtained are presented in Table III.

TABLE III

Rate constants for acid-catalyzed hydrolysis of *p*-nitrophenyl esters at 34.9°C

X	HCl (M)	$k_{obs} \times 10^2$ (min^{-1})	$k \times 10^2$ ($l \cdot mol^{-1} \cdot min^{-1}$)	*r*	$\log(k/k_0)$	E_s
	1.52	1.35				
H	2.00	1.64	1.25(k_0)	0.996	0	0[9]
	4.00	4.55				
	5.00	5.46				
	1.52	1.30				
	2.00	1.84				
CH_3	3.00	3.43	1.21	0.994	−0.014	−0.07[9]
	4.00	4.51				
	5.00	5.41				
	2.00	2.05				
Cl	3.00	2.69	0.53	0.997	−0.373	−0.24[9]
	4.00	3.09				
	5.00	3.67				
	1.52	0.75				
	2.00	0.99				
CH_3S	3.00	1.52	0.63	0.997	−0.298	−0.34
	4.00	2.33				
	5.00	2.89				
	1.52	0.62				
	2.00	0.90				
$CH_3\overset{\overset{O}{\uparrow}}{S}$	3.00	1.49	0.53	0.997	−0.373	−0.40
	4.00	2.04				
	5.00	2.44				
	1.52	0.32				
CH_3SCH_2	2.00	0.49	0.39	0.999	−0.506	−0.55
	4.00	1.31				
	5.00	1.65				
	1.52	0.30				
$CH_3\overset{\overset{O}{\uparrow}}{S}CH_2$	2.00	0.42	0.18	0.992	−0.842	−0.90
	3.00	0.61				
	4.00	0.81				
	5.00	0.91				

$XCH_2CO_2C_6H_4NO_2$-*p*

3

(a) X = H
(b) X = CH_3
(c) X = Cl
(d) X = CH_3S
(e) X = $CH_3S(O)$
(f) X = CH_3SCH_2
(g) X = $CH_3S(O)CH_2$

Plots of these k_{obs} values vs. concentration of HCl are shown to be linear. Thus, both the second-order rate constants of acid hydrolyses k, at $\mu = 4.80M$, and $\log(k/k_0)_A$ values (since k_0 is the second-order rate constant for acid-catalyzed hydrolysis of *p*-nitrophenyl acetate) were obtained and are given in Table III. The second-order rate constants $(k/k_0)_A$ obtained in this experiment were correlated with their corresponding E_s values. The plots of $\log(k/k_0)$, in which k_0 is the rate constant of the *p*-nitrophenyl acetate, k is that of CH_3, Cl, SCH_3, against E_s, reveals that the slope is roughly 1.0 which is in contrast with that of Fife's results. The discrepancy of δ^* in these esters is not known accurately but the steric effects on the transition state may be altered by changing the substituent. The unknown E_s values of the substituents, $CH_3S(O)$, CH_3SCH_2, $CH_3S(O)CH_2$, were determined tentatively by fitting the k/k_0 values on this line and are shown in Table III and Figure 2.

Base-catalyzed hydrolyses of the esters **3** proceeded fast and the rates were followed by a stopped-flow technique. The pseudo-first-order rate constants for base-catalyzed hydrolysis of esters **3a–g**, measured at various temperatures (20–35°C) in a mixed solvent of water and dioxane (1 : 1 v/v) containing NaOH, are given in Table IV. From these results, the activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated and the values are shown in Table IV. Figure 3 represents an isokinetic relationship, namely, the plots of $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$. The plots for **3a**, **b**, **f**, **g** afforded a good straight line, indicating that the base-catalyzed hydrolysis of these esters

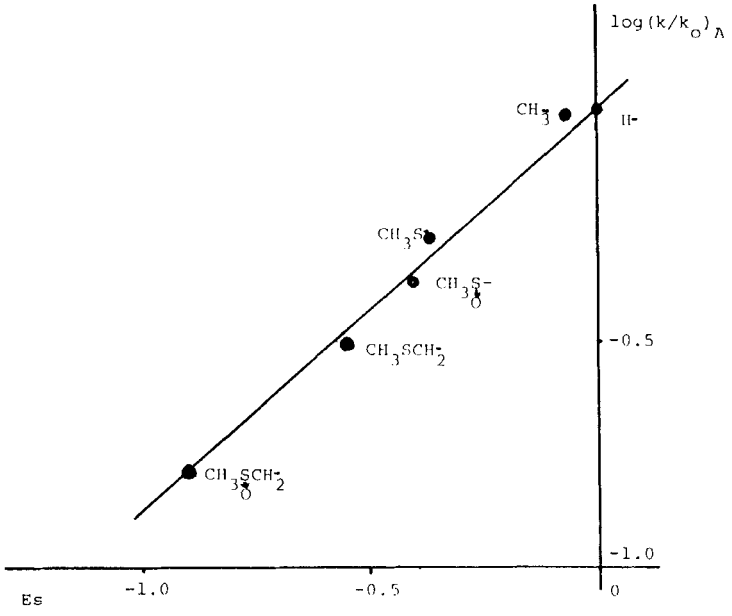


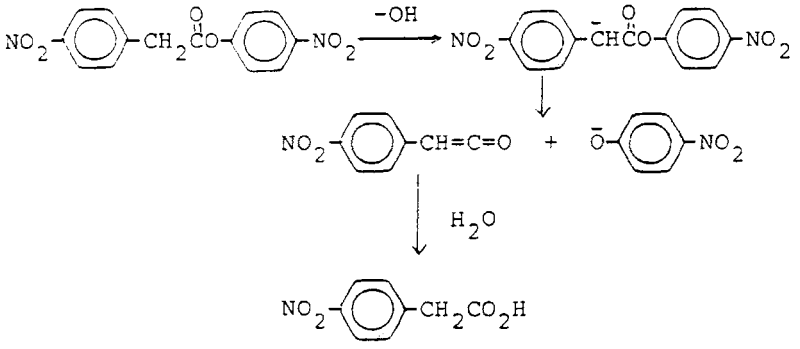
FIGURE 2 E_s values.

TABLE IV

Rate constants for alkaline hydrolysis of *p*-nitrophenyl acetates and activation parameters

X	Temp. (°C)	k (sec^{-1})	$\Delta H^{\ddagger}$ kcal/mol	$\Delta S^{\ddagger}$ e.u.	E_a kcal/mol
	34.9	7.44 ± 0.20			
H	29.85	5.46 ± 0.04	9.2 ± 0.3	-33.9 ± 1.0	9.8
	24.50	4.29 ± 0.12			
	21.15	3.45 ± 0.07			
CH_3	34.90	$5.40 \pm 0.10 \times 10^{-2}$	9.8 ± 0.4	-32.7 ± 1.2	10.4
	29.85	$3.84 \pm 0.19 \times 10^{-2}$			
	24.50	$2.92 \pm 0.04 \times 10^{-2}$			
	21.15	$2.42 \pm 0.00 \times 10^{-2}$			
Cl	35.00	$2.89 \pm 0.05 \times 10$			
	34.90	1.51 ± 0.06			
CH_3S	29.80	1.10 ± 0.01	10.5 ± 0.2	-23.6 ± 0.6	11.2
	24.50	$7.83 \pm 0.07 \times 10^{-1}$			
	21.20	$6.51 \pm 0.04 \times 10^{-1}$			
	34.90	$1.38 \pm 0.02 \times 10^{2}$			
O ↑					
CH_3S	29.80	$9.62 \pm 0.27 \times 10$	12.1 ± 0.3	-9.4 ± 1.1	12.7
	24.50	$6.91 \pm 0.02 \times 10$			
	21.15	$5.12 \pm 0.03 \times 10$			
	34.90	$9.48 \pm 0.13 \times 10^{-2}$			
CH_3SCH_2	29.80	$7.73 \pm 0.05 \times 10^{-2}$	10.4 ± 0.9	-29.3 ± 3.1	11.1
	21.15	$4.15 \pm 0.07 \times 10^{-2}$			
	34.90	$8.92 \pm 0.13 \times 10^{-1}$			
O ↑					
CH_3SCH_2	29.85	5.94×10^{-1}	14.0 ± 0.1	-13.4 ± 0.3	14.6
	21.15	$2.92 \pm 0.09 \times 10^{-1}$			

proceeds via a B_{acyl}-1 mechanism. However, plots for **3d** and **3e** largely deviate from the straight line. Therefore, the mechanism for the base catalyzed hydrolysis of the esters, **3d** and **3e**, seems to be different from that of the other esters. Broxton *et al.*, reported that *p*-nitrophenyl *p*-nitrophenylacetate is hydrolyzed by the following path, namely, involving a ketene as an intermediate.[11]



The hydrolysis of **3d** and **3e** is considered to proceed analogously with that of *p*-nitrophenyl *p*-nitrophenylacetate because sulfenyl and sulfinyl are relatively strong

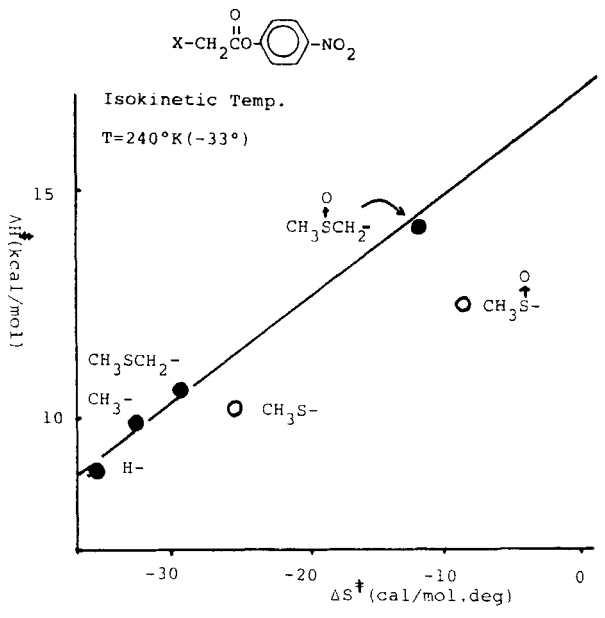


FIGURE 3 Isokinetic relationship.

electron-withdrawing groups. In addition, $\log(k/k_0)_B$ values (k_0 represents the pseudo-first-order rate constant for the base catalyzed hydrolysis of **3a** at 35°C) were calculated. The results are shown in Table V.

Although the question still remains whether the alkaline hydrolyses of **3d** and **3e** proceed differently from the other esters, $\log[(k/k_0)_B - \log(k/k_0)_A]$ values of **3b–g** were plotted against the corresponding σ^* values listed in Table II and afforded a straight line with $\rho^* = 3.0$, $r = 0.998$ as shown in Figure 4.

Therefore, the σ^* values obtained by the pKa measurement seem to be of the right magnitude and can be used in the following discussion.

TABLE V

$[\log(k/k_0)_B - \log(k/k_0)_A]$ values

X	$\log(k/k_0)_B$[a]	$\log(k/k_0)_A$[b]	$\log(k/k_0)_B - \log(k/k_0)_A$
H	—	—	—
CH_3	−0.139	−0.014	−0.125
Cl	+2.591	−0.373	+2.964
CH_3S	+1.307	−0.298	+1.605
$CH_3S(O)$	+3.268	−0.373	+3.641
CH_3SCH_2	+0.105	−0.506	+0.611
$CH_3S(O)CH_2$	+1.079	−0.842	+1.921

[a] Calculated from Table IV.
[b] Calculated from Table III.

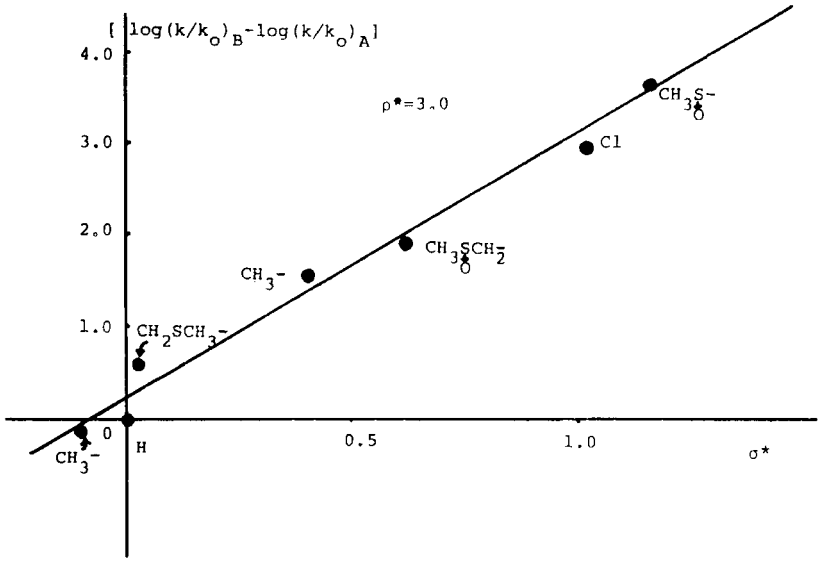
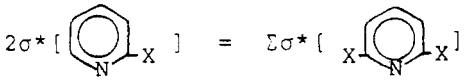


FIGURE 4 Hammett-Taft relation of acid and alkaline hydrolyses of *p*-nitrophenyl esters.

Additivity of σ Values of Substituents*

Normally, the additivity of the Taft σ* values (Σσ*) can hold with most substituents except such bulky groups as *t*-butyl.[12] If this additivity can hold in the present system, the substituent effect on the acid dissociation of the protonated 2,6-disubstituted pyridine can be summed up by using the following relationship. Thus, multiplying twice the σ* value of the substituent (X) at the 2-position of the pyridine nucleus should be theoretically equal to the sum of that of the substituents at the 2- and 6-positions of the pyridine ring.



The pKa value of 2-methylpyridine is 5.94, whereas the σ* value of the methyl group is −0.10. If the additivity is maintained, the pKa value of 2,6-disubstituted pyridine can be calculated by the following equation obtained from Figure 1: pKa = $-4.5\Sigma\sigma^* + 5.5$. Thus, for example, the calculated pKa value of 2,6-dimethylpyridine should be 6.42 which is obtained by multiplying by the σ* value of methyl group. The observed pKa value of 2,6-dimethylpyridine is 6.42[6b] which agrees well with the calculated value (6.42). Therefore, the additivity of the σ* value applies to the methyl group. However, in the case of the *t*-butyl group, the measured pKa value (3.58)[13] of 2,6-di-*t*-butylpyridine is lower than that calculated (6.56). This abnormal behavior can be explained in terms of the bulkiness of *t*-butyl, namely, the approach of the proton to the nitrogen atom of the pyridine ring is sterically hindered by both bulky *t*-butyl groups at the 2,6-positions of the pyridine ring.

In the present investigation, the pKa of 2,6-bis(methylsulfinyl)pyridine is immeasurably small and hence was neglected for calculation, whereas the pKa values of 2,6-bis(methylthiomethyl)pyridine **2b**, 2,6-bis(methylsulfinylmethyl)pyridine **2c** and 2,6-bis(methoxymethyl)pyridine **2d** have been calculated from the σ^* value of the substituent by using the above relationship. The calculated pKa values of **2b–d** are 5.39 **2b**, 3.39 **2c**, and 0.81 **2d**, respectively. The observed pKa value of 2,6-bis(methylthiomethyl)pyridine **2b** (4.10) are lower than the corresponding calculated values, 5.39. This result is similar to that observed when the *t*-butyl group is the substituent. Therefore, the steric effect of the CH_3SCH_2 group at the 2,6-positions of the pyridine ring is considered to be large enough to prevent the approach of a proton to the nitrogen atom of the pyridine ring. However, although the pKa value of 2,6-bis(methoxymethyl)pyridine **2c**, which has a similar structure to 2,6-bis(methylthiomethyl)pyridine **2b**, is expected to be lower than calculated since the steric effect of the methoxymethyl group, CH_3OCH_2, is considered to be of almost the same size as that of CH_3SCH_2, the measured pKa value of 2,6-bis(methoxymethyl)pyridine **2c** (3.50) was nearly identical to that calculated (3.29). This similarity between the calculated and observed pKa values of 2,6-bis(methoxymethyl)pyridine seems to be due to the greater ability for intramolecular hydrogen bonding to the protonated pyridine species by both oxygen atoms than that by sulfur atoms above in 2,6-bis(methylthiomethyl)pyridine **2b**. Furthermore, it is interesting to see that the observed pKa value of 2,6-bis(methylsulfinylmethyl)pyridine **2d** (1.53) is higher than the calculated value (0.81). Although the steric effect of the sulfinyl group should be larger than that of the sulfenyl group, the observed higher pKa value of 2,6-bis(methylsulfinylmethyl)pyridine **2d** indicates clearly that a proton can be coordinated or hydrogen bonded strongly by both sulfinyl oxygen atoms at the 2,6-positions of the pyridine ring and the nitrogen atom, thus preventing the departure of the proton. The ability of sulfinyl oxygen to coordinate a proton seems to be larger than that of methoxyl oxygen.

Ion-Transfer Experiment

The ion-transfer experiment was carried out in order to confirm the abilities of sulfoxides containing pyridine rings to chelate metal cations.[14] The ion-transfer experiment mediated by 2,6-bis(methylsulfinylmethyl)pyridine **2d** through an organic liquid membrane was investigated by using a specifically designed double cylindrical glass cell in which an inner aqueous phase (Tris buffer solution containing picrate metal cation) and the outer aqueous phase (a Tris buffer solution) were separated by a methylene chloride solution containing the sulfoxide as shown in Figure 5. Practically no ion transfer occurred in the absence of the sulfoxide. The transfer was followed by a UV technique. In the case of lithium cation, the transfer curve of lithium picrate by the sulfoxide is shown in Figure 6. The result clearly reveals that the ion transfer takes place, although it is very slow. Thus, the sulfoxide, 2,6-bis(methylsulfinylmethyl)pyridine **2d** has now been found to chelate lithium cation. In addition, the cation selectivity by the sulfoxide was also compared by measuring the rates of the ion transfer among lithium, sodium, and potassium cations under the same conditions. Figure 7 presents the curves for each of these ion transfers. Apparently, the transfer of lithium cation is faster than that of sodium or potassium,

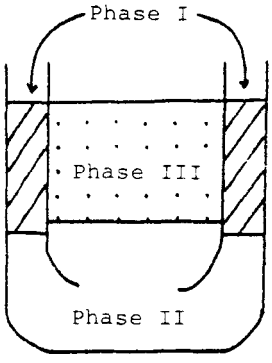


FIGURE 5 Ion-transfer system.

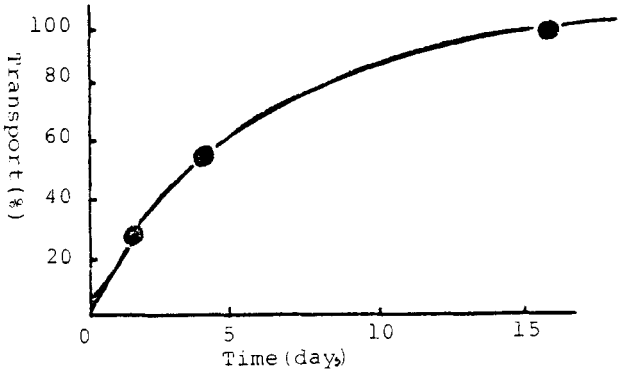


FIGURE 6 Transfer curve of lithium picrate by 2,6-bis(methylsulfinylmethyl)pyridine.

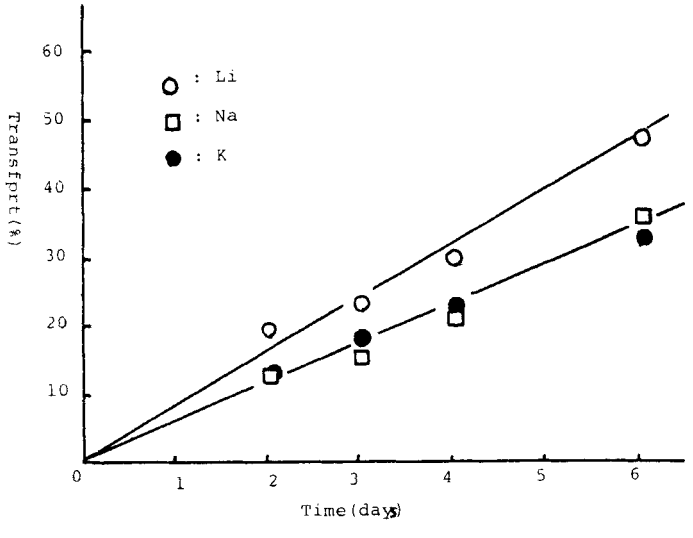


FIGURE 7 Transfer curves of alkali metal picrates by 2,6-bis(methylsulfinylmethyl)pyridine.

although only a small difference was found between the rates of sodium and potassium cations. This result seems to indicate that 2,6-bis(methylsulfinylmethyl)-pyridine **2d** can transfer such a comparably small cation as lithium selectively.

EXPERIMENTAL

General. UV spectra were taken on a HITACHI Model 200-20 Spectrophotometer and a Union Giken RAPID REACTION ANALYZER RA-601. Constant temperature (±0.1°C) was maintained by circulating water from a Komatsu-Yamato COOLNICS Model CTR-220 and COOLNICS CIRCULATOR Model CTE-220. pH Values were determined using a HORIBA Model F-7 LC pH meter.

pKa Measurement. A typical procedure is as follows: A solution of 2,6-bis(methylthiomethyl)pyridine (2.8 mg, 1.4×10^{-5} mol) in 100 ml distilled water was prepared. To a 25 ml measuring flask, 5 ml of the aqueous solution of the sulfide and 5 ml of 0.001*N* aqueous HCl solution was poured accurately using a hole pipette. Then the flask was exactly filled to 25.00 ml with distilled water. Similarly, aqueous solutions having several different pH values were prepared. The pH values of the solutions were then measured using the pH meter. The UV absorbances (A) of the solutions at 300 nm were measured. Substitution of A_{HL}, A_L, A, and the corresponding pH values obtained in equation (1) gave the pKa value of 2,6-bis(methylthiomethyl)pyridine (pKa = 4.10). A typical UV spectrum in the present measurement is shown in Figure 8. The pKa value of 2,6-bis(methylthio)pyridine which did not dissolve in water was determined in the following manner: Solutions of 2,6-bis(methylthio)pyridine in water–methanol (1 : 1 v/v) mixture was prepared. The pKa value in the solution was measured. Similarly, pKa values measured in several water–methanol ratios (3 : 2, 3 : 1, 4 : 1) were obtained. These values were plotted against water/(water + methanol) (v/v), affording a straight line. Thus, the pKa value of 2,6-bis(methylthio)pyridine was determined to be 2.37 by extrapolating to the point at which water/(water + methanol) is 1.

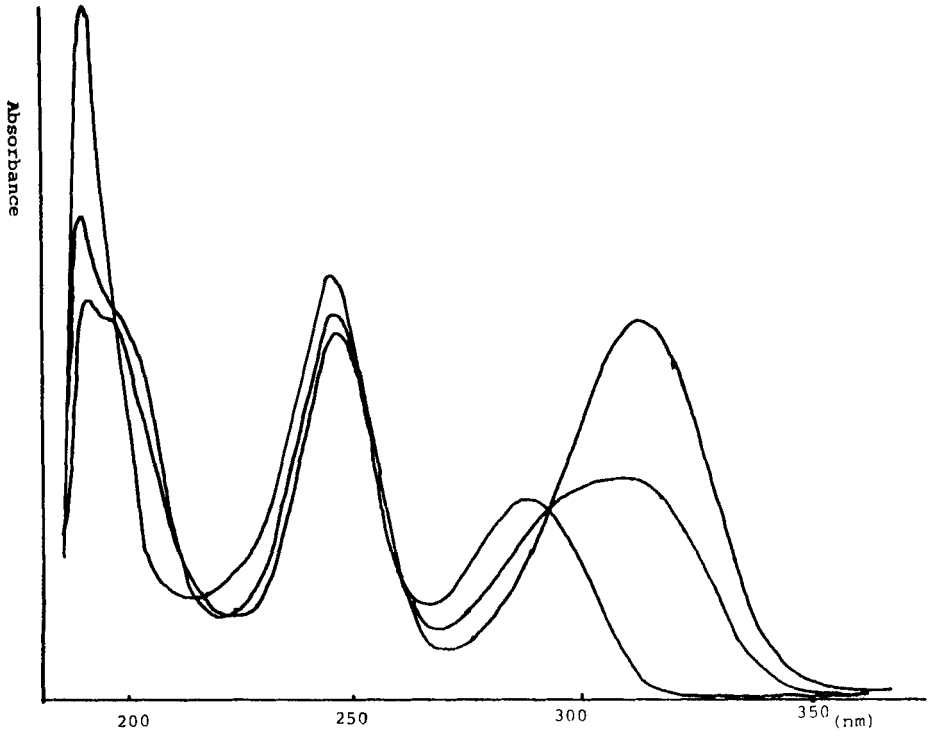


FIGURE 8 UV spectra of methyl 2-pyridyl sulfide in HCl solutions.

Preparation of p-Nitrophenyl Esters. A typical experimental procedure is as follows: To a solution of *p*-nitrophenol (2.10 g, 15.1 mmol) and triethylamine (2.1 ml, 1.51 mmol) in benzene (10 ml) was added chloroacetyl chloride (1 ml, 12.6 mmol) in benzene (10 ml) dropwise with stirring and cooling with an ice-water bath. The mixture was heated at 50°C overnight. The solvent was removed after filtration. The residue was separated by silica-gel column chromatography using benzene as an eluent, affording *p*-nitrophenyl chloroacetate (88%). The ester was purified by recrystallization from benzene–hexane(m.p. 99–99.5°C). mp., Ir and Nmr spectra, and elemental analyses are summarized in Tables VI and VII.

Acid-Catalyzed Hydrolysis of Esters. The rates of acid-catalyzed hydrolysis of *p*-nitrophenyl esters were followed by measuring the appearance of the UV absorbance of *p*-nitrophenol at 330 nm. The esters were dissolved in acetonitrile and 0.1 ml of this solution was added by a microsyringe to 3.5 ml of aqueous acid solution in the cuvette with vigorous stirring. The concentrations of HCl solutions were 1.52*M*, 2.00*M*, 3.00*M*, 4.00*M*, and 5.00*M*, and the ion strength was held constant at 4.80*M* with LiCl. Then the reactions were followed with a UV spectrophotometer thermostatted at 35°C. Thus, pseudo-first-order rate constants (k_{obs}) were obtained.

Base-Catalyzed Hydrolysis of Esters. The rates of based-catalyzed hydrolysis of *p*-nitrophenyl esters were followed by measuring the appearance of the UV absorbance of *p*-nitrophenol at 400 nm using a stop-flow technique. The solutions of esters ($1 \times 10^{-4}M$) were prepared in a mixed solvent of water and dioxane (1 : 1 v/v). A sodium hydroxide solution ($1.3 \times 10^{-2}M$) was prepared in water and dioxane (1 : 1 v/v). Solutions of ester in water-dioxane and sodium hydroxide in water–dioxane were thermostatically equilibrated in the drive syringes of the stopped-flow apparatus. The reaction was then initiated by mixing equal volumes of each solution, and the rate of appearance of *p*-nitrophenol was followed at 400 nm. Thus, pseudo-first-order rate constants (k_{obs}) were calculated.

Ion Transfer. Ion-transfer experiments were conducted using an apparatus shown in Figure 5. A double cylindrical glass cell (diameter; inner cylinder 20 mm, outer cylinder 30 mm) in which the inner cylinder had a channel connecting inner and outer areas at its bottom. A methylene chloride solution (12 ml, Phase

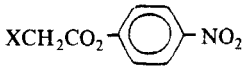
TABLE VI

The Mps. IR and NMR spectra of *p*-nitrophenyl esters XCH_2CO_2–  –NO_2

X	Mp. (°C)	IR (cm^{-1})	NMR (δ, ppm)
H	79–80	1760 (CO)	2.47 (s, 3 H, CH_3), 7.35 (d, J = 9.6 Hz, 2 H, ArH), 8.30 (d, J = 9.6 Hz, 2 H, ArH)
CH_3	63–64	1760 (CO)	1.35 (t, J = 7 Hz, 3 H, CH_3), 2.70 (q, J = 7.7 Hz, 2 H, CH_2), 7.28 (d, J = 9.0 Hz, 2 H, ArH), 8.26 (d, J = 9.0 Hz, 2 H, ArH)
Cl	99–99.5	1780 (CO)	4.42 (s, 2 H, CH_2), 7.37 (d, J = 9.6 Hz, 2 H, ArH), 8.32 (d, J = 9.6 Hz, 2 H, ArH)
CH_3S	40–42	1740 (CO)	2.43 (s, 3 H, CH_3), 3.52 (s, 2 H, CH_2), 7.33 (d, J = 9.6 Hz, 2 H, ArH), 8.27 (d, J = 9.6 Hz, 2 H, ArH)
CH_3S ↓ O	125–127	1740 (CO) 1030 (SO)	2.77 (s, 3 H, CH_3), 4.23 (d, 2 H, CH_2), 7.12 (d, J = 9.2 Hz, 2 H, ArH), 8.02 (d, J = 9.2 Hz, 2 H, ArH)
CH_3SCH_2	41.5–46.5	1760 (CO)	2.15 (s, 3 H, CH_3), 2.86 (s, 4 H, C_2H_4), 7.18 (d, J = 8.4 Hz, 2 H, ArH), 8.12 (d, J = 8.4 Hz, 2 H, ArH)
CH_3SCH_2 ↓ O	94–97	1760 (CO) 1051 (SO)	2.63 (s, 3 H, CH_3), 3.10 (s, 4 H, C_2H_4), 7.20 (d, J = 8.6 Hz, 2 H, ArH)

TABLE VII

Elemental analyses of *p*-nitrophenyl esters



X	Analysis
H	Found C, 53.06; H, 3.86; N, 7.71
	Calcd. C, 53.04; H, 3.89; N, 7.73
CH_3	Found C, 55.33; H, 4.57; N, 7.13
	Calcd. C, 55.38; H, 4.64; N, 7.17
Cl	Found C, 44.57; H, 2.74; N, 6.41
	Calcd. C, 44.56; H, 2.80; N, 6.49
CH_3S	Found C, 47.47; H, 3.88; N, 6.09
	Calcd. C, 47.57; H, 3.99; N, 6.16
$\overset{O}{\uparrow}$	
CH_3S	Found C, 44.21; H, 3.54; N, 5.56
	Calcd. C, 44.44; H, 3.72; N, 5.75
CH_3SCH_2	Found C, 49.70; H, 4.44; N, 5.82
	Calcd. C, 49.78; H, 4.59; N, 5.80
$\overset{O}{\uparrow}$	
CH_3SCH_2	Found C, 46.47; H, 4.22; N, 5.39
	Calcd. C, 46.68; H, 4.31; N, 5.44

II) containing $5 \times 10^{-3}M$ of 2,6-bis(methylsulfinylmethyl)pyridine was placed at the bottom. Atop the methylene chloride solution inside the inner cylinder was carefully placed a Tris buffer (6 ml, Phase I) containing $2 \times 10^{-3}M$ of lithium picrate and $0.14M$ of lithium chloride. Simultaneously, atop the outer ring of the methylene chloride solution, was placed a Tris buffer solution (4 ml, Phase III). These three phases were gently stirred without mixing using a magnetic stirrer at room temperature (ca. 20°C). At specified time intervals, the concentrations of lithium picrate in both aqueous phases were determined with a UV spectrophotometer (357 nm).

REFERENCES AND NOTES

1. (a) N. Furukawa, K. Kishimoto, S. Ogawa, T. Kawai and S. Oae, *Tetrahedron Lett.*, 4409 (1981); (b) N. Furukawa, S. Ogawa, T. Kawai, K. Kishimoto and S. Oae, *Heterocycles*, **16**, 1927 (1981); (c) N. Furukawa, S. Ogawa, T. Kawai, K. Kishimoto, H. Fujihara and S. Oae, *Heterocycles*, **19**, 2041 (1982).
2. PTC reactions using sulfoxides have been reported by others. (a) M. Mikołajczyk, S. Grzejszczak, A. Zatorski, F. Montanari and M. Cinquini, *Tetrahedron Lett.*, 3757 (1975); (b) S. Banfi, M. Cinquini and S. Colonna, *Bull. Chem. Soc., Jpn.*, **54**, 1841 (1981); (c) H. Fujihara, K. Imaoka, N. Furukawa and S. Oae, *Chem. Lett.*, 1293 (1981); (d) N. Furukawa, K. Imaoka, H. Fujihara and S. Oae, *Chem. Lett.*, 1421 (1982).
3. R. Hilgenfeld and W. Saenger, Host Guest Complex Chemistry II in Topics in Current Chemistry, Ed. by F. Vögtle, Springer-Verlag, Berlin Vol. 1, p. 1 (1982).
4. A. Albert and G. B. Berlin, *J. Chem. Soc.*, 1959, 2384.
5. (a) M. Charton, *J. Am. Chem. Soc.*, **86**, 2033 (1964); (b) P. Tomasik and C. D. Johnson, Adv. in Heterocycles, Vol. 20, p. 1, (1976), Academic Press, New York.
6. (a) P. O. Lumme, *Suomen Kemistilehti*, **30B**, 168 (1957). (b) D. D. Perrin, Dissociation Constants of Organic Bases in Aqueous Solution, p. 150, Butterworths, London, 1965.
7. (a) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958); (b) F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **79**, 717 (1957); (c) C. C. Price and J. J. Hydock, *J. Am. Chem. Soc.*, **74**, 1943 (1952).

8. R. W. Taft Jr., Steric Effects in Organic Chemistry, Ed. by M. S. Newman, p. 13, Wiley, New York, 1956.
9. R. W. Taft, Jr., *J. Am. Chem. Soc.*, **74**, 3120 (1952).
10. T. H. Fife and D. M. McMahon, *J. Am. Chem. Soc.*, **91**, 7481 (1969).
12. Reference 8, p. 636.
13. H. C. Brown and B. Kanner, *J. Am. Chem. Soc.*, **75**, 3865 (1953).
14. (a) F. Vögtle and E. Weber, Supplement E. The Chemistry of Ethers, Crown Ethers, and Hydroxyl Groups and their Sulphur Analogues, part 1, p. 59, Ed. by S. Patai, Wiley, New York, 1980; (b) G. W. Gokel and S. H. Korzeniowski, Macrocyclic Polyether Syntheses, Springer-Verlag, Berlin, 1982.