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Studies on Chemical Carcinogens and Mutagens. XXV.[1] Chemoselectivity of Alkyl Sulfonates toward 4-(*p*-Nitrobenzyl)pyridine (NBP) in Phosphate Buffer

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Methyl, ethyl, and isopropyl esters of six alkanesulfonic acids and five *p*-substituted benzenesulfonic acids were synthesized and their alkylating abilities were evaluated in terms of the chemoselectivity toward 4-(*p*-nitrobenzyl)pyridine (NBP) in phosphate buffer (pH 6.0) containing 60% acetone. The chemoselectivity constant toward NBP, S_{NBP}, was defined as the logarithm of the ratio of the molar fraction of an alkylating sulfonate which is consumed for alkylation of NBP *versus* the molar fraction of the residual alkylating agent which is hydrolyzed in the buffer medium. It was found that S_{NBP} was not only markedly dependent on the structure of the alkyl moiety of the molecule, but also appreciably dependent on the electronic nature of the leaving sulfonic acid moiety. The structure–chemoselectivity relationship is discussed.

Keywords——chemoselectivity; alkyl sulfonate; alkylating agent; 4-(*p*-nitrobenzyl)pyridine

In recent years, much attention has been paid to the alkylating ability of some synthetic and environmental mutagens and carcinogens, because their mutagenesis and carcinogenesis are thought to be initiated by alkylations of cellular informational biopolymers, probably deoxyribonucleic acid (DNA).[2] The alkyl group incorporated into the biopolymers must be responsible for these biological phenomena, but the leaving group of the molecule must also be important because the reaction rate and chemoselectivity in alkylations are crucially dependent on the leaving group.[2-5] Among biological alkylating agents, methyl methanesulfonate and its analogues have been widely used for the study of molecular mechanisms involved.[2-4] This study was undertaken to evaluate the alkylating ability of various types of alkyl sulfonates for analysis of the structure–chemoselectivity relationship. Thus, methyl, ethyl, and isopropyl esters of six alkanesulfonic acids and five benzenesulfonic acids were synthesized and their chemoselectivities were evaluated in terms of the ratio of the molar fraction of alkylating agent which is consumed for alkylation of the ring nitrogen of 4-(*p*-nitrobenzyl)pyridine (NBP) to the molar fraction of the residual alkylating agent which is hydrolyzed in an acetone–phosphate buffer medium. As previously reported, S_{NBP} is a good measure of chemoselectivity, and is defined as follows:[5]

$$S_{NBP}=\log\left\{\frac{[H_2O]}{[NBP]}\times\frac{N}{(100-N)}\right\} \quad (1)$$

where N is the % molar fraction of the alkylating agent having reacted with the nitrogen of the NBP molecule after completion of the alkylation reaction and the residual % fraction, $(100-N)$, is that consumed in hydrolysis, mainly alkylation of H_2O,[6] and $[H_2O]$ and [NBP] are the concentrations of H_2O and NBP in the reaction medium, respectively. S_{NBP} in S_N2-type reactions can be approximated[6] to $\log(k_{NBP}/k_{water})$, where k_{NBP} and k_{water} are the second-order rate constants in the reactions with NBP and H_2O, respectively, while S_{NBP} in S_N1-type reactions represents the logarithm of the competition factor[3] of the carbonium ion intermediate toward NBP with respect to H_2O.[3,5] Isopropyl esters, which are known to

undergo substitution reactions through the S_N1 mechanism,[3] may also undergo elimination in a minor extent. Therefore, S_{NBP} values in such cases should regarded as an approximate measure of chemoselectivity.

As previously reported,[5] S_{NBP} is well correlated with the substrate constant, s, in the Swain–Scott equation.[3,7,8] A linear correlation was found between s and S_{NBP}, the regression equation for the correlation being given below.[5]

$$s=0.123(\pm 0.0078)S_{NBP}+0.318(\pm 0.019)$$

The correlation coefficient was 0.997 (10 samples) and the 95% confidence limits are given in parentheses in the equation.

Although the substrate constant, s, can be used as a measure of chemoselectivity of alkylating agents, S_{NBP} seems to be preferable because it can be determined by a simpler procedure and is generally applicable to a wide variety of alkylating agents, as described in our previous paper.[5]

In this paper, we discuss the dependence of S_{NBP} on the structure of the alkyl moiety and the electronic properties of the leaving group of alkyl sulfonates.

Experimental

Materials

Methyl and ethyl methanesulfonates were purchased from Nakarai Chemicals Ltd., Kyoto. Methyl and ethyl benzenesulfonates and methyl and ethyl *p*-toluenesulfonates were purchased from Tokyo Kasei Kogyo Co., Tokyo. Methyl, ethyl, and isopropyl isethionates (2-hydroxyethanesulfonates) were the preparations previously synthesized in our laboratory.[9] All the other sulfonates examined were synthesized by appropriate methods and their purities were checked by elementary analysis, nuclear magnetic resonance (NMR) spectroscopy, and silica gel thin-layer and high performance liquid chromatographies. Among the compounds listed in Table I, compounds **9**, **11**, **14**—**17**, and **30** have not been reported in the literature. Synthetic procedures are described below, including those of the known sulfonates synthesized systematically in the present study. Chromatographic data will be described elsewhere in connection with the partition properties of these compounds.

Methyl Ethanesulfonate (2)[10]——Ethanesulfonyl chloride (5.00 g) was added with stirring to a mixture of 5.04 g of 2,6-lutidine and 3.62 g of CH_3OH under cooling. The whole was allowed to stand for 2.5 h at room temperature, then 100 ml of 2 N H_2SO_4 was added and the mixture was extracted with $CHCl_3$. Distillation of the extract under reduced pressure gave a colorless oil of bp 79 °C (10 Torr) in 68% yield. *Anal.* Calcd for $C_3H_8O_3S$: C, 29.02; H, 6.50. Found: C, 28.83; H, 6.61.

Methyl Propanesulfonate (3)[10]——The treatment of 5.00 g of 1-propanesulfonyl chloride with 4.50 g of 2,6-lutidine and 3.26 g CH_3OH as described for (**2**) gave a colorless oil of bp 82 °C (10 Torr) in 62% yield. *Anal.* Calcd for $C_4H_{10}O_3S$: C, 34.77; H, 7.29. Found: C, 34.64; H, 7.38.

Methyl Butanesulfonate (4)[10]——The treatment of 5.00 g of 1-butanesulfonyl chloride with 4.10 g of 2,6-lutidine and 3.06 g of CH_3OH as described for (**2**) gave a colorless oil of bp 93 °C (10 Torr) in 65% yield. *Anal.* Calcd for $C_5H_{12}O_3S$: C, 39.46; H, 7.95. Found: C, 39.55; H, 8.77.

Methyl Pentanesulfonate (5)[10]——Silver pentanesulfonate was prepared by neutralizing pentanesulfonic acid dissolved in acetonitrile with silver oxide, followed by evaporation of the solvent. The silver salt thus prepared (5.00 g) was dissolved in 100 ml of acetonitrile and 7.70 g of methyl iodide was added. The mixture was kept at room temperature for 24 h, then the solvent was evaporated off. Distillation of the residue under reduced pressure gave a colorless oil of bp 100 °C (7 Torr) in 72% yield. *Anal.* Calcd for $C_6H_{14}O_3S$: C, 43.35; H, 8.49. Found: C, 43.34; H, 8.77.

Ethyl Ethanesulfonate (8)[11]——The treatment of 5.00 g of ethanesulfonyl chloride with 5.04 g of 2,6-lutidine and 5.37 g ethanol as described for (**2**) gave a colorless oil of bp 76 °C (6.5 Torr) in 54% yield. *Anal.* Calcd for $C_4H_{10}O_3S$: C, 34.77; H, 7.29. Found: C, 34.69; H, 7.47.

Ethyl Propanesulfonate (9)——The treatment of 5.00 g of propanesulfonyl chloride with 4.50 of 2,6-lutidine and 4.83 g of ethanol as described for (**2**) gave a colorless oil of bp 85.5 °C (8 Torr) in 55% yield. *Anal.* Calcd for $C_5H_{12}O_3S$: C, 43.35; H, 8.49. Found: C, 43.11; H, 8.70.

Ethyl Butanesulfonate (10)[12]——The treatment of 5.00 g of butanesulfonyl chloride with 4.07 g of 2,6-lutidine and 4.40 g of ethanol as described for (**2**) gave a colorless oil of bp 98 °C (8 Torr) in 58% yield. *Anal.* Calcd for $C_6H_{14}O_3S$: C, 43.35; H, 8.49. Found: C, 43.11; H, 8.70.

Ethyl Pentanesulfonate (11)——The treatment of 5.00g of silver pentanesulfonate with 8.4 g of ethyl iodide as

described for (**5**) gave a colorless oil of bp 102 °C (6 Torr) in 88% yield. *Anal.* Calcd for $C_7H_{16}O_3S$: C, 46.46; H, 8.95. Found: C, 46.42; H, 9.07.

Isopropyl Methanesulfonate (13)[13]——The treatment of 5.00 g of methanesulfonyl chloride with 5.57 g of 2,6-lutidine and 7.80 g of isopropanol as described for (**2**) gave a colorless oil of bp 67 °C (5 Torr) in 57% yield. *Anal.* Calcd for $C_4H_{10}O_3S$: C, 34.77; H, 7.29. Found: C, 34.47; H, 7.39.

Isopropyl Ethanesulfonate (14)——The treatment of 5.00 g of ethanesulfonyl chloride with 5.01 g of 2,6-lutidine and 7.02 g of isopropanol as described for (**2**) gave a colorless oil of 86 °C (8 Torr) in 48% yield. *Anal.* Calcd for $C_5H_{12}O_3S$: C, 39.46; H, 7.95. Found: C, 39.22; H, 8.12.

Isopropyl Propanesulfonate (15)——The treatment of 5.00 g of propanesulfonyl chloride with 4.50 g of 2,6-lutidine and 6.30 g of isopropanol as described for (**2**) gave a colorless oil of bp 86 °C (8 Torr) in 39% yield. *Anal.* Calcd for $C_6H_{14}O_3S$: C, 43.35; H, 8.49. Found: C, 43.13; H, 8.65.

Isopropyl Butanesulfonate (16)——The treatment of 5.00 g of butanesulfonyl chloride with 4.07 g of 2,6-lutidine and 5.76 g of isopropanol as described for (**2**) gave a colorless oil of bp 93 °C (6 Torr) in 38% yield. *Anal.* Calcd for $C_7H_{16}O_3S$: C, 46.64; H, 8.95. Found: C, 46.41; H, 9.19.

Isopropyl Pentanesulfonate (17)——The treatment of 5.00 g of silver pentanesulfonate with 9.18 g of isopropyl iodide as described for (**5**), followed by silica gel chromatographic separation, gave a colorless oil in 68% yield. *Anal.* Calcd for $C_8H_{16}O_3S$: C, 49.46; H, 9.34. Found: C, 49.61; H, 9.48.

Methyl *p*-Nitrobenzenesulfonate (19)[14]——The treatment of 3.00 g of silver *p*-nitrobenzenesulfonate with 4.12 g of methyl iodide as described for (**5**), followed by silica gel chromatographic separation and recrystallization from CH_3OH, gave yellow prisms of mp 90—92.5 °C in 76% yield. *Anal.* Calcd for $C_7H_7NO_5S$: C, 38.71; H, 3.25; N, 6.45. Found: C, 38.60; H, 3.21; N, 6.59.

Methyl *p*-Chlorobenzenesulfonate (20)[15]——The treatment of 3.00 g of silver *p*-chlorobenzenesulfonate with 4.26 g of methyl iodide as described for (**5**), followed by silica gel chromatographic separation, gave a white solid of mp 47—50 °C in 82% yield. *Anal.* Calcd for $C_7H_7ClO_3S$: C, 40.69; H, 3.41. Found: C, 40.57; H, 3.29.

Methyl *p*-Methoxybenzenesulfonate (23)[14]——The treatment of 5.00 g of *p*-methoxybenzenesulfonyl chloride with 3.09 g of 2,6-lutidine and 2.23 g of CH_3OH as described for (**2**), followed by silica gel chromatographic separation, gave colorless oil in 52% yield. *Anal.* Calcd for $C_8H_{10}O_4S$: C, 47.52; H, 4.98. Found: C, 47.41; H, 4.90.

Ethyl *p*-Nitrobenzenesulfonate (24)[14]——The treatment of 3.00g of silver *p*-nitrobenzenesulfonate with 4.52 g of ethyl iodide as described for (**5**), followed by silica gel chromatographic separation and recrystallization from CH_3OH, gave a yellow powder of mp 92.5—94 °C in 76% yield. *Anal.* Calcd for $C_8H_9NO_5S$: C, 41.56; H, 3.92; N, 6.05. Found: C, 41.43; H, 3.91; N, 6.12.

Ethyl *p*-Chlorobenzenesulfonate (25)[16]——The treatment of 3.00 g of silver *p*-chlorobenzenesulfonate with 4.68 g of ethyl iodide as described for (**5**), followed by silica gel chromatographic separation, gave a colorless oil in 70% yield. *Anal.* Calcd for $C_8H_9ClO_3S$: C, 43.54; H, 4.11. Found: C, 43.64; H, 4.07.

Ethyl *p*-Methoxybenzenesulfonate (28)[14]——The treatment of 5.00 g of *p*-methoxybenzenesulfonyl chloride with 3.09 g of 2,6-lutidine and 3.30 g of ethanol as described for (**2**), followed by silica gel chromatographic separation, gave a colorless oil in 48% yield. *Anal.* Calcd for $C_9H_{12}O_4S$: C, 49.99; H, 5.59. Found: C, 49.85; H, 5.59.

Isopropyl *p*-Nitrobenzenesulfonate (29)[14]——The treatment of 3.00 g of silver *p*-nitrobenzenesulfonate with 4.93 g of isopropyl iodide as described for (**5**), followed by silica gel chromatographic separation and recrystallization from CH_3OH, gave a yellow powder of mp 90.5—92.5 °C in 72% yield. *Anal.* Calcd for $C_9H_{11}NO_5S$: C, 44.08; H, 4.52; N, 5.71. Found: C, 43.85; H, 4.45; N, 5.66.

Isopropyl *p*-Chlorobenzenesulfonate (30)——The treatment of 3.00 g of silver *p*-chlorobenzenesulfonate with 5.10 g of isopropyl iodide as described for (**5**), followed by silica gel chromatographic separation, gave a white solid of mp 37—39 °C in 68% yield. *Anal.* Calcd for $C_9H_{12}ClO_3S$: C, 46.06; H, 4.72. Found: C, 46.10; H, 4.65.

Isopropyl Benzenesulfonate (31)[14]——The treatment of 3.00 g of silver benzenesulfonate with 5.76 g of isopropyl iodide as described for (**5**), followed by silica gel chromatographic separation, gave a colorless oil in 83% yield. *Anal.* Calcd for $C_9H_{12}O_3S$: C, 53.98; H, 6.04. Found: C, 53.75; H, 5.95.

Isopropyl *p*-Methylbenzenesulfonate (32)[14]——The treatment of 3.00 g of silver tosylate with 5.50 g of isopropyl iodide as described for (**5**), followed by silica gel chromatographic separation, gave a colorless oil in 86% yield. *Anal.* Calcd for $C_{10}H_{14}O_3S$: C, 56.05; H, 6.59. Found: C, 56.00; H, 6.43.

Isopropyl *p*-Methoxybenzenesulfonate (33)[14]——The treatment of 5.00 g of silver *p*-methoxybenzenesulfonate with 8.62 g of isopropyl iodide as described for (**5**), followed by silica gel chromatographic separation, gave a colorless oil in 79% yield. *Anal.* Calcd for $C_{10}H_{14}O_4S$: C, 52.16; H, 6.13. Found: C, 52.40; H, 6.17.

Analytical Procedure for Determination of Chemoselectivity toward NBP[5]

The reaction mixture consisted of 20 ml of 1/15 M phosphate buffer (pH 6.0), 20 ml of 0.25 M NBP (5×10^{-3} mol) in acetone, and 10 ml of acetone solution of a sulfonate which had been exactly weighed in the range of 10^{-4} to 5×10^{-6} mol (usually 1.36×10^{-5}). About 1.5 ml of reaction mixture was placed in each of 10 to 15 small tubes and the tubes were sealed under an argon or nitrogen atmosphere. These tubes were warmed at 37 °C and worked up one by one at appropriate intervals. Thus, 1.0 ml of the content of each tube was poured onto 4 ml of water and 5 ml of benzene. The mixture was thoroughly mixed with a vibromixer after addition of 0.5 ml of 1 N NaOH. The wine-

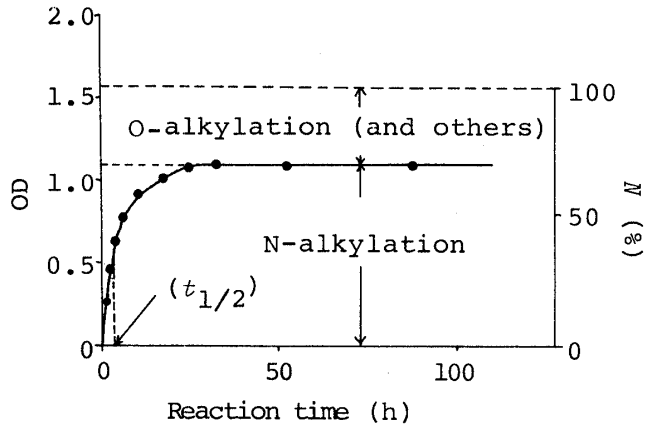

Fig. 1. Time Course Changes in OD of the Benzene Extract from the Reaction of Ethyl *p*-Nitrobenzenesulfonate with NBP in Phosphate Buffer According to the Method Described in Experimental

The OD value expected for quantitative alkylation of NBP with this sulfonate was 1.62, which corresponds to 100% N value. The apparent half-life, ($t_{1/2}$), is read from the figure as indicated.

colored benzene layer was taken up with a pipette and dried over KOH pellets. The optical density (OD) of the solution was measured at the λ_{max} of the peak at around 534 nm. The wine-colored compound thus extracted was quite stable in the absence of moisture, CO_2, and light. The OD finally reached a plateau when the reaction was completed. From the maximum OD thus obtained, the % ratio, N, of alkylation of NBP was calculated on the basis of the molar extinction coefficient previously determined with authentic specimens of alkylated NBP's ($\varepsilon = 29900 \pm 100$ in all the cases examined in the present study). Using the $N(\%)$ value thus obtained, S_{NBP} was calculated by the use of Eq. 1, where [H_2O] and [NBP] were 22.2 and 0.10 M, respectively, in most cases. Figure 1 illustrates the procedure for the case of ethyl *p*-nitrobenzenesulfonate.

Results and Discussion

The compounds examined are methyl, ethyl, and isopropyl esters of aliphatic and aromatic sulfonic acids. Table I includes a list of the sulfonates examined and the chemoselectivity constant toward NBP, S_{NBP}. The term $N(\%)$, which is the observable obtained under the analytical condition described in Experimental, is variable depending on the concentration of NBP employed. The apparent half-life, ($t_{1/2}$), is a rough measure of the relative reaction rate, but not that defined in the pseudo-first order kinetics with respect to NBP.

When one takes a broad view of the relationship between structure and chemoselectivity, S_{NBP}'s can apparently be classified into three groups depending on the structure of the alkyl moiety; those of methyl, ethyl, and isopropyl sulfonates fall in narrow ranges of magnitude, 4.03 ± 0.31, 2.79 ± 0.25, and 1.08 ± 0.10, respectively. Thus, as far as the sulfonates examined are concerned, regardless of the structure of the leaving group, the selectivity is about 10000 times greater for methylation at the nitrogen of the pyridine ring than at the oxygen of water, 500 times greater for ethylation, and only 10 times greater for isopropylation. Since, according to Pearson's principle of hard and soft acids and bases, water oxygen is a harder base than pyridine nitrogen,[17] isopropyl sulfonates, which tend to be readily polarized so as to produce carbonium ion intermediates, can be regarded as harder electrophiles than the ethyl sulfonates, which are in turn harder than the methyl esters.

Looking at the structural dependence of S_{NBP} more precisely, one can recognize a small but definite linear dependence on the electronic nature of the leaving group. For most of the *p*-substituted benzenesulfonates, S_{NBP} is linearly correlated with Hammett's σ_p of the substituent of the benzene ring, in other words, the pK_a of the acid moiety[18] of the sulfonic acid esters, as shown in Figs. 2 and 5. An electron-deficient sulfo group tends to decrease the selectivity toward NBP in almost all the alkyl sulfonates examined. The only exception is ethyl *p*-methoxybenzenesulfonate (**28**). This deviation cannot yet be accounted for. A detailed kinetic study including precise product analysis is now in progress. It is worth mentioning, in this connection, that the apparent rates of disappearance of all the alkylating agents including

TABLE I. Chemoselectivity, S_{NBP}, of 33 Sulfonates toward NBP in Phosphate Buffer (1/15 M, pH 6.0) Containing 60% Acetone at 37 °C

Comp. No.	Sulfonate	$(t_{1/2})$ (h)[a]	N (%)[b]	S_{NBP}[c]
	Alkanesulfonates			
1	Methyl methanesulfonate	3.3	98.0	4.04
2	Methyl ethanesulfonate	4.5	99.0	4.34
3	Methyl 1-propanesulfonate	5.0	99.0	4.34
4	Methyl 1-butanesulfonate	5.2	98.5	4.16
5	Methyl 1-pentanesulfonate	5.3	99.0	4.34
6	Methyl isethionate	2.3	97.0	3.86
7	Ethyl methanesulfonate	50	63.0	2.58
8	Ethyl ethanesulfonate	56	61.5	2.55
9	Ethyl 1-propanesulfonate	61	62.2	2.56
10	Ethyl 1-butanesulfonate	64	61.0	2.54
11	Ethyl 1-pentanesulfonate	68	67.1	2.66
12	Ethyl isethionate	28	68.0	2.67
13	Isopropyl methanesulfonate	19	6.50	1.18
14	Isopropyl ethanesulfonate	28	4.87	1.06
15	Isopropyl 1-propanesulfonate	32	4.78	1.05
16	Isopropyl 1-butanesulfonate	33	4.68	1.04
17	Isopropyl 1-pentanesulfonate	36	5.35	1.10
18	Isopropyl isethionate	20	8.36	1.31
	p-Substituted benzenesulfonates			
19	Methyl *p*-nitrobenzenesulfonate	0.15[d]	92.2[d]	3.72
20	Methyl *p*-chlorobenzenesulfonate	0.92[d]	94.5[d]	3.88
21	Methyl benzenesulfonate	2.2[d]	94.6[d]	3.86
22	Methyl *p*-methylbenzenesulfonate	2.6[d]	96.0[d]	4.03
23	Methyl *p*-methoxybenzenesulfonate	7.3[d]	96.4[d]	4.08
24	Ethyl *p*-nitrobenzenesulfonate	3.3	64.9	2.61
25	Ethyl *p*-chlorobenzenesulfonate	22	75.6	2.84
26	Ethyl benzenesulfonate	34	76.7	2.86
27	Ethyl *p*-methylbenzenesulfonate	45	83.2	3.04
28	Ethyl *p*-methoxybenzenesulfonate	46	61.6	2.55
29	Isopropyl *p*-nitrobenzenesulfonate	1.0	4.15	0.98
30	Isopropyl *p*-chlorobenzenesulfonate	4.5	5.19	1.08
31	Isopropyl *p*-benzenesulfonate	11	5.62	1.12
32	Isopropyl *p*-methylbenzenesulfonate	25	6.04	1.15
33	Isopropyl *p*-methoxybenzenesulfonate	30	6.24	1.17

a) A rough measure of the half-life of a given sulfonate in the alkylation of NBP under the reaction condition described in Experimental.
b) Percent molar fraction of the sulfonate consumed for the alkylation of NBP at the final stage of the reaction.
c) Chemoselectivity constant in the NBP-alkylation, defined as follows.

$$S_{NBP}=\log\left\{\frac{[H_2O]}{[NBP]}\times\frac{N}{(100-N)}\right\}$$

where N is the % molar fraction of a sulfonate consumed for the alkylation of NBP, and $[H_2O]$ and [NBP] are the concentration of H_2O and NBP in the reaction medium, respectively.
d) The N value given here was obtained from the reaction with half as much NBP as compared with that described in Experimental.

ethyl *p*-methoxybenzenesulfonate are linearly correlated with Hammett's σ_p, as expected.[19] The plot is shown in Fig. 3.

Setting aside this exceptional case, it seems that a better leaving group with an electron-withdrawing substituent makes the alkyl sulfonate more susceptible to attack of a harder

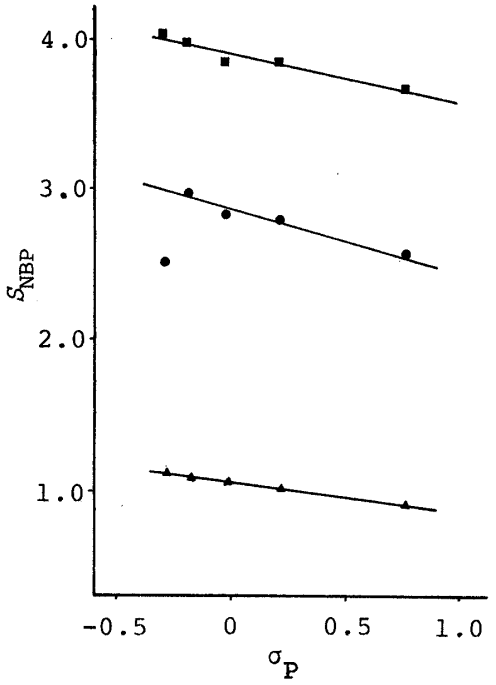

Fig. 2. Plots of S_{NBP} *versus* Hammett's σ_p of Alkyl *p*-Substituted Benzenesulfonates on a log–log Scale

■, methyl esters; ●, ethyl esters; ▲, isopropyl esters. The point not on the line in the case of the ethyl ester group is that of ethyl *p*-methoxybenzenesulfonate.

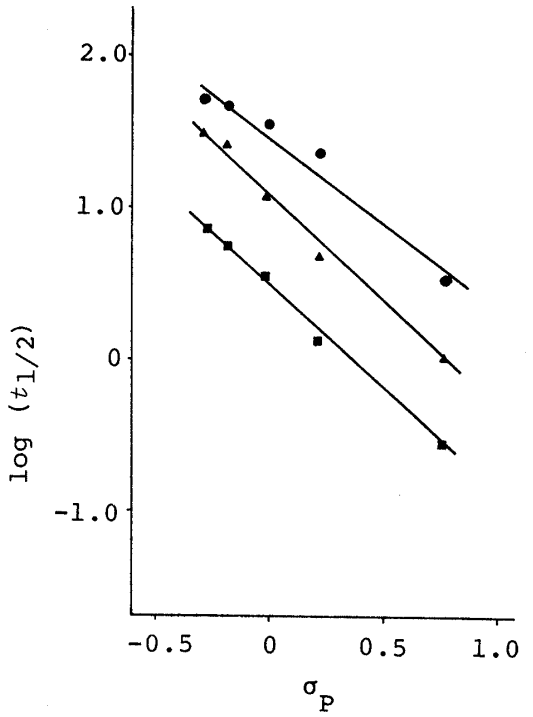

Fig. 3. Plots of the Apparent Half-Life *versus* Hammett's σ_p on a log–log Scale

■, methyl esters; ●, ethyl esters; ▲, isopropyl esters.

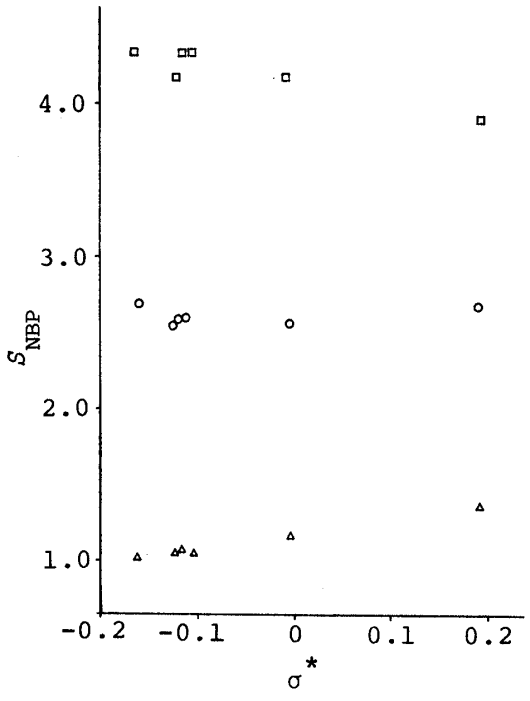

Fig. 4. Plots of S_{NBP} *versus* Hammett's σ^* of Alkyl Alkanesulfonates

σ^* values used are those of the alkyl moieties of the sulfonates, described by Taft, Jr. (R. W. Taft, Jr., "Steric Effects in Organic Chemistry," John Wiley & Sons, Inc., New York, 1956, pp. 556—675). □, methyl esters; ○, ethyl esters; △, isopropyl esters.

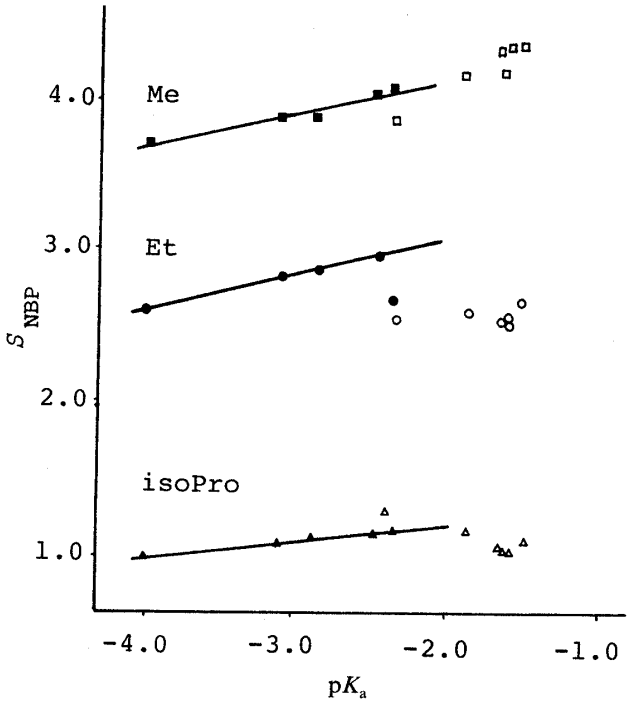

Fig. 5. Plots of S_{NBP} *versus* pK_a of Alkane- and Benzenesulfonates on a log–log Scale

■, methyl benzenesulfonates; ●, ethyl benzenesulfonates; ▲, isopropyl benzenesulfonates; □, methyl alkanesulfonates; ○, ethyl alkanesulfonate; △, isopropyl alkanesulfonates.

base, H_2O;[20] in other words, it makes the sulfonate less sensitive to the nucleophilicity of the more nucleophilic pyridine nitrogen. It is to be excepted that the molecularity of the reaction, the chemoselectivity and the hardness-softness of the alkylating agents are mutually related.[20]

With regard to alkanesulfonates, as shown in Fig. 4, the dependence on the leaving group becomes much smaller, and electron-deficiency of the leaving group slightly decreases the selectivity toward NBP of the methyl sulfonates, while ethyl and isopropyl derivatives do not show any marked dependence on the leaving group.

Finally, it may be worth adding that the structure of the alkyl moiety and the leaving capacity of the acid moiety do not constitute all the determinants for the chemoselectivity of alkyl sulfonates. Thus, as shown in Fig. 5, the linear correlation of S_{NBP} with the pK_a of the acid moiety[18] becomes poorer when the benzenesulfonates and alkanesulfonates are combined together in the sample for regression (especially in the case of ethyl derivatives). Steric factors of the leaving group, *i.e.*, the presence or absence of a benzene ring, may have some role in determining the chemoselectivity. The role of the chemoselectivity in various biological phenomena is now under investigation using these derivatives in our laboratory.

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