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QUANTITATIVE STRUCTURE-CHEMOSELECTIVITY RELATIONSHIP AMONG ALKANESULFONATES OF PRIMARY ALCOHOLS(1)

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The Swain-Scott's substrate constants (s) of 22 alkanesulfonates of primary alcohols, R^1-CH_2-OSO_2-R^2, were well correlated with Taft's σ^* and Es values of the substituents on the alkyl moiety and with σ^* of that on the leaving group: $s = 0.110\sigma^*(R^1) + 0.111Es(R^1) - 0.033\sigma^*(R^2) + 0.645$.

In order to correlate the chemoselectivity of alkylating agents with their structural characteristics, the present study evaluated the chemoselectvities of primary alkyl alkanesulfonates in terms of the substrate constant (s) as defined by Swain and Scott.(2) Six triflates (Table I, **1** to **6**) were synthesized and their s-values were evaluated by the method previously reported.(3) The substrate constants thus obtained, together with those of alkyl alkanesulfonates previously reported,(2-6) were subjected to a multiple linear regression analysis on Taft's σ^* and Es values(7) of the substitutents on both the alkyl moiety and the leaving group. The sample number is 22 in all. The results reveal that the substrate constant is satisfactorily described by a linear equation in the variables, σ^* and Es, which are related to the electronic and steric effects of the substituents, respectively. To our knowledge, the present study provides the first successful example of demonstrating a quantitative structure-chemoselectivity relationship although the samples are limited to a specific class of alkylating agents, the sulfonic acid esters of primary alcohols. A brief discussion is also included on the reactivity-selectivity principle.(8)

Results

Quantitative Description of Chemoselectivity by a Linear Equation in σ^* and Es of the Substituents

The substrate constants of fluorinated sulfonates listed in Table I were estimated by the correlation equation:(3) $s = 0.163\ S_{py} + 0.209$. S_{py} is a measure for chemoselectivity defined by $\log\{N/(1-N) \times [H_2O]/[\text{pyridine}]\}$, where N is the molar fraction of an alkylating agent consumed for the quaternization of pyridine at 37°C in 1/15 M phosphate buffer (pH 6.0) containing a large excess of pyridine as the nucleophile and 4% acetone as the solubilizer of the alkylating agents.3) Estimations were based on the ε values of N-alkylated pyridines as follows: 4370 for alkyl = CH_3-; 4710 for C_2H_5- and C_3H_7-; 4580 for CH_2FCH_2-; 4740 for CHF_2CH_2-; and 5180 for CF_3CH_2-. All the other s values are as reported.2-6) The correlation of the s-values with σ^* and Es were tested for statistical significance by a multiple linear regression analysis using SALS (Statistical Analysis of Least Square Fitting) program.9) The Taft's parameters used for correlation are those reported in refs. 7 and 10 for σ^* and ref. 10 for Es: H (σ^* 0.49, Es 1.24); CH_3 (σ^* 0.00, Es 0.00); C_2H_5 (σ^* -0.10, Es -0.07); C_3H_7 (σ^* -0.12, Es -0.36); C_4H_9 (σ^* -0.13, Es -0.39); C_5H_{11} (σ^* -0.16, Es -0.40); $(CH_3)_2CH$ (σ^* -0.19, Es -0.47); $(CH_3)_3C$ (σ^* -0.30, Es -1.54); CH_2F (σ^* 1.10, Es -0.24); CHF_2 (σ^* 2.05, Es -0.67); CF_3 (σ^* 2.85, Es -1.16); $HOCH_2$ (σ^* 0.56, Es 0.03); CH_3OCH_2 (σ^* 0.52, Es -0.19).

The 95% confidence limit is given in parentheses for each term of the correlation equation. The sample number (n), the correlation coefficient (r) and the contribution ratio (r^2) are also given. The $\boldsymbol{\sigma^*}(R^1)$ and $\boldsymbol{\sigma^*}(R^2)$ are those of the substituents R^1 and R^2, respectively and the **Es**(R^1) and **Es**(R^2) are those of R^1 and R^2, respectively.

$$s = 0.110(\pm0.015)\boldsymbol{\sigma^*}(R^1) + 0.111(\pm0.012)\mathbf{Es}(R^1) - 0.033(\pm0.009)\boldsymbol{\sigma^*}(R^2) + 0.645(\pm0.011)$$

$$\underline{r=0.987} \qquad \underline{r^2=0.973} \qquad \underline{n=22}$$

Thus, this equation explains 97% of the variance in the s-values for alkylating alkanesulfonates. All the coefficients are less than 0.01 levels of significance. It is worth noting that no contribution of **Es**(R^2) for the

Table I Swain-Scott's Substrate Constants (s-values) of Alkyl Alkanesulfonates

$$\underline{R}^1\text{-}CH_2\text{-}O\text{-}SO_2\text{-}\underline{R}^2$$

	R^1	R^2	s-value		R^1	R^2	s-value
(1)	H-	$-CF_3$	0.74	**(12)**	$(CH_3)_2CH$-	$-CH_3$	0.55 4)
(2)	CH_3-	$-CF_3$	0.54	**(13)**	$HOCH_2$-	$-CH_3$	0.68 4)
(3)	C_2H_5-	$-CF_3$	0.53	**(14)**	CH_3OCH_2-	$-CH_3$	0.68 4)
(4)	CH_2F-	$-CF_3$	0.66	**(15)**	H-	$-C_2H_5$	0.85 6)
(5)	CHF_2-	$-CF_3$	0.71	**(16)**	H-	$-C_3H_7$	0.85 6)
(6)	CF_3-	$-CF_3$	0.71	**(17)**	H-	$-C_4H_9$	0.83 6)
(7)	H-	$-CH_3$	0.83 2,4)	**(18)**	H-	$-C_5H_{11}$	0.85 6)
(8)	CH_3-	$-CH_3$	0.64 3,4)	**(19)**	CH_3-	$-C_2H_5$	0.63 6)
(9)	C_3H_7-	$-CH_3$	0.65 4)	**(20)**	CH_3-	$-C_3H_7$	0.63 6)
(10)	C_4H_9-	$-CH_3$	0.61 5)	**(21)**	CH_3-	$-C_4H_9$	0.63 6)
(11)	$(CH_3)_3C$-	$-CH_3$	0.45 4)	**(22)**	CH_3-	$-C_5H_{11}$	0.65 6)

substituents on the leaving group was definitely proved. Thus, incorporation of **Es**(R^2) did not improve the correlation at all, the t-test showing a completely negligible contribution of **Es**(R^2). Fig. 1 shows a fairy good correlation between the observed and calculated s-values.

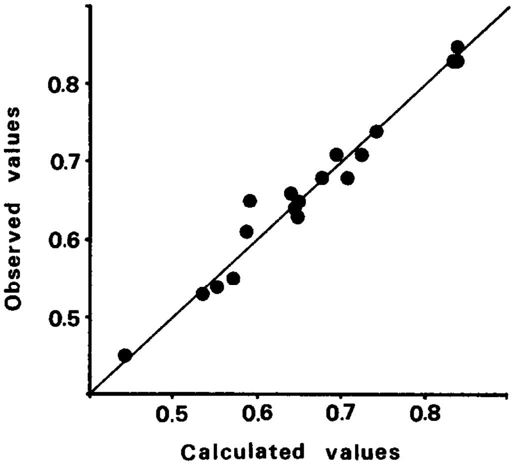

Fig. 1 Fittings of Observed and Calculated Swain-Scott's Substrate Constants for Alkyl Alkanesulfonates

Among the sulfonic acid esters of primary alcohols examined in the this study, it is apparent that chemoselectivity is perturbed mainly by the electronic and steric characteristics of alkyl moiety and to a lesser degree by the nucleofugality of leaving group. Thus, both the electron-abundance and bulkiness of the alkyl moiety and the high nucleofugality of leaving group seem to make the transition state more reactant-type[8)] due to the ready charge separation of the R-O bond, i.e., such as a transition state in S_N1 type reactions. As a result, the nucleophile participates to a lesser degree in the formation of transition state, resulting in lower chemoselectivity. The fact that only the σ^* term, but not the Es, of the leaving group is effective in the correlation may indicate that the σ^* term may be substituted by the pKa of the leaving sulfonate moiety because pKa is, in general, linearly correlated only with σ^*.

Validity of Reactivity-Selectivity Principle among Alkyl Alkanesulfonates

In a set of similar reactions, the transition state of a highly reactive substrate tends to resemble the reactant so that the reaction is less selective toward nucleophiles because of less participation of nucleophiles in the transition state formation, and vice versa. This argument is known as the reactivity-selectivity principle.[8)] The validity of this principle was tested using some of the compounds examined here by comparing the s-value with the rate of hydrolysis in 0.25 M phosphate buffer (pH 7.4) containing 0.5% DMSO at 37°C, as shown below.

	$t_{1/2}$(hr)	s
$CH_3CH_2-OSO_2CF_3$ (**2**)	very fast	0.54
$CH_2FCH_2-OSO_2CF_3$ (**4**)	0.1	0.66
$CHF_2CH_2-OSO_2CF_3$ (**5**)	1.15	0.71
$CH_3-OSO_2CH_2CH_3$ (**15**)	2.22	0.85
$CH_3-OSO_2CH_3$ (**7**)	2.24	0.83
$CH_3CH_2-OSO_2CH_2CH_3$ (**19**)	6.35	0.63
$CH_3CH_2-OSO_2CH_3$ (**8**)	6.63	0.64

In conclusion, no correlation was found between the rate and selectivity.

Discussion

The chemoselectivity must be related to the intrinsic natures of the atoms and bonds of the substrate which directly participate in the reaction. The present study does not aim a quantitative description of such the intrinsic chemoselectivity, but a quantitative analysis of the perturbation of chemoselectivity induced by the substituents.

$R^1\text{-}CH_2\text{-}O\text{-}SO_2\text{-}R^2$

R^1	R^2		Transition state		Chemo-selectivity
electron-donating bulky	electron-withdrawing (high nucleofugic)	⟶	reactant-type	⟶	low
electron-withdrawing less bulky	electron-donating (low nucloefugic)	⟶	product-type	⟶	high

The conclusion derived here seems to be reliable as far as the series of compound examined are concerned. It may, however, be suspected that this type of correlation might be valid only for a series of alkylating agents involving a transient range of the transition state from a unimolecular-like (reactant-type) to a bimolecular-like (product-type).

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