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Studies on Chemical Carcinogens and Mutagens. XXVI.[1] Chemical Properties and Mutagenicity of Alkyl Alkanesulfonates on *Salmonella typhimurium* TA100

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The mutagenic and cytotoxic effects of 18 kinds of methyl, ethyl, and isopropyl esters of straight-chain alkanesulfonic acids including isethionic acid were investigated on *Salmonella typhimurium* TA100. In order to correlate these biological activities with the chemical and/or physicochemical properties, the hydrolytic rates (as a measure of alkylating ability) and the capacity factors (as a measure of hydrophobicity) were determined. Some structural correlations were apparent, although quantitative structure–activity relationships were not obtained.

Keywords——methyl methanesulfonate; alkanesulfonate; sulfonate; isethionate; mutagenicity; capacity factor; van der Waals volume; hydrolysis

It has been suggested that chemical mutagenesis, and probably chemical carcinogenesis, are initiated through chemical modifications of the informational biopolymers by genotoxic compounds.[2-4] Alkyl sulfonates constitute a representative class of direct-acting mutagens and their genotoxicity is thought to be attributable to their alkylating ability.[2-4] Therefore, the quantitative structure–mutagenicity relationship among a given series of alkyl sulfonates might possibly be expressed by a regression equation including terms reflecting chemoselectivity, reaction rate, and partition properties of the compounds. As we have already reported,[1] the chemoselectivity[1,5] of a series of methyl, ethyl, and isopropyl alkanesulfonates is governed mainly by the structure of the alkyl moiety of the molecule and is scarcely affected by the carbon chain length of the alkanesulfonic acid moieties.

In this study, mutagenic and cytotoxic activities of 18 alkyl alkanesulfonates were examined on *Salmonella typhimurium* TA100 and an attempt was made to correlate the biological activities with the rate of hydrolysis in phosphate buffer (pH 7.4) and the partition properties estimated from the retention time on high performance liquid chromatography (HPLC).

Materials and Methods

Materials——All the sulfonates used in the present study, listed in Table I, were synthesized in our laboratory. The synthetic methods and the analytical data were reported in our previous paper.[1] The purity of all the compounds examined were checked by elementary analysis, and thin-layer and high performance liquid chromatographies.

Measurements of the Rate of Hydrolysis——An appropriate amount of the sulfonate to be examined was dissolved in 0.25 ml of dimethyl sulfoxide (DMSO) and diluted to 50 ml with 0.25 M sodium phosphate buffer (pH 7.4). The concentration of the sulfonate solutions thus prepared ranged from 5 to 20 mM. The test solution was placed in small sealed tubes (2.0 ml each) and these tubes were kept at 37 ± 0.2 °C in a water bath incubator. The tubes were broken one by one after appropriate periods of time. An aliquot of test solution was taken from each tube (exactly 0.8 ml) and combined with 0.8 ml of $CHCl_3$ containing an appropriate amount of the internal standard for quantitative analysis by gas chromatography. The internal standard used for quantitative analysis was either mesitylene, cymene, or tetralin. The $CHCl_3$ extract thus obtained was dried over anhydrous $MgSO_4$. Quantitative

analysis of the sulfonate extracted was done with a Shimadzu GC-8APF gas chromatography apparatus equipped with an FID detector, and a 3.2 mm i.d. × 2.0 m 5% SE30 column (column temperature between 60 and 110 °C). The quantification was carried out by measuring the peak area relative to that of the internal standard with the help of the working curves previously prepared. All the data listed in Table I are the averages of duplicate or triplicate separate experiments; the deviations fell within ±5% in all cases.

Determination of Retention Times on HPLC——Chromatography was carried out with a JASCO TWINCLE HPLC apparatus equipped with a refractometer, and a 4.0 mm i.d. × 20 cm JASCO Finepak SIL C-18 column. The sample was dissolved in MeOH at a concentration of 1.2×10^{-2}—5×10^{-3} mol/ml. Elution was done with MeOH–H_2O (60 : 40 v/v) at room temperature (*ca.* 23 °C) and the flow rate was 1.0 ml/min. The eluted sulfonates are detected by measuring their refraction. The capacity factor, k',[6,7] which is a measure of the partition properties, was calculated as $((t_R - t_0)/t_0)$, where t_R and t_0 are the retention times of the sulfonate tested and the solvent itself, respectively.

Calculation of the van der Waals Volume, V_W——The van der Waals volumes of the sulfonates were calculated according to Moriguchi's method,[8] the values used for calculation being given below.

van der Waals volumes (10^2 Å^3) of atoms: C, 0.206; H, 0.056; O, 0.115; S, 0.244. Correction values of van der Waals volume for spheral overlapping due to covalent bonding and branching: C–C, −0.078; C–H, −0.043; C–O, −0.056; C–S, −0.066; S=O and S–O, −0.057; branching, −0.05.

The V_w is defined by Moriguchi *et al.*[8] as [(sum of van der Waals volumes of all the constituent atoms) − (sum of correction values due to covalent bondings and branching)].

Determinations of Mutation Frequency and 50% Lethal Dose for *Salmonella typhimurium* TA100[9,10]——The tester strain of TA100 was kindly supplied by Dr. Sohei Kondo, Medical School of Osaka University. The cells were grown to an early stationary phase in liquid nutrient broth (0.8% Difco nutrient broth containing 0.5% NaCl) in an L-tube at 37 °C for 10—12 h. Next, 0.1 ml of this cell culture containing about 1.0×10^8 cells, followed by 0.1 ml of DMSO containing an appropriate amount of a sulfonate to be tested, were added to 0.8 ml of 0.25 M phosphate buffer (pH 7.4) under ice-cooling. This "reaction mixture" was shaken at 37 °C for 60 min. The reaction was stopped by ice-cooling.

For the measurement of surviving cells, 0.04 ml of the "reaction mixture" was diluted with 4 ml of the phosphate buffer, and 0.04 ml of this diluted suspension was further diluted with 4 ml of the phosphate buffer. Finally, 0.1 ml of this cell suspension was added to 2.5 ml of a solution, maintained at 45 °C, consisting of 0.8% Bacto-Agar containing 0.6% NaCl and 1/10 volume of a solution of 0.5 mM L-histidine and 0.5 mM biotin. This mixture was immediately layered on a nutrient broth agar plate (prepared with 200 ml of deionized water containing 1.6 g of nutrient broth 3 g of Bacto-Agar and 1.0 g NaCl) in an 86 mm disposable plastic Petri dish. The colonies obtained by incubation at 37 °C for 1 d were counted.

For the measurement of revertants, the residual fraction of the "reaction mixture" was diluted with 3 ml of the phosphate buffer and centrifuged at 3000 rpm ($1900 \times g$) for 20 min. The supernatant was decanted and the cells were resuspended in 0.5 ml of the phosphate buffer. This suspension was mixed with 2.0 ml of a solution, maintained at 45 °C, consisting of 0.8% Bacto-Agar containing 0.6% NaCl and 1/10 volume of a solution of 0.5 mM L-histidine and 0.5 mM biotin. This mixture was immediately layered on a minimum glucose agar plate (prepared with 970 ml of deionized water containing 15 g of Bacto-Agar and 20 ml of 50-fold concentrated medium E,[11] supplemented with 10 ml of 40% glucose) in an 86 mm Petri dish. The plate was incubated at 37 °C for 2 d and the revertant colonies formed were counted.

Mutation frequency (MF) was calculated as $[(M - M_0)/N]$, where M and M_0 are the numbers of revertant cells per 1 ml of the "reaction mixture" of the test compound and DMSO, respectively, and N is the number of surviving cells per 1 ml of the "reaction mixture" containing the test compound.

Conventional Assessments of Mutagenicity and Lethality——The "reaction mixture" treated as described above was diluted with 3 ml of the phosphate buffer and centrifuged at 3000 rpm for 20 min. The supernatant was decanted and the cells were resuspended in 0.5 ml of the phosphate buffer. This suspension was mixed with 2.0 ml of a solution, maintained at 45 °C, consisting of 0.8% Bacto-Agar containing 0.6% NaCl and 1/10 volume of a solution of 0.5 mM L-histidine and 0.5 mM biotin. This was layered on a minimum glucose agar plate (prepared as described above). The plate was incubated at 37 °C for 2 d and the revertant colonies formed were counted. The maximum number of revertants/plate (per 1 ml of the "reaction mixture" containing about 1.0×10^8 cells), R_{max}, is the number at the maximum of the dose–response curve, minus the number of spontaneous revertants found on the control plate (usually 130 ± 40). The number of revertants per mM, rev/mM, was calculated from the linear portion of the dose–response curve, *i.e.*, the maximum number of rev/mM observed on the plates examined. C_{max} is the concentration of mutagen at which the maximum number of revertants per plate were produced.

Results

Hydrolytic Rates

The rates of hydrolysis of alkyl alkanesulfonates were measured at 37 °C in 0.25 M

TABLE I. Capacity Factors and van der Waals Volumes of Alkyl Alkanesulfonates and Their Solvolytic Rates in Phosphate Buffer (0.25 M, pH 7.4) at 37 °C

Compound number	Alkanesulfonate	$\log k'$ [a]	V_w (10^2 Å^3)[b]	k_{obs} (h^{-1})[c]	$t_{1/2}$ (h)[c]
1	$CH_3OSO_2CH_3$	−0.588	0.786	0.310	2.24
2	$CH_3OSO_2CH_2CH_3$	−0.371	0.940	0.312	2.22
3	$CH_3OSO_2(CH_2)_2CH_3$	−0.149	1.094	0.269	2.57
4	$CH_3OSO_2(CH_2)_3CH_3$	0.085	1.248	0.262	2.65
5	$CH_3OSO_2(CH_2)_4CH_3$	0.322	1.402	0.282	2.46
6	$CH_3OSO_2CH_2CH_2OH$	−0.860	1.008	0.823	0.842
7	$CH_3CH_2OSO_2CH_3$	−0.439	0.940	0.105	6.63
8	$CH_3CH_2OSO_2CH_2CH_3$	−0.184	1.094	0.109	6.35
9	$CH_3CH_2OSO_2(CH_2)_2CH_3$	0.025	1.248	0.0968	7.16
10	$CH_3CH_2OSO_2(CH_2)_3CH_3$	0.244	1.402	0.0945	7.34
11	$CH_3CH_2OSO_2(CH_2)_4CH_3$	0.482	1.556	0.0874	7.93
12	$CH_3CH_2OSO_2CH_2CH_2OH$	−0.652	1.162	0.283	2.45
13	$(CH_3)_2CHOSO_2CH_3$	−0.202	0.988	3.59	0.193
14	$(CH_3)_2CHOSO_2CH_2CH_3$	−0.024	1.142	2.99	0.232
15	$(CH_3)_2CHOSO_2(CH_2)_2CH_3$	0.181	1.296	2.83	0.245
16	$(CH_3)_2CHOSO_2(CH_3)_3CH_3$	0.398	1.450	2.77	0.250
17	$(CH_3)_2CHOSO_2(CH_2)_4CH_3$	0.630	1.604	2.94	0.236
18	$(CH_3)_2CHOSO_2CH_2CH_2OH$	−0.349	1.266	8.99	0.0771

a) The capacity factor is expressed as $\log((t_R - t_0)/t_0)$, where t_R and t_0 are the retention times of the sulfonate examined and the solvent on HPLC under the conditions described in Experimental.
b) The van der Waals volume calculated according to Moriguchi's method.[8]
c) The k_{obs} and $t_{1/2}$ are the averages of duplicate or triplicate measurements, each observations being within ±5% of the average.

phosphate buffer (pH 7.4) containing 0.5% dimethyl sulfoxide, the observed rate constants, k_{obs} (h^{-1}), and the half-lives, $t_{1/2}$ (h), being shown in Table I. The hydrolytic rates are markedly dependent on the structure of the alkyl moiety of the esters, whereas they are only slightly dependent on the carbon-chain length of the acid moieties:

$$\text{rates of methyl esters} = 0.287 \pm 0.025\ h^{-1}$$

$$\text{rates of ethyl esters} = 0.0982 \pm 0.0108\ h^{-1}$$

$$\text{rates of isopropyl esters} = 3.18 \pm 0.41\ h^{-1}$$

The isopropyl esters are most rapidly hydrolyzed, followed by the methyl esters. Methyl, ethyl, and isopropyl esters of β-hydroxylated ethanesulfonic acid (isethionic acid) are hydrolyzed about 2.85 times more quickly than the corresponding non-substituted alkanesulfonates. It is of interest that similar sizes of increase in the rate were apparently produced by the electron-withdrawing inductive effects of the β-hydroxy group, regardless of methyl, ethyl, or isopropyl ester.

Capacity Factors and van der Waals Volumes

Partition properties of these alkanesulfonates were estimated from the retention times on HPLC and the van der Waals volume were calculated by Moriguchi's method, $\log k'$ and V_w, respectively, as shown in Table I. It was confirmed that, among all the non-substituted alkanesulfonates, both measures of partition properties were linearly correlated with each other, as shown in Fig. 1. The regression equation is as follows.

$$\log k' = 1.447\, V_w - 1.728$$

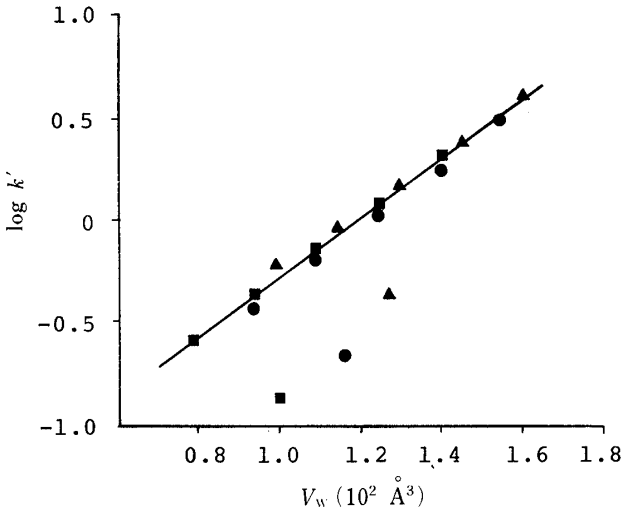

Fig. 1. Plots of Logarithmic Capacity Factor, $\log k'$, *versus* van der Waals Volume of Alkanesulfonates

■, methyl; ●, ethyl; ▲, isopropyl esters. Three points deviating from the linearity in the figure are those of methyl, ethyl, and isopropyl isethionates which have a hydrophilic OH group in the molecules.

TABLE II. Mutagenic and Lethal Effects of Alkyl Sulfonates on *S. typhimurium* TA100[a]

Compound number	R	LD_{50} (mM)	MF at 1 mM	MF at 10 mM	MF at LD_{50}	Slope[b]
	CH_3OSO_2–R					
1	$-CH_3$	9.3	3.08×10^{-7}	4.68×10^{-6}	4.30×10^{-6}	1.18
2	$-C_2H_5$	12.7	nd	nd	nd	nd
3	$-C_3H_7$	10.2	3.94×10^{-9}	2.56×10^{-6}	2.71×10^{-6}	2.81
4	$-C_4H_9$	1.4	nd	nd	nd	nd
5	$-C_5H_{11}$	3.5	nd	nd	nd	nd
6	$-C_2H_4OH$	6.8	7.96×10^{-8}	6.50×10^{-6}	3.11×10^{-6}	1.91
	$C_2H_5OSO_2$–R					
7	$-CH_3$	69.0	1.38×10^{-10}	3.36×10^{-7}	2.32×10^{-4}	3.39
8	$-C_2H_5$	79.0	8.91×10^{-12}	5.05×10^{-8}	1.18×10^{-4}	3.75
9	$-C_3H_7$	42.0	3.09×10^{-10}	2.25×10^{-7}	1.37×10^{-5}	2.86
10	$-C_4H_9$	2.1	nd	nd	nd	nd
11	$-C_5H_{11}$	5.0	nd	nd	nd	nd
12	$-C_2H_4OH$	53.0	2.06×10^{-8}	6.11×10^{-6}	3.78×10^{-4}	2.47
	$(CH_3)_2CHOSO_2$–R					
13	$-CH_3$	9.3	7.71×10^{-6}	2.24×10^{-4}	2.02×10^{-4}	1.46
14	$-C_2H_5$	7.8	8.18×10^{-6}	2.62×10^{-4}	1.80×10^{-4}	1.51
15	$-C_3H_7$	12.6	2.77×10^{-6}	1.12×10^{-4}	1.62×10^{-4}	1.61
16	$-C_4H_9$	6.1	7.53×10^{-6}	1.31×10^{-4}	7.05×10^{-5}	1.24
17	$-C_5H_{11}$	3.2	9.12×10^{-6}	1.73×10^{-4}	4.03×10^{-5}	1.28
18	$-C_2H_4OH$	8.7	6.10×10^{-6}	1.90×10^{-4}	1.55×10^{-4}	1.49

a) "nd" means that revertants did not significantly exceed the background control level (130 ± 40) at any dose examined.
b) The slope of the linear dose–response plot (log–log scale).

where the number of samples is 15 and the correlation factor, r, is 0.9914. It is not surprising that the isethionates, which have a hydrophilic group in their molecules, deviated from the linearity found for non-substituted sulfonates. The structure–mutagenicity relationship will be discussed, in this paper, on the basis of $\log k'$ values experimentally obtained as a measure of partition properties.

Mutagenicity and Toxicity

Table II lists the 50% lethal doses (LD_{50}), mutation frequencies at 1 mM (MF at 1 mM), mutation frequencies at 10 mM (MF at 10 mM), mutation frequencies at LD_{50} (MF at LD_{50}),

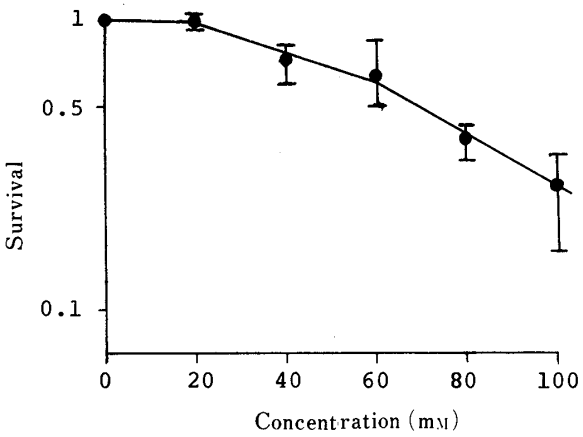

Fig. 2. Plots of Logarithmic Survival Fraction *versus* Concentration of Ethyl Methanesulfonate

● indicates the average of triplicate determinations.

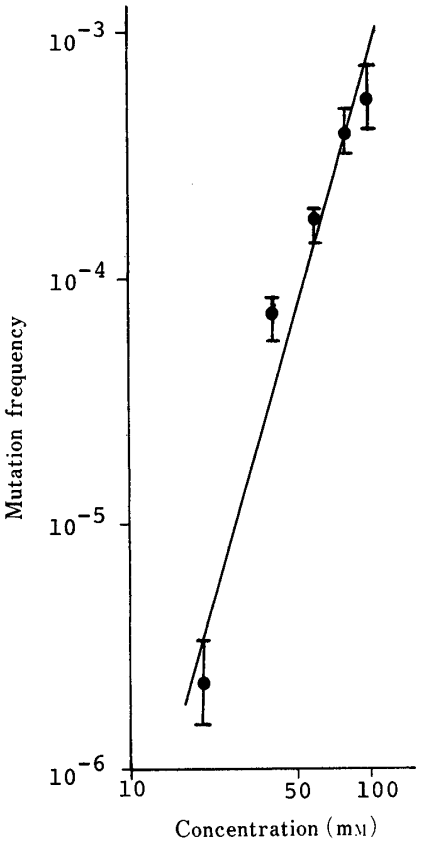

Fig. 3. Plots of Logarithmic Mutation Frequency *versus* Logarithmic Concentration of Ethyl Methanesulfonate

● indicates the average of triplicate determinations.

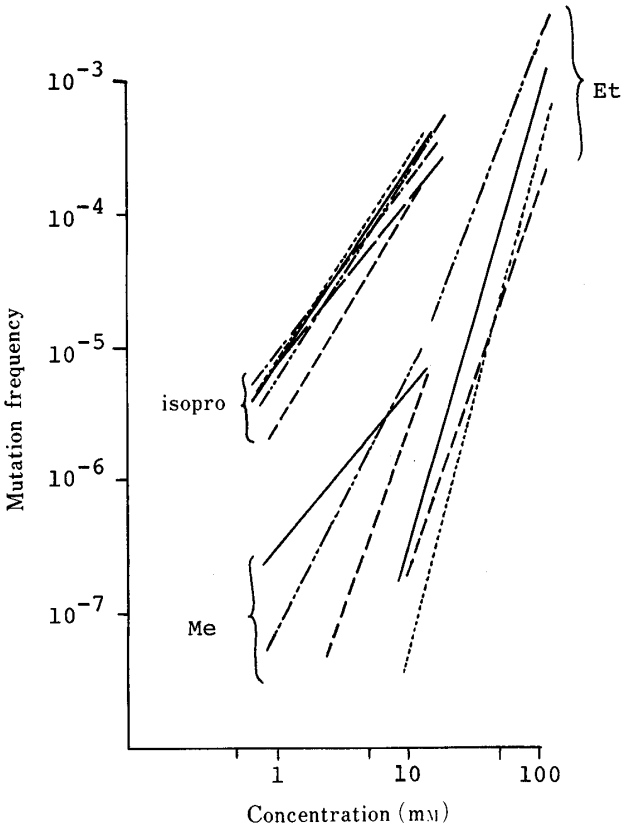

Fig. 4. Plots of Mutation Frequency *versus* Concentration of Methyl, Ethyl, and Isopropyl Alkanesulfonates

——, methanesulfonates; ------, ethanesulfonates; – – – –, propanesulfonates; — —, butanesulfonates; — · — ·, pentanesulfonates; — · · —, isethionates.

and the slopes (n) of the dose–mutagenicity plots (log–log scale) of 18 alkyl alkanesulfonates on *Salmonella typhimurium* TA 100. These were obtained by incubation of the tester cells with appropriate concentrations of sulfonate to be tested at 37 °C for 60 min. A set of experimental data are shown in Figs. 2 and 3, for the case of ethyl ethanesulfonate. All the data shown in Table II were obtained similarly. The plots of mutation frequency *versus* dose are shown in Fig. 4.

Table III lists the mutagenic and toxic properties of these sulfonates obtained by a simpler experimental procedure which involved only countings of the revertants without

TABLE III. Conventional Parameters of Mutagenicity of Alkyl Sulfonates on *S. typhimurium* TA100

Compound number	R[a]	R_{max}[b]	C_{max}[c]	rev/mM[d]
	CH_3OSO_2R			
1	(C_1)	269	9	48
3	(C_3)	173	16	18
6	(C_2–OH)	174	9	26
	$C_2H_5OSO_2R$			
7	(C_1)	14102	80	325
8	(C_2)	7450	80	180
9	(C_3)	751	48	25
12	(C_2–OH)	12763	45	425
	$(CH_3)_2CHOSO_2R$			
13	(C_1)	11227	12	1564
14	(C_2)	7891	12	1164
15	(C_3)	7053	16	799
16	(C_4)	3309	4.8	977
17	(C_5)	2114	2.4	961
18	(C_2–OH)	8977	16	1021

a) C_n in parentheses denotes the number of carbons of the alkane moiety of alkanesulfonates.
b) The maximum number of revertants per plate, per 1 ml of the "reaction mixture" (see Experimental) containing about 1.0×10^8 cells.
c) The concentration at which the maximum number of revertants is produced.
d) The number of revertants per mM, calculated from the linear portion of the dose–response curve.

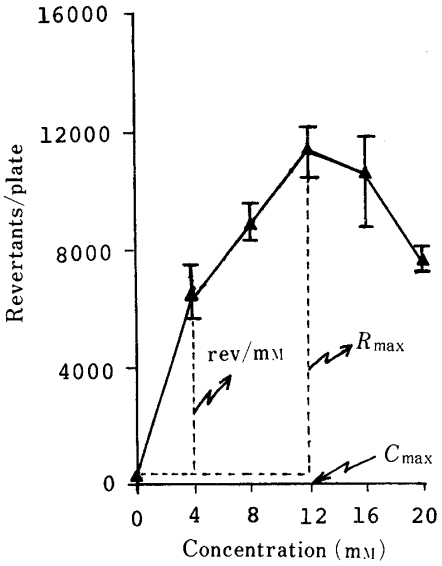

Fig. 5. Number of Revertants Plotted *versus* Concentration of Isopropyl Methanesulfonate

▲ indicates the average of triplicate determinations. R_{max}, C_{max}, and rev/mM are illustrated in the figure.

counting of the survivors, as described in Experimental. Thus, rev/mM is the number of revertants per mM, calculated from the linear portion of the dose–response curve, *i.e.*, the maximum number of rev/mM observed on the plates examined; R_{max} is the maximum number of revertants per plate (minus spontaneous revertants found on the control plate) among all those examined; and C_{max} is the concentration of a mutagen at which the maximum number of revertants was produced. A set of experimental data is shown in Fig. 5, for the case of isopropyl methanesulfonate. All the data shown in Table III are average values from duplicate or triplicate measurements.

Discussion

Assessment of Mutagenic Potency

The original Ames method, which was developed to detect mutagenicity as sensitively and to be applicable as widely as possible, has been commonly used for screening of genotoxic substances all over the world. Yahagi *et al.*[10] slightly modified this method by incubating the tester cells with a mutagen to be tested before plating. Mutagenicity is usually assessed in these conventional methods in terms of the number of revertants per plate or per nmol or μmol of a mutagen tested. Here, the mutagen can interact with the cells during a period from before to after the cell proliferation, if the mutagen remains undecomposed. The high sensitivity of this detection method may be due to the interaction of the mutagen with the cells in the proliferation stage, including S-phase.[12] In spite of its superiority as a screening assay method, it is difficult to correlate the mutagenic potency with chemical and/or physicochemical properties of mutagens, because one can hardly estimate how long the mutagen interacts with the cells, which are in various phases of sensitivity to the mutagen. Therefore, the orthodox assay method for mutagenicity might be better for investigating quantitative structure–mutagenicity relationships. Thus, in this paper, the cells were incubated in appropriate concentrations of a test compound at 37 °C for 60 min and the mutation frequency was calculated. Mutagenic potencies are assessed in terms of the mutation frequencies at 1 and 10 mM. The mutation frequency at LD_{50} is also given as a measure of relative efficiency of mutagenic and killing activities of mutagens.

It is worth mentioning here that, as shown in Figs. 6 and 7, LD_{50} and MF at LD_{50} thus obtained were well correlated with C_{max} and R_{max}, respectively, which are the conventional parameters obtained from the dose–response curves. The regression equations are as follows (the doses are given in mM).

$$\log LD_{50} = 0.9514 \log C_{max} - 0.0051$$

$$r = 0.9641,\ n = 13$$

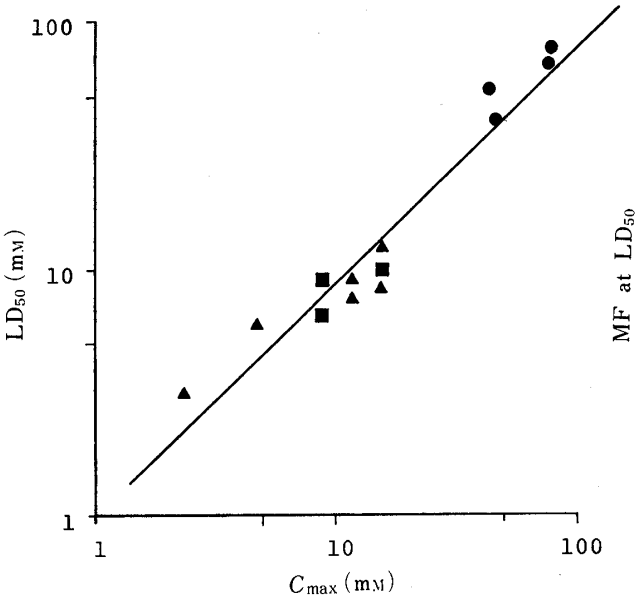

Fig. 6. Correlation between LD_{50} and C_{max} on a log–log Scale

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

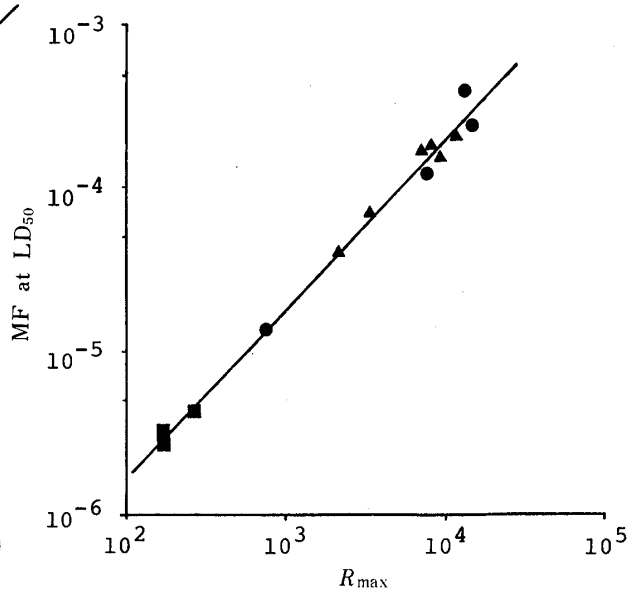

Fig. 7. Correlation between Mutation Frequency at LD_{50} and R_{max} on a log–log Scale

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

$$\log(\text{MF at } LD_{50}) = 1.048 \log R_{max} - 7.886$$

$$r = 0.9955,\ n = 13$$

Toxicity

As can be seen in Table II, LD_{50} values of methyl and isopropyl sulfonates fall in rather narrow ranges of concentration; 1.4—12.7 mM and 3.2—12.6 mM, respectively, whereas those of ethyl esters are distributed in a wider range of 2.1—79.0 mM. When one compares the toxicity of methyl, ethyl, and isopropyl esters of each sulfonic acid, it seems that the ethyl esters of C_1- to C_3-sulfonic acids (see Table III) are less toxic and that methyl and ethyl esters of C_4-sulfonic acid are the most toxic among those examined, as shown in Fig. 8. It is of interest to note that β-hydroxy derivatives of ethanesulfonates (isethionates) have similar degrees of toxicity to the parent ethanesulfonates, regardless of whether they are methyl, ethyl, or isopropyl esters.

Mutagenicity

It is worth noting that the mutagenicity and also toxicity of the isopropyl esters are not greatly dependent on the leaving group, *i.e.*, the partition properties or hydrolytic rate, and that, as seen in Fig. 4, the isopropyl esters seem to be more mutagenic than the methyl and ethyl esters. It appears that the mutagenicity, in addition to the toxicity, of the methyl and ethyl esters is more dependent on the structure of the leaving group of the molecule, as compared with the isopropyl esters. Some of the methyl and ethyl esters were not mutagenic, possibly because they are too toxic for the mutagenicity to be detectable. The killing process may involve some other molecular mechanisms in addition to the mechanism involving alkylation of DNA.

Among isethionates containing an OH in the leaving group, it is of interest that the hydroxy group, which does not affect the toxicity of methyl, ethyl, or isopropyl esters, produced a profound increase in the mutagenicity of the ethyl ester, whereas it did not produce any such effect in the methyl and isopropyl esters. As already described, the presence of the hydroxy group makes the rate (k_{obs}) larger by about 2.85 times and makes the capacity factors ($\log k'$) smaller to similar extents throughout the series of the esters.

Another interesting feature is the structure dependence of the slope (n) of the dose–mutation frequency correlation plots (log–log scale). It is reasonabe that all the isopropylating sulfonates have similar sizes of n, ranging from 1.24 to 1.61. However, methylating sulfonates showed n values ranging from 1.18 to 2.81. It is not clear why the methylating sulfonates, which cause the same type of damage in a similar chemoselective reaction process, show different dose–response correlations.

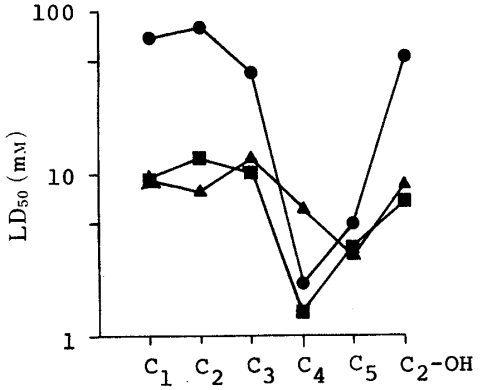

Fig. 8. Dependence of LD_{50} on Carbon Chain Length of the Alkyl Moiety of Alkanesulfonates

C_1, methanesulfonates; C_2, ethanesulfonates; C_3, propanesulfonates; C_4, butanesulfonates; C_5, pentanesulfonates; C_2–OH, isethionates. ■, methyl; ●, ethyl; ▲, isopropyl esters.

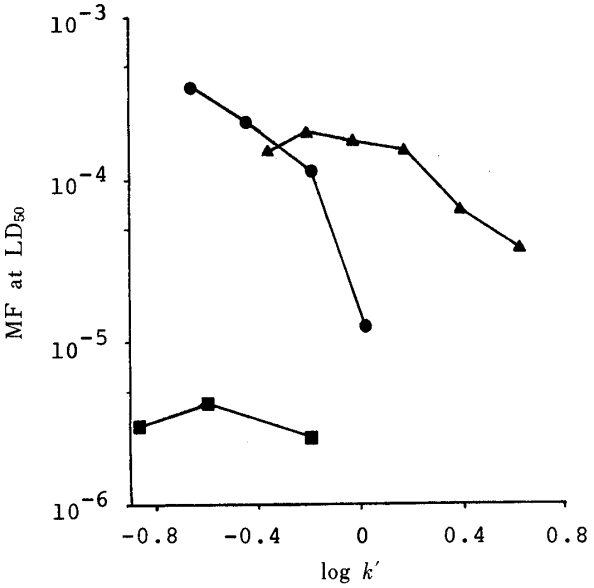

Fig. 9. Plots of Logarithmic Mutation Frequency at LD_{50} *versus* Logarithmic Capacity Factor, $\log k'$, of Alkanesulfonates

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

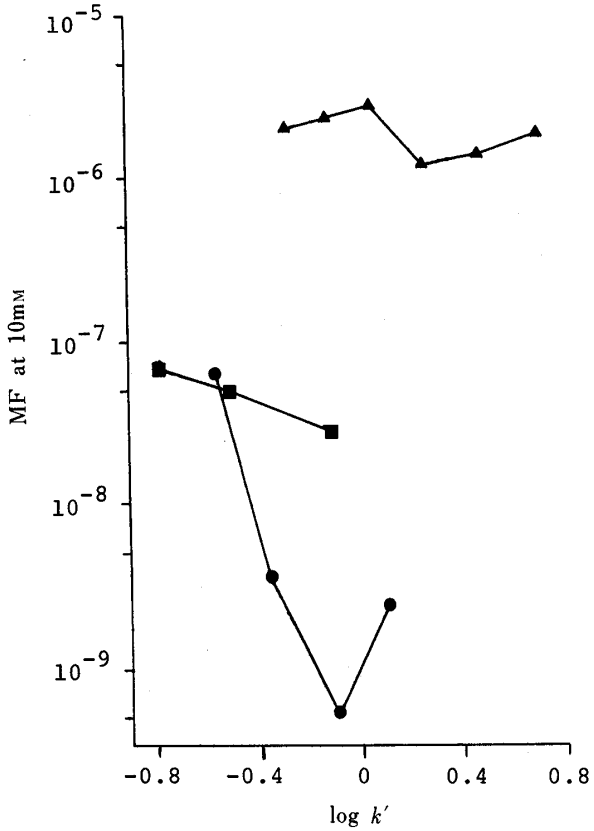

Fig. 10. Plots of Logarithmic Mutation Frequency at 10 mM *versus* Logarithmic Capacity Factor of Alkanesulfonates

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

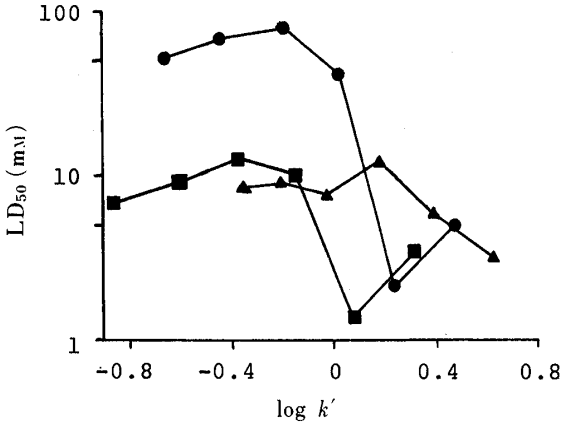

Fig. 11. Plots of Logarithmic LD_{50} *versus* Logarithmic Capacity Factor of Alkanesulfonates

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

Dependence of Mutagenicity and Toxicity on Capacity Factor

The reaction rate (k_{obs}) and chemoselectivity (S_{NBP})[1] have been found to be common in each series of non-substituted alkanesulfonates examined, *i.e.*, methyl, ethyl, and isopropyl esters, respectively. Therefore, it is expected that the biological data obtained here might be correlated with the partition properties, *i.e.*, capacity factor k'. log–log plots of MF at LD_{50}, MF at 10 mM and LD_{50} *versus* k' are shown in Figs. 9 to 11, respectively. No significant correlations are apparent among the sulfonate series. Attempts to find quantitative correlations among mutagenicity, LD_{50}, and capacity fractor were all unsuccessful.

In conclusion, it seems very difficult to find quantitative structure–activity relationships even among a structurally closely related series of mutagens, as seen in the present study. A suitable parameter of mutagenic potency might be necessary to obtain clear correlations with chemical and/or physicochemical properties, based on the molecular mechanism of mutation induction.

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