Table 3. Standard Calibration Curves for Nitrophenols Measured in GC/MS-SIM Mode With Flash Heater Derivatization Technique

Compound	Equation of calibration	Correlation coefficient
2-nitrophenol	$Y=(3.33\times10^{-2})X-0.107$	0.9989
4-nitrophenol	$Y=(6.25\times10^{-2})X+0.106$	0.9987
4-chloro-2-nitrophenol	$Y=(5.74\times10^{-2})X-0.115$	0.9991
2,4-dinitrophenol	$Y=(2.85\times10^{-2})X-0.112$	0.9994
2-methyl-4,6-dinitrophenol	$Y=(7.02\times10^{-2})X-0.229$	0.9988

OTMS derivatization was not greatly affected by these factors.

In general, the base peak for all nitrophenol-OTMS derivatives was $(M-15)^+$ ion whereas the intensities of molecular ions were weak. Therefore, $(M-15)^+$ ions should be used in selected ion monitoring mode for quantitative or confirmative purposes. Typical total ion chromatograms are shown in Figure 2 where extracts by C_{18}-bonded phase cartridge from the wasted water sample spiked with nitrophenols at 0.1 ppm were analyzed by GC/MS- in scan and SIM modes. The advantage of SIM over scan mode in the signal to noise ratio is quite obvious, as shown in Figure 2.

In order to check the linearity of the derivatization method, calibration curves in the concentration range of 15-200 ng/μl were constructed for each nitrophenol and calculated according to the method of least squares, relating y (the peak area ratio of the OTMS-derivative to the internal standard) to x (the concentration of the nitrophenol in ng/μl). Table 3 lists the data for the calibration curves which were linear over the concentration range for the five nitrophenols. The minimal detectable amount was about 0.5 ng for 4-nitrophenol and 2-methyl-4,6-dinitrophenol and about 1.5 ng for 2-nitrophenol, 4-chloro-2-nitrophenol and 2,4-dinitrophenol.

The flash heater derivatization technique can be successfully used for nitrophenolic compounds which are not easily derivatized with the conventional derivatization method. This method eliminates the hydrolysis and requires less time in forming TMS derivatives when the sample and derivatizing agent are injected directly into a gas chromatograph. The specificity and the sensitivity are improved by the use of a capillary column and selected ion monitoring mode. The use of SIM mode has provided a choice for the detection of several ions of interest in any analysis. The presence of one to two ions at specific retention time is presumptive evidence that specific nitrophenols are present. This makes the method suitable for identification of complex mixtures and for quantitative analysis in nanogram range.

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Nucleophilic Substitution Reaction and Elimination Reaction of 2-Phenylethyl Arenesulfonates

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The substitution reaction of 2-phenylethyl substituted (*X*)-benzenesulfonates with substituted (*Y*)-pyridines and elimination reaction of 2-substituted (*Z*)-phenylethyl (*X*)-substituted benzenesulfonate with *tert*-BuO^- are found to follow a concerted S_N2 and a concerted E2 mechanism, respectively, on the analysis of ρ_i by applying multiple Hammett equation.

Menschutkin-type reaction of substituted benzyl arenesulfonates[1] and phenacyl arenesulfonates[2] with *tert*-amines have been studied in detail using cross interaction terms of three moieties of substrate, leaving group, and nucleophile.

Although the effect of substituent on the reaction of 2-phenylethyl arenesulfonates[3,4] with pyridines have been studied previously, cross interaction terms mentioned above have not been studied. In the present paper, we report the interaction of 2-phenylethyl arenesulfonates with pyridines and apply the method to the elimination reaction of a series of 2-(*Z*)-phenylethyl *p*-substituted (*X*)-arenesulfonates[5] with potassium *tert*-butoxide in *tert*-butanol at 40℃.

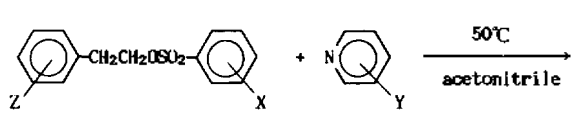
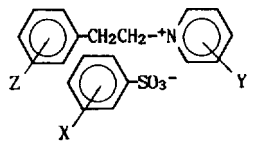


Table 1. Relative Rate Constants at 50℃ for the Reaction of 2-Phenylethyl Substituted (*X*)-Benzenesulfonates with Substituted (*Y*)-Pyridines in Acetonitrile (k_{XY}/k_{HH} value)

Y/*X*	*p*-CH_3	H	*p*-Br	*m*-NO_2	ρ_X
4-NH_2	8.29	11.0	18.8	168	1.52 (R=0.981)
3-CH_3	1.39	1.73	2.97	20.6	1.37 (R=0.982)
H	0.940	1.00*	1.72	9.22	1.18 (R=0.976)
3-$CONH_2$	0.729	0.770	1.33	7.12	1.18 (R=0.976)
ρ_Y	−1.18	−1.29	−1.29	−1.54	
(R=)	(0.979)	(0.979)	(0.979)	(0.975)	
β_Y	0.19	0.21	0.21	0.25	

*k_{HH}=11.0×10^{-4} (L/mol·min) at 50℃.



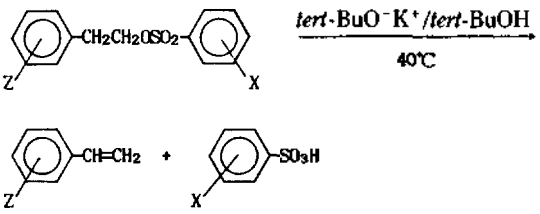
(1)

The reactions, carried out in a large exess of pyridine, followed a pseudo first-order kinetics,

$$k_{obs}=k_2\cdot[\text{pyridine}] \quad (2)$$

Second-order rate constants were obtained from the slope of the plot of k_{obs} against pyridine concentration according to Eq. (2).

As listed in Table 3, the rate of elimination reaction was measured by monitoring the appearance of the substituted styrene under the following Eq. (3) by Banger and his coworkers[5a]



(3)

As shown in Table 1, the ρ_X values gradually decrease in the order of 4-NH_2, 3-CH_3, H, and 3-$CONH_2$ pyridine, indicating that the partially negative charge on the oxygen atom in the sulfonate group becomes greater with the electron-donating ability of the substituents in the nucleophile; the cleavage of C···O bond proceeds further (the reduction of C···O bond order) in the transition state. The $|\rho_Y|$ and Brönsted β_Y values increase on going from electron-donating *p*-CH_3 to electron-withdrawing *m*-NO_2 in the substituent *X*. These results can be explained on the basis of increasing electron transfer in the transition state from the attacking *N* atom of pyridine to the reaction center.

From the change of ρ_X, $|\rho_Y|$ and β_Y values, it was shown that the increasing tendencies of bond breaking are 4-NH_2> 3-CH_3>H>3-$CONH_2$ pyridine and bond making has greatly increased from *p*-CH_3 to *m*-NO_2 in the leaving groups. The plot of ρ_X *vs.* σ_Y (substituent constant of pyridine *Y*) shows a linear relation with a slope of −0.35 as in Eq. (4).

$$\rho_X=-0.35\sigma_Y+1.304 \quad (r=0.977, \text{ except pyridine}) \quad (4)$$

Table 2. Relative Rate Constants, ρ and Brönsted β_Y Values for the Reaction of 2-Substituted (*Z*)-Phenethyl *m*-Nitrobenzenesulfonates with Substituted (*Y*)-Pyridines in Acetonitrile at 60℃ [4]

Y	ρ_Z	*Z*	ρ_Y	β_Y
4-NH_2	−0.008	*p*-MeO	−1.381	0.246
3-CH_3	−0.060	H	−1.638	0.259
H	−0.150	*p*-Br	−1.682	0.275
3-$CONH_2$	−0.222	*p*-NO_2	−1.740	0.284

and that of ρ_Y *vs.* σ_X (substituent constant of the leaving group *X*) is in Eq. (5),

$$\rho_Y=-0.38\sigma_X-1.251 \quad (r=0.969) \quad (5)$$

In previous papers[1,2] we examined the mechanistic significance of the Hammett-type cross interactions, ρ_{XY}, as substituent effect between *X* and *Y* in Eq. (6)

$$\log k_{XY}/k_{oo}=\rho_X\sigma_X+\rho_Y\sigma_Y+\rho_{XY}\sigma_X\sigma_Y \quad (6)$$

In the Eq. (6), if ρ_{XY} is constant the reaction proceeds with the same mechanism for all *X* and *Y*. The most important point is that the coefficient of the interaction term, $\sigma_X\sigma_Y$, is about the smae value, −0.35~−0.38, drived from either ρ_X or ρ_Y. This indicates the degree of concertedness in the N···C···O between the nucleophile and the leaving group, *i.e.* the bond making and bond breaking are synchronous in the S_N2 transition state within the substituents *X* and *Y*.

Table 2 was taken from the report of Yoh and his coworkers[4] and when the substituents *Y* and *Z* were changed with *X* being fixed to *m*-NO_2, the $|\rho_Y|$ and β_Y values at 60℃ increase gradually from electron-donating to electron-withdrawing substituents in the substrate where the value is larger than that of the reaction at 50℃. These results suggest that bond making increases in this order of substituents and more extensive at higher temperature, in the transition state.

The ρ_Z values are small and increase as the substituent moieties change from electron-donating to electron-withdrawing group in the nucleophile. For the case of pyridine having an electron-withdrawing substituent, the cation density of reaction center was increased because S_N1 character was increased by their weak nucleophilicity. But for the case of pyridine having an electron-donating substituent, the cation density of reaction center was nearly zero because the transition state has synchronous S_N2. The multiple Hammett interaction term, ρ_{YZ} was −0.26 when evaluated from Eq. (7),

$$\log k_{YZ}/k_{oo}=-1.55\sigma_Y-0.134\sigma_Z-0.26\sigma_Y\sigma_Z \quad (7)$$

The $|\rho_Y|$ value was greater than that of $|\rho_Z|$. This result shows that the bond making of C···N is the tight and the bond breaking of C···O is more loosened because the ρ_Z values have negative. Therefore the bond making and bond breaking develop each other and the transition state within the substituents *Y* and *Z* has synchronous S_N2.

And, we first attempted to apply the Eq. (6) to the elimination reaction of the same substrates, 2-substituted(*Z*)-phenylethyl substituted(*X*)-benzenesulfonates, with *tert*-BuO^- in *tert*-BuOH as shown in Eq. (3) and considered the interac-

Table 3. Hammett Reaction Constants ρ_X and ρ_Z for the Elimination from 2-Substituted (*Z*)-Phenyletyl Substituted (*X*)-Benzenesulfonates with *tert*-BuO^- in *tert*-Butyl alcohol at 40℃ [5a]

Z	ρ_X	*R*	*X*	ρ_Z	*R*
p-CH_3O	1.24± 0.02	0.999	*p*-CH_3	2.49± 0.03	0.998
p-CH_3	1.24± 0.05	0.997	H	2.50± 0.02	0.998
H	1.08± 0.03	0.999	*p*-Br	2.36± 0.02	0.999
m-CH_3O	1.06± 0.04	0.999	*p*-NO_2	2.03± 0.04	0.998
p-Cl	1.01± 0.04	0.996			
m-Cl	0.94± 0.02	0.997			

tion between *Z* and *X*.

Banger *et al.*[5a] reported that ρ_Z values decrese linearly with increase of the electron-withdrawing power of the leaving group *X* (see Table 3), which indicates the shift to transition state of less carbanion character. The ρ_X values become less positive as *Z* becomes more electron-withdrawing (Table 3), suggesting that increased C_β-H bond-breaking is accompanied by decreased C_α-O bond-breaking, and the shift to transition state with greater carbanion character.

We also examined the plot of ρ_Z *vs.* σ_X to give a linear correlation with a slope of -0.51 ($r=0.979$), and that of ρ_X *vs.* σ_Y to give the same slope of -0.50 ($r=0.979$). Therefore, within these series of substituents of *Z* and *X*, the rate constants of the elimination reaction are correlated with general Eq. (6), and it can be written as

$$\log k_{ZX}/k_{oo} = 2.45\sigma_Z - 0.51\sigma_Z\sigma_X + 1.12\sigma_X \quad (8)$$

In the presence of a base, 2-phenylethyl arensulfonates undergoes E2 elimination reaction (Eq. 3).[5a] The same interaction coefficient of -0.51 which derived from either ρ_Z and ρ_X, probably indicates that the deprotonation of C_β-H and C_α-O bond-breaking in these elimination reaction are concerted in the E2 transition state within the range of variations of substituents *Z* and *X*. From these results, it was possible to apply the multiple Hammett equation to the bimolecular elimination reaction (E2 reaction). In conclusion, cross interaction term, ρ_{XY}, ρ_{YZ}, and ρ_{ZX}, in the substituent effects are useful tool in elucidating not only an S_N2 reaction mechanism but also an E2 reaction.

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Photoinitiated Radical Cyclization of a Penicillin-derived 4-mercaptoazetidin-2-one

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Many researchers have attempted to prepare cephalosporins from readily available penicillins. The efficient methods of the penam-cepham conversion involve primarily interaction between an electrophilic sulfur or its equivalent groups and an appropriately situated isopropenyl double bond of the N-side chain in the azetidinone intermediates.[1]

Mercaptoazetidinones have been proposed as intermediates on penicillin biosynthesis,[2] but free mercapto compounds have not been directly used in the biosynthesis of β-lactam antibiotics.[3] Mercapto compounds can be prepared by simple hydrolysis of the corresponding thiazolinoazetidinones.[4,5] The intramolecular cyclization of mercaptan **1b** was reported by us.[6] Treatment of mercaptan **1b** with *t*-BuOCl yielded chloromethyl penam which was converted to 3-chlorocepham **2c** upon heating in DMSO. A similar result was obtained in the reaction with NBS or other positive halogen precursors.

Photoirradiation of disulfide **1a** in acetonitrile gave cepham **2a**, and other cephalosporins and penams.[7] The photoreaction was significantly concentration dependent; irradiation at lower concentration resulted in the predominant formation of cephalosporin derivatives.[8] Recently cepham **2d** was prepared from mercaptan **1d** *via* metal promoted thinyl radical cyclization.[9]

We now wish to report the photoreaction of a penicillin-derived 4-mercaptoazetidin-2-one (**1e**).[10] Free radical addition of thiols to unsaturated compounds has been reported.[11] The mercaptan **1d** was prepared by Baldwin's procedure.[4] Using 2,2'-azobisisobutyronitrile (AIBN) as an initiator, irradiation of mercaptan **1e** afforded cepham **2e** and small amount of few unknown compounds.

A solution of mercaptan **1e** (100 mg, 0.23 mmol) and AIBN (50 mg, 0.3 mmol) in ethyl acetate (10 mL) in a quartz vessel was degassed with nitrogen for 15 min and then irradiated with 2539 Å U.V. lamp at room temperature for 3 hr. After removal of the solvent the residue was chromatographed on a silica gel column with ethyl acetate-hexane (2 : 3) as an eluent.

The major component (50%, mp. 116-119°) was assigned structure **2e** based on spectroscopic evidence.[12] Any cyclized products were not given in the reaction without AIBN.[13]