

## Solvent Effect on the Reactions of DANSYL and BANSYL Chlorides with Substituted Pyridines

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Solvent effects on the reactions of DANSYL and BANSYL chlorides with substituted pyridines have been investigated using two parameters of Taft's solvatochromic correlation and four parameters of Kirkwood-Onsager, Parker, Marcus, Hildebrand equation. The acetonitrile molecules accelerate charge separation of the reactants and stabilize the transition state. The coefficient of the solvent parameters provide a good information to predict and to analyze the reaction mechanism. The nucleophilic substitution reaction of DANSYL and BANSYL chlorides with substituted pyridines are ruled by the contribution of the change in dipole moment term and polarity-polarizability term.

### Introduction

5-Dimethylamino-1-naphthalenesulfonyl (DANSYL) chloride and 5-dibutyl- amino-1-naphthalenesulfonyl (BANSYL) chloride are well known to use for identifying<sup>1</sup> the *N*-terminal amino acid in peptide or protein, as well as 1-fluoro-2, 4-dinitrobenzene and *N*-(2,4-dinitrophenyl)-1,4-phenylenediamine.<sup>2-3</sup>

However, the reactions of DANSYL chloride and *N*-terminal amino acid are influenced by solvent composition and solvent structure. DANSYL and BANSYL chlorides are very sensitive to protic solvents such as water, methanol, ethanol etc. and their reactions are fast even at room temperature.

In general, the nucleophilic substitution reactions of arenesulfonyl chlorides show a wide range of mechanisms like from dissociative  $S_N2$  to  $S_N1$ .<sup>4</sup> In sulfonyl transfer reactions, each mechanism reveals also variable transition state structures, e.g., from dissociative  $S_N2$  to  $S_N1$  with increasing nucleophilic solvent assistance.<sup>5</sup> The nucleophilic substitution reaction of DANSYL and BANSYL chlorides would be expected to have a wide range mechanisms from dissociative  $S_N2$  through concerted  $S_N2$  to associative  $S_N2$ . It accordingly is requested for a detailed mechanism of the reactions of DANSYL and BANSYL chlorides with nucleophiles in various solvent compositions to find a new information on solvent effect. In this report we have investigated the reactions of DANSYL and BANSYL chlorides with substituted pyridines in methanol (MeOH) and acetonitrile (MeCN) binary solvent mixture by means of conductometry.

### Experimental

**Materials.** DANSYL and BANSYL chlorides were obtained commercially from Tokyo Kasei Co. (TCI) and recrystallized from *n*-hexane/H<sub>2</sub>O. Pyridine (Py) and substituted pyridines [ $\alpha$ -picoline (2-Me-Py),  $\beta$ -picoline (3-Me-Py),  $\gamma$ -picoline (4-Me-Py) and 3-amino-pyridine (3-NH<sub>2</sub>-Py)] were

purchased from Aldrich Chemical Co. and purified. All nucleophiles and substrates were characterized and verified according to the literature values<sup>6</sup> and by characteristic IR and NMR spectra. MeOH and MeCN used in this experiments were spectroscopic grade and were purified by distillation from calcium hydride.

**Kinetics.** The rates were followed conductometrically<sup>7</sup> and the  $k_{obs}$  values were obtained by the Guggenheim method.<sup>8</sup>

### Results and Discussion

The second order rate constants,  $k_2$  for the reactions of DANSYL and BANSYL chlorides with substituted pyridines in MeOH-MeCN solvent mixtures are given in Tables 1 and 2.

The pseudo-first order rate constants are linearly correlated with the concentration of the nucleophile to obtain the second order rate constants,

$$k_{obs} = k_2 [Nu] \quad (1)$$

where [Nu] represents the concentration of substituted pyridines. Good second order kinetics are observed ( $r \geq$

**Table 1.** The Second Order Rate Constants ( $k_2 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$ ) for the Reactions of DANSYL Chloride with Substituted Pyridines in MeOH-MeCN Binary Solvent Mixtures at 0 °C

MeOH Content (v/v)%	Py	2-Me-Py	3-Me-Py	4-Me-Py	3-NH <sub>2</sub> -Py
100	4.44	0.628	6.68	10.8	23.4
90	5.81	0.675	7.25	12.2	32.6
80	6.37	0.795	8.76	19.4	50.5
70	8.24	0.951	9.89	22.4	62.7
60	10.2	1.01	13.1	30.9	89.8
50	11.5	1.54	17.7	44.8	113
30	17.7	2.07	30.7	85.7	213
10	35.8	3.44	58.4	179	-

**Table 2.** The Second Order Rate Constants ( $k_2 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$ ) for the Reactions of BANSYL Chloride with Substituted Pyridines in MeOH-MeCN Binary Solvent Mixtures at 0 °C

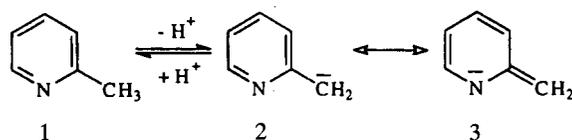
MeOH Content (v/v)%	Py	2-Me-Py	3-Me-Py	4-Me-Py	3-NH <sub>2</sub> -Py
100	2.67	—	3.81	5.99	18.4
90	3.46	0.432	5.12	9.25	29.8
80	4.74	0.576	7.58	13.1	46.5
70	5.92	0.740	8.10	16.6	59.4
60	7.22	0.993	9.16	20.7	71.8
50	8.96	1.24	12.9	25.8	93.1
30	15.2	1.44	28.6	73.4	172
10	23.7	1.67	57.1	175	—

0.9993) in all cases. The reactivity in the same solvent composition is in the order of 3-NH<sub>2</sub>-Py > 4-Me-Py > 3-Me-Py > Py > 2-Me-Py as shown in Tables 1 and 2. This trend would basically be caused by the basicity<sup>9</sup> of the substituted pyridines except for 2-Me-Py. Even though the *pK<sub>a</sub>* value of 2-Me-Py is higher than the one for Py or 3-Me-Py, the rate constants of 2-Me-Py in the same solvent mixture show very low. This discrepancy might be regarded as a base-catalyzed deprotonation<sup>10</sup> from -CH<sub>3</sub> of 2-Me-Py. It is known that the methyl group attached to the 2-position of 2-Me-Py is a potential carbanion source.<sup>11</sup> Deprotonation yields the carbanion (2 in Scheme 1) which may be stabilized by delocalization (2 and 3 in Scheme 1) of  $\pi$ -bond<sup>12</sup> as shown in Scheme 1.

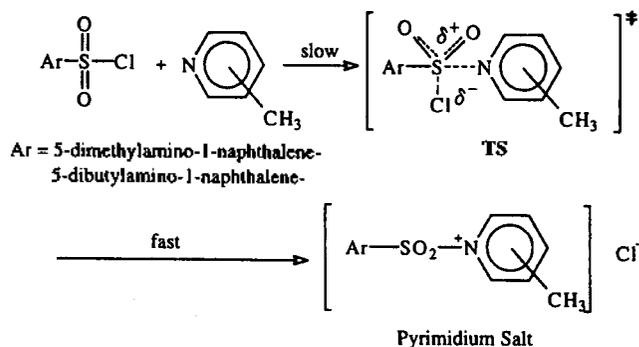
It has been known that the nucleophilic substitutions of aromatic acid halides with substituted pyridines undergo to form pyridinium salt easily with the order of 3-Me-Py > 2-Me-Py  $\approx$  4-Me-Py<sup>13</sup> as the correlation with the acidity of substituted pyridines. Our results as shown in Tables 1 and 2, however, are quite different from the mechanism of forming pyridinium salt since the rate constants,  $k_2$  of 4-Me-Py show higher than those of 3-Me-Py. The reactions of DANSYL and BANSYL chlorides with substituted pyridines seem to be affected by the effect of base-catalyzed deprotonation and the simultaneous formation of pyridinium salt.

It has been proposed that pyridinium salt formation in the nucleophilic substitution reactions of pyridines with acid halides might be induced in nonpolar media.<sup>14</sup> The tendency of the rate constants in Tables 1 and 2 is interpreted that the reaction proceeds through somewhat different route from the formation mechanism of pyridinium intermediate because our experiments have been carried out in the polar media. The rate constant becomes much higher increasing with the content of MeCN in the mixture of MeOH-MeCN. It is also consistent with the increase in dielectric constant of MeOH-MeCN solvent mixture.

The rates in low constant of MeOH are smaller than those in high content of MeOH. The enhancement of rate in high content of MeCN may be due to the rapid formation



**Scheme 1.**



**Scheme 2.**

of polar transition state (TS in Scheme 2) as shown in Scheme 2.

Our results are a great contrast to the rate trend of the reactions of 1-phenylethyl benzenesulfonates with substituted anilines that the rates are shown to decrease with increase in the MeCN content in the corresponding binary solvent mixtures.<sup>15</sup>

The enhancement of rate in high content of MeCN for the reactions of DANSYL and BANSYL chlorides with substituted pyridines may be due to acceleration of N-S bond formation in the transition state with ease in the more polar solvent composition as shown in Scheme 2. The formation of N-S bond in the transition state would be accelerated by the charge separation of the two reactants at high MeCN content. The MeCN molecules besieged with the reactants may accelerate the charge separation of the reactants and stabilize the transition state similar to the reactant structure. Pyridines are known as bases, however, pyridinium compounds are much less reactive toward positive species than the free base.<sup>16</sup>

Our results could be analyzed by the simple resonance theory.<sup>17</sup> The cationic pyridinium salt intermediate does not require more a partial positive charge since the nitrogen atom attracts the extra electrons based on the prediction of the simple resonance theory.<sup>17</sup> It is also consistent with electron-density calculation.<sup>17</sup> The enhancement of rate in high content of MeCN is due to that the MeCN solvent molecules act as a charge-separator with the above consequence. Reactive contribution of polarity in MeOH-MeCN binary solvent mixture on the transition state structure may be assessed by the *a/s* ratio of Taft's solvatochromic equation (2).<sup>18</sup>

$$\log k = A + a\alpha + b\beta + s\pi^* \quad (2)$$

where *a*, *b* and *s* are susceptibilities of the parameters for hydrogen bond donor (HBD) acidity ( $\alpha$ ), hydrogen bond acceptor (HBA) basicity ( $\beta$ ) and polarity-polarizability ( $\pi^*$ ) in the transition state. *A* is a constant in equation (2). The hydrogen bond acceptor basicity contribution of solvent ( $b\beta$ ) has been found to be negligible for pyridine.<sup>18</sup>

The solvatochromic parameters, *a* and *s*, with *a/s* values are shown in Table 3.

The correlation coefficients (*r*) determined by multiple regression analysis show to be satisfactory in all cases. Relatively small values of *a/s* (<1) indicate that the effect of polarity-polarizability ( $\pi^*$ ) is more contributed than that of HBD acidity of solvents. The polarity-polarizability ( $\pi^*$ ) of

**Table 3.** Solvatochromic Correlation for the Reactions of DANSYL and BANSYL Chlorides with Substituted Pyridines in MeOH-MeCN Binary Solvent Mixtures

	Py	2-Me-Py	3-Me-Py	4-Me-Py	3-NH <sub>2</sub> -Py	
DANSYL Chloride	A	-10.8	-11.4	-9.82	-8.47	-7.94
	a	-2.44	-2.23	-2.99	-3.24	-3.59
	s	-3.61	-3.46	-4.80	-4.48	-5.29
	a/s	0.683	0.647	0.624	0.728	0.686
	r <sup>†</sup>	0.998	0.963	0.983	0.978	0.957
BANSYL Chloride	A	-7.98	-8.57	-7.42	-7.28	-6.94
	a	-2.06	-0.47	-8.14	-3.97	-2.17
	s	-2.21	-1.85	-16.2	-5.87	-3.64
	a/s	0.936	0.235	0.051	0.682	0.604
	r <sup>†</sup>	0.989	0.983	0.953	0.988	0.981

<sup>†</sup>Correlation coefficients.

the solvent is proved to enhance the charge separation in the nucleophilic substitution reaction.<sup>19</sup> According to our results the contribution of polarity-polarizability ( $\pi^*$ ) seems to reflect on the degree of bond formation between the S-atom and N-atom and the degree of bond cleavage between the S-atom and Cl-atom at the transition state of the reaction of DANSYL and BANSYL chlorides with substituted pyridines.

In an effort to provide more accurate solvent effects, a four parameter equation is derived by Beak.<sup>20</sup> The correlation with four parameter gives:

$$\ln k = p(\epsilon - 1)/(2\epsilon + 1) + a\alpha' + b\beta' + v\delta^2 \quad (3)$$

where  $(\epsilon - 1)/(2\epsilon + 1)$  is the Kirkwood-Onsager<sup>21</sup> function.  $\alpha'$  and  $\beta'$  values are derived from single ion transference data which have been measured by Parker<sup>22</sup> and Marcus.<sup>23</sup> And  $\alpha'$  and  $\beta'$  represent the specific donation ability of a hydrogen bond and the specific hydrogen bond accepting ability of the solvent, respectively.  $\delta^2$  represents a volume difference between ground state and transition state.<sup>24</sup>  $\delta^2$  is known to the solvent cohesive energy density, as defined by Hildebrand<sup>24</sup> and it plays an important correlator of the stability of the solute in a wide range of solvents. This equation is called the KOMPHE equation (3) quoted after Kirkwood, Onsager, Marcus, Parker and Hildebrand. In order to quantify solvent effects over the entire range of solvent parameters the rates of the reactions are applied to KOMPHE equation (3). The four calculated parameters [ $(\epsilon - 1)/(2\epsilon + 1)$ ,  $\alpha'$ ,  $\beta'$  and  $\delta^2$ ] in MeOH-MeCN binary solvent mixture are given Table 4. The  $\alpha'$  value is derived from the following correlation equation.

$$\alpha = 5.28\alpha' - 0.15 \quad (4)$$

The equation (4) has been generalized by Gajewski *et al.*<sup>25</sup> Where the  $\alpha$  is the solvent hydrogen bond donating acidity in Taft's equation.<sup>18</sup> The  $\beta'$  and  $\delta^2$  values are obtained from the equation (5).<sup>25</sup>

$$\ln k = 18.9(\epsilon - 1)/(2\epsilon + 1) + 52.8\alpha' - 0.76\beta' + 10.1\delta^2 - 15.4 \quad (5)$$

Where  $k$  is the rate constant of the *tert*-butyl chloride solvolysis. The  $\beta'$  and  $\delta^2$  values can be obtained by the regression analysis after substituted the values of  $k$ ,  $\alpha'$  and  $(\epsilon - 1)/(2\epsilon + 1)$  for the equation (5). The  $k$  and  $(\epsilon - 1)/(2\epsilon + 1)$

**Table 4.** Solvent Parameters for the Kirkwood, Onsager, Parker, Marcus, Hildebrand Equation in MeOH-MeCN Binary Solvent Mixture

Solvent Composition (v/v)%	$\epsilon - 1/2\epsilon + 1$	$\alpha'$	$\beta'$	$\delta^2$
100 MeOH	0.477	0.181	0.130	0.346
90 MeOH	0.477	0.168	0.131	0.323
80 MeOH	0.477	0.147	0.131	0.301
70 MeOH	0.478	0.122	0.132	0.292
60 MeOH	0.478	0.118	0.133	0.285
50 MeOH	0.478	0.114	0.133	0.272
40 MeOH	0.479	0.107	0.134	0.266
30 MeOH	0.479	0.0894	0.134	0.254
20 MeOH	0.479	0.0715	0.135	0.248
10 MeOH	0.479	0.0692	0.135	0.241
100 MeCN	0.480	0.0653	0.136	0.233

values are quoted from the reported data<sup>26</sup> and then  $\alpha'$  value is calculated from the equation (4).

The coefficients,  $p$ ,  $a$ ,  $b$  and  $v$  are correlated using the four parameters in the Table 4 and are given Table 5.

It is important to note that the coefficient of the Kirkwood-Onsager function,  $p$  and the coefficient of  $\beta'$ ,  $b$  are highly compared with other two coefficients ( $a$  and  $v$ ) as shown in Table 5. The coefficient of the Kirkwood-Onsager function,  $p$  is related to the square of dipole moment change from ground state to transition state divided by the cube of the solvent cavity.<sup>20</sup> This suggests that the dipole moment change contributes to accelerate bond cleavage between the S-atom and Cl-atom and bond formation between the S-atom and N-atom at the transition state for the reactions of DANSYL and BANSYL chlorides.

The coefficient of the  $\beta'$  term is substantial and it represents some stabilization of the ground state by electron donors.<sup>19</sup> Therefore the stabilization of the ground state seems to be important that the hydrogen bond accepting ability contributes to move the transition state in the polar solvent.

The present results indicate that the effect of solvents on the reactions of DANSYL and BANSYL chlorides with substituted pyridines is ruled by the contribution of polarity-po-

**Table 5.** Coefficients Calculated from the Kirkwood, Onsager, Parker, Marcus, Hildebrand Equation for the Reactions of DANSYL and BANSYL Chlorides with Substituted Pyridines in MeOH-MeCN Binary Solvent Mixtures

	Py	2-Me-Py	3-Me-Py	4-Me-Py	3-NH <sub>2</sub> -Py	
DANSYL Chloride	p	-3.25	-3.78	-3.21	-3.19	-3.05
	a	1.92	1.95	1.90	1.88	1.74
	b	-2.78	-2.92	-2.72	-2.69	-2.61
	v	0.0833	0.0852	0.0794	0.0752	0.0735
	r <sup>†</sup>	0.995	0.994	0.957	0.986	0.943
BANSYL Chloride	p	-2.98	-3.11	-2.94	-2.87	-2.79
	a	0.982	1.547	0.942	0.930	0.841
	b	-1.95	-2.13	-1.87	-1.82	-1.69
	v	0.0462	0.0381	0.0325	0.0302	0.0287
	r <sup>†</sup>	0.991	0.983	0.938	0.941	0.985

<sup>†</sup>Correlation coefficients.

larizability based on Taft's solvatochromic equation and is also dependent on the term of the Kirkwood-Onsager function.

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