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Aminolysis of Y- Substituted Phenyl Benzenesulfonates in MeCN: Effect of Medium on Reactivity and Reaction Mechanism†

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Second-order rate constants for nucleophilic substitution reactions of 2,4-dinitrophenyl benzenesulfonate **1a** with a series of alicyclic secondary amines in MeCN have been measured spectrophotometrically and compared with those reported previously for the corresponding reactions performed in aqueous medium to investigate the effect of medium on reactivity and reaction mechanism. The amines employed in this study are found to be more reactive in the aprotic solvent than in H_2O. The reactions of **1a** in MeCN result in a linear Brønsted-type plot with $\beta_{nuc} = 0.58$, which contrasts to the curved Brønsted-type plot reported previously for the corresponding reactions performed in the aqueous medium (i.e., $\beta_2 = 0.86$ and $\beta_1 = 0.38$). Accordingly, it has been concluded that the reaction mechanism changes from a stepwise mechanism to a concerted pathway upon changing the medium from H_2O to MeCN. Reactions of Y-substituted phenyl benzenesulfonates **1a-c** with piperidine in MeCN result in a linear Brønsted-type plot with $\beta_{lg} = -1.31$, indicating that expulsion of the leaving group is significantly more advanced than bond formation in the transition state. The trigonal bipyramidal intermediate ($TBPy^{\pm}$) proposed previously for the reactions in H_2O would be highly unstable in MeCN due to strong repulsion between the negative charge in $TBPy^{\pm}$ and the negative dipole end of MeCN. Thus, destabilization of $TBPy^{\pm}$ in MeCN has been concluded to change the reaction mechanism from a stepwise mechanism to a concerted pathway.

Key Words : Aminolysis, Aryl benzoates, Reaction mechanism, Medium effect, Brønsted-type plot

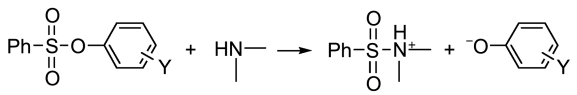
Introduction

Medium effects on reactivity and reaction mechanism have extensively been investigated.[1-10] It is well known that rate of solvolysis increases with increasing solvent polarity and/or solvent nucleophilicity.[4-6] Besides, the effect of medium on rates of nucleophilic substitution (S_N) reactions is known to be highly dependent on the nature of reactants, e.g., significant rate acceleration for reactions involving anionic nucleophiles while a decrease in rate for reactions between neutral molecules upon changing reaction medium from H_2O to dipolar aprotic solvents (e.g., DMSO and MeCN).[1-10]

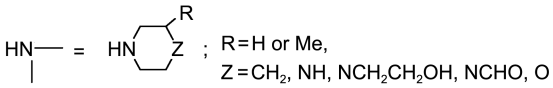
We have shown that solvent effect on reactivity is significant for S_N reactions of 4-nitrophenyl acetate with anionic nucleophiles (e.g., butan-2,3-dione monoximate Ox^- and 4-chlorophenoxide 4-$ClPhO^-$) in DMSO/H_2O mixtures of varying compositions.[7] We found that the ratio of their second-order rate constants (i.e., $k_{Ox^-}/k_{4\text{-}ClPhO^-}$) increases as the DMSO content in the medium increases up to near 50 mol % and then decreases thereafter.[7] Similar results have been obtained for the corresponding reactions of aryl acetates,[8] 4-nitrophenyl benzoate,[9] 4-nitrophenyl diphenylphosphinate,[10a] and 4-nitrophenyl benzenesulfonate,[10b] and related compouns.[10c-f]

However, the effect of medium on aminolysis has not well been understood. Aminolysis of esters in aqueous medium has generally been reported to proceed through a stepwise mechanism, in which the rate-determining step (RDS) is dependent on the basicity of the incoming amine and the leaving group.[11-23] Nonlinear Brønsted-type plots often reported for aminolyses of esters possessing a good leaving group (e.g., 2, 4-dinitrophenoxide) have been suggested as evidence for a change in RDS.[11-23] In fact, we have concluded that aminolysis of 2,4-dinitrophenyl bezenesulfonate **1a** in H_2O proceeds through a stepwise mechanism with a change in RDS on the basis of a nonlinear Brønsted-type plot.[23g]

We have extended our study to the reactions of Y-substituted phenyl benzenesulfonates **1a-c** with a series of alicyclic secondary amines in MeCN (Scheme 1). The kinetic data have been compared with those reported previously for the corresponding reactions performed in the aqueous medium to study the effect of medium on reactivity and reaction mechanism.



Y = 2,4-$(NO_2)_2$ (**1a**), 3,4-$(NO_2)_2$ (**1b**), 4-NO_2 (**1c**).



Scheme 1

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.

Results and Discussion

All reactions obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were determined from the equation ln ($A_\infty - A_t$) = $-k_{obsd}t + C$. The plots of k_{obsd} *vs.* amine concentration were linear passing through the origin, indicating that general base catalysis by a second amine molecule is absent. Thus, the rate law is given by eq (1), in which [S] and [NH] represent the concentration of the substrate and amine nucleophile, respectively. The second-order rate constants (k_N) were determined from the slope of linear plots of k_{obsd} *vs.* [NH] and are summarized in Tables 1 and 2. From replicate runs, it was estimated that the uncertainty in the k_N values is less than ± 3 %.

$$\text{Rate} = k_{obsd}[S], \text{ where } k_{obsd} = k_N[NH] \quad (1)$$

Effect of Medium on Reactivity. As shown in Table 1, amines are more reactive in MeCN than in the aqueous medium. It is well known that the effect of medium on reactivity is strongly dependent on the nature of reactants.[1-10] Anionic nucleophiles are stabilized in H_2O through H-bonding interaction but would be destabilized in dipolar aprotic solvents such as MeCN and DMSO due to strong repulsion between the anion and the negative dipole end of the aprotic solvents. Accordingly, nucleophilic substitution reactions involving anionic nucleophiles have often been reported to exhibit a significant increase in reactivity, e.g., rate enhancement up to 10^6 times in the reactions of 4-nitrophenyl acetate with OH^- upon changing medium from H_2O to DMSO.[2] On the contrary, reactions between neutral species, which proceed through a partially charged transition state (TS), have been reported to exhibit a decrease in reactivity due to destabilization of the charged TS in aprotic solvents.[1-3] Thus, the fact that amines are more reactive in MeCN than in the aqueous solution is quite interesting.

Table 1 shows that the second-order rate constant k_N decreases as the amine basicity decreases, e.g., from 16.7 $M^{-1}s^{-1}$ to 3.05 and 1.01 $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of amines decreases from 18.8 to 17.6 and 16.6, in turn. A similar result is demonstrated for the corresponding reaction run in H_2O containing 20 mol % DMSO. It is noted that the amines are 7 ~ 9 pK_a units more basic in MeCN than in the aqueous medium. Furthermore, our calorimetric study has shown that piperidine and morpholine are 18.1 ~ 20.0 kJ/mol less solvated in MeCN containing 10 mol % H_2O than in pure H_2O.[25] Thus, one might attribute the enhanced reactivity of the amines in MeCN to the enhanced amine basicity as well as to desolvation of the amines in the dipolar aprotic solvent.

Effect of Medium on Reaction Mechanism. However, we propose that the nature of reaction mechanism is also responsible for the enhanced reactivity of these amines in MeCN. To investigate the reaction mechanism, Brønsted-type plots have been constructed in Figures 1(a) and 1(b) for the reactions of **1a** with alicyclic secondary amines in MeCN and in H_2O containing 20 mol % DMSO, respectively.

As shown in Figures 1(a) and 1(b), the Brønsted-type plot for the reactions performed in MeCN (a) is linear with β_{nuc} = 0.58 when k_N and pK_a values are statistically corrected using *p* and *q* (i.e., *p* = 2 and *q* = 1 except *q* = 2 for piperazine),[26] while the one for the corresponding reactions in the aqueous medium (b) exhibits downward curvature (i.e., β_2 = 0.86, β_1 =0.38). The linear Brønsted-type plot found for the reactions in MeCN is interesting. Because aminolysis or pyridinolysis of carboxylic esters possessing a good leaving group (e.g., 2,4-dinitrophenoxide) has often been reported to result in a curved Brønsted-type plot, which has been taken as evidence for a change in the RDS.[11-23] In fact, aminolysis of **1a** performed in the aqueous medium has been concluded to proceed through a stepwise mechanism with a change in the RDS on the basis of the nonlinear Brønsted-type plot shown in Figure 1(b).[23g] A similar conclusion has been drawn for aminolysis of 2,4-dinitrophenyl benzoate, *S*-4-nitrophenyl thiobenzoate and 4-nitrophenyl phenyl thionocarbonate, and pyridinolysis of *O*-4-dinitrophenyl thionobenzoate, *O*-2,4-dinitrophenyl thionobenzoate and phenyl carbonate on the basis of nonlinear Brønsted-type plots.[23]

A linear Brønsted-type plot with β_{nuc} = 0.5 ± 0.1 is typical for nucleophilic substitution reactions reported previously to proceed through a concerted mechanism. In fact, we have concluded that aminolysis of organophosphorus esters (e.g., 2,4-dinitrophenyl diphenylphosphinate[23f] and diphenylpho sphinothioate[23d]) proceeds through a concerted mechanism on the basis of linear Brønsted-type plots with β_{nuc} = 0.38 ~ 0.52. Similarly, Castro *et al.* have concluded that pyridinolysis of

Table 1. Summary of second-order rate constants (k_N) for reactions of 2,4-dinitrophenyl benzenesulfonate **1a** with alicyclic secondary amines in MeCN and in H_2O containing 20 mol % DMSO at 25.0 ± 0.1 °C

entry	amine	in MeCN		in H_2O^a	
		pK_a^b	k_N/ $M^{-1}s^{-1}$	pK_a	k_N/ $M^{-1}s^{-1}$
1	piperidine	18.8	16.7	11.02	11.1
2	3-methylpiperidine	18.6	15.3	10.80	10.5
3	piperazine	18.5	15.8	9.85	5.04
4	1-(2-hydroxyethyl)piperazine	17.6	3.05	9.38	-
5	1-formylpiperazine	17.0	1.60	7.98	0.211
6	morpholine	16.6	1.01	8.65	0.853
7	piperazinium ion	-	-	5.95	0.0119

[a]The data in H_2O have been taken from ref. 23g. [b]The pK_a data in MeCN were taken from ref. 24.

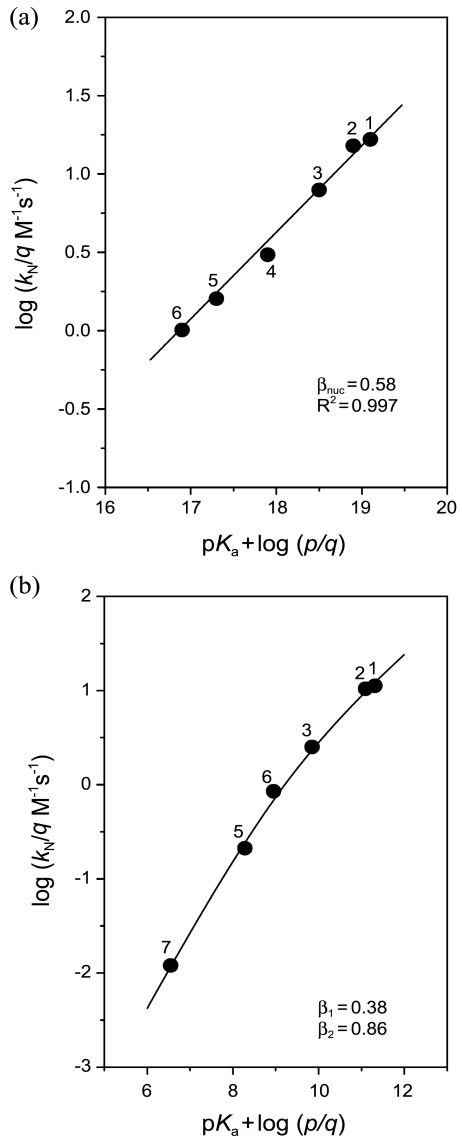


Figure 1. Brønsted-type plots for reactions of 2,4-dinitrophenyl benzenesulfonate **1a** with alicyclic secondary amines in MeCN (a) and in H_2O containing 20 mol % DMSO (b) at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

aryl 2,4,6-trinitrophenyl carbonates and phenolysis of *S*-4-methylphenyl 4-nitrophenyl thiocarbonate proceed through a concerted mechanism on the basis of linear Brønsted-type plots with β_{nuc} = 0.53 ~ 0.56[12c] and β_{nuc} = 0.62,[12b] respectively. Thus, one can conclude that the aminolysis of **1a** performed in MeCN proceeds through a concerted mechanism on the basis of the linear Brønsted-type plot with β_{nuc} = 0.58.

Effect of Leaving-group Basicity on Reactivity. To investigate the effect of leaving-group basicity on reactivity, reactions of Y-substituted phenyl benzenesulfonates **1a-c** with piperidine have been performed in MeCN. As shown in Table 2, the k_N value decreases significantly as the leaving aryloxide becomes more basic. It is also noted that phenols are over 12 pK_a units weaker acids in MeCN than in H_2O. Clearly, the increase in pK_a upon the medium change from H_2O to MeCN is more significant for phenols than for amines. This supports the preceding argument that the enhanced amine basicity in MeCN is not solely responsible for the increased k_N in the aprotic solvent.

Table 2. Summary of second-order rate constants (k_N) for reactions of Y-substituted phenyl benzenesulfonates (**1a-c**) with piperidine in MeCN at 25.0 ± 0.1 °C [a]

entry	Y	pK_a	k_N/ $M^{-1}s^{-1}$
1a	2,4-$(NO_2)_2$	16.7	16.7
1b	3,4-$(NO_2)_2$	18.7	9.99×10^{-2}
1c	4-NO_2	20.9	5.28×10^{-5}

[a]The pK_a values of Y-substituted phenols in MeCN were calculated from the equation p$K_a^{\text{in MeCN}}$ = 1.65 p$K_a^{\text{in } H_2O}$ + 9.8, which was derived from the pK_a data in ref. 27.

In Figure 2 is illustrated the effect of leaving-group basicity on reactivity. The Brønsted-type plot for the reactions of **1a-c** with piperidine is linear with β_{lg} = −1.31. Such a linear Brønsted-type plot with a large negative slope suggests that expulsion of the leaving group in the TS is significantly advanced. Thus, one might suggest that the aminolysis of **1a** in MeCN proceeds through TS_1, in which expulsion of the leaving group is significantly more advanced than the bond formation between the amine and the electrophilic center on the basis of the fact that β_{nuc} = 0.56 and β_{lg} = –1.31.

As mentioned above, aminolysis of **1a** in the aqueous medium has been reported to proceed through a stepwise mechanism with a trigonal bipyramidal intermediate $TBPy^{\pm}$,[23g] in which the RDS is dependent on the basicity of the incoming amine. The zwitterionic $TBPy^{\pm}$ would be stabilized in H_2O through H-bonding interaction. However, such H-bonding interaction is absent in MeCN. Furthermore, the negative charge developed on the oxygen atoms of the sulfonyl moiety in $TBPy^{\pm}$ would experience strong repulsion from the negative dipole end of MeCN. Thus, one might expect that the intermediate $TBPy^{\pm}$ would be highly

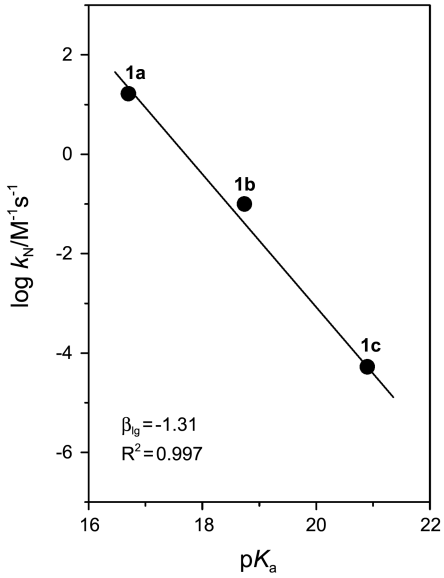
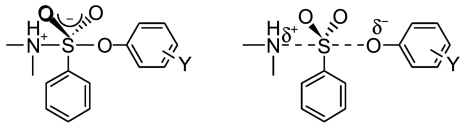


Figure 2. Brønsted-type plot for reactions of Y-substituted phenyl benzenesulfonates **1a-c** with piperidine in MeCN at 25.0 ± 0.1 °C. The identity of points is given in Table 2.



$TBPy^{\pm}$ TS_1

unstable in the dipolar aprotic solvent.

On the other hand, the negative charge, developed partially on the oxygen atom of the leaving aryloxide in TS_1, would be delocalized on the NO_2 group through resonance interaction. Thus, the charge dispersed TS_1 would be less unstable than the charge localized $TBPy^{\pm}$ in MeCN. This idea can explain why the aminolysis of **1a** in MeCN proceed through a concerted mechanism with a TS structure similar to TS_1.

Conclusions

The current study has allowed us to conclude the following: (1) Amines are more reactive in MeCN than in H_2O. (2) The aminolysis of **1a** in MeCN results in a linear Brønsted-type plot with $\beta_{nuc} = 0.58$, which contrasts to the curved Brønsted-type plot reported for the corresponding reactions performed in the aqueous medium (i.e., $\beta_2 = 0.86$ and $\beta_1 = 0.38$). (3) The reaction mechanism of aminolysis of **1a** changes from a stepwise mechanism to a concerted pathway upon changing the medium from H_2O to MeCN. (4) Reactions of **1a-c** with piperidine in MeCN results in a linear Brønsted-type plot with $\beta_{lg} = -1.31$, indicating that expulsion of the leaving group in the TS is significantly advanced. (5) TS_1, in which the partial negative charge is delocalized through resonance interaction, is less unstable than $TBPy^{\pm}$ in MeCN due to a decrease in the electronic repulsion.

Experimental Section

Materials. Compounds **1a-c** were readily prepared from the reaction of benzenesulfonyl chloride with the respective Y-substituted phenol in anhydrous ether in the presence of triethylamine as reported previously.[23g] Their purity was confirmed from melting points and ^{1}H NMR characteristics. The amines and other chemicals used were of the highest quality available. MeCN was distilled over P_2O_5 and stored under nitrogen.

Kinetics. The kinetic study was performed using a UV-vis spectrophotometer equipped with a constant temperature circulating bath to keep the reaction temperature at 25.0 ± 0.1 °C. All the reactions were carried out under pseudo-first-order conditions in which the amine concentration was at least 20 times greater than the substrate concentration. Typically, the reaction was initiated by adding 5 μL of a 0.01 M of substrate stock solution in MeCN by a 10 μL syringe to a 10 mm UV cell containing 2.50 mL of the reaction medium and amine. The reactions were followed by monitoring appearance of Y-substituted phenoxide.

Product Analysis. Y-Substituted phenoxide was liberated and identified as one of the reaction products by comparison of the UV-vis spectra after completing the reactions with those of authentic samples under the same kinetic conditions.

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