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Kinetics and Mechanism of the Benzylaminolysis of *O,O*-Diethyl *S*-Aryl Phosphorothioates in Dimethyl Sulfoxide

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The reactions of *O,O*-diethyl Z-*S*-aryl phosphorothioates with X-benzylamines are kinetically investigated in dimethyl sulfoxide at 85.0 °C. The Hammett (log k_2 *vs* σ_X) and Brönsted [log k_2 *vs* pK_a(X)] plots are biphasic concave downwards for substituent X variations in the nucleophiles with a break point at X = H. The signs of the cross-interaction constants (ρ_{XZ}) are positive for both the strongly and weakly basic nucleophiles. Considerably great magnitude of ρ_{XZ} (= 6.56) value is observed with the weakly basic nucleophiles, while ρ_{XZ} = 0.91 with the strongly basic nucleophiles. Proposed reaction mechanism is a stepwise process with a rate-limiting leaving group expulsion from the intermediate involving a backside nucleophilic attack with the strongly basic nucleophiles and a frontside attack with the weakly basic nucleophiles. The kinetic results are compared with those of the benzylaminolysis of *O,O*-diphenyl Z-*S*-aryl phosphorothioates.

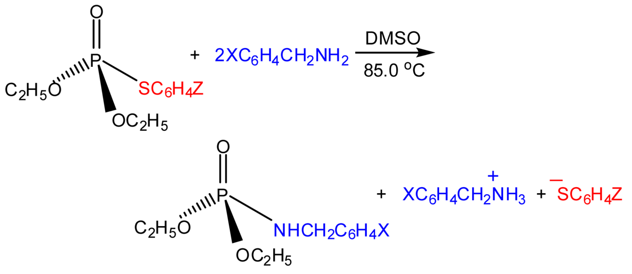
Key Words : Phosphoryl transfer reaction, Benzylaminolysis, *O,O*-Diethyl Z-*S*-aryl phosphorothioate, Cross-interaction constant, Concave downward free energy correlation

Introduction

The various phosphoryl and thiophosphoryl transfer reactions have been studied kinetically by this lab: anilinolysis,[1] pyridinolysis,[2] benzylaminolysis,[3] and theoretical studies.[4] Continuing the study followed by the benzylaminolysis of *O,O*-diphenyl Z-*S*-aryl phosphorothioates [**2:** $(PhO)_2P(=O)$-SC_6H_4Z], the nucleophilic substitution reactions of *O,O*-diethyl Z-*S*-aryl phosphorothioates [**1:** $(EtO)_2P(=O)SC_6H_4Z$] with X-benzylamines have been investigated kinetically in DMSO at 85.0 ± 0.1 °C (Scheme 1) to gain further information into the aminolysis mechanism and stereochemistry on the basis of the sign and magnitude of the cross-interaction constants (CICs, ρ_{XZ}).

Results and Discussion

The pseudo-first-order rate constants observed (k_{obsd}) for all reactions obeyed eq. (1) with negligible k_0 (= 0) in DMSO. The clean second-order rate constants (k_2) obtained as the slope of the plot of k_{obsd} against benzylamine concentration are summarized in Table 1 together with selectivity parameters (ρ_X, β_X, ρ_Z, and ρ_{XZ}). The second-order rate constants were determined for at least five concentrations of benzylamines. The linear plots of eq. (1) suggest that there is no base-catalysis or noticeable side reactions and that the overall reaction is described by Scheme 1.



X = 4-MeO, 4-Me, H, 4-Cl, 3-Cl; Z = 4-MeO, 4-Me, H, 4-Cl

Scheme 1. The studied reaction system.

$$k_{obsd} = k_0 + k_2\,[XC_6H_4CH_2NH_2] \qquad (1)$$

The Brönsted β_X value was obtained by correlating log k_2(DMSO) with pK_a(H_2O). The β_X values listed in Table 1 seem to be less reliable since the pK_a values used are not those determined in DMSO, but rather in water. Using the pK_a values for the anilinium ions determined in DMSO, an approximate straight line is obtained when they are plotted against those determined in water.[5] Spillane and coworkers reported that the β_X value for the reactions of *N*-phenyl sulfamoyl chloride ($PhNHSO_2Cl$) with X-anilines in DMSO is similar when determined using the pK_a values of anilines measured in water (β_X = 0.69) and DMSO (β_X = 0.62).[6] Accordingly, it may be inferred that the β_X values in Table 1 are considered to indicate the trends of changes with substituents, but not far from real values.

The rate increases with a more electron-donating substituent X in the nucleophile and a more electron-withdrawing substituent Z in the leaving group, which is consistent with a typical nucleophilic substitution reaction with positive charge development at the nucleophilic nitrogen atom ($\rho_X < 0$ and $\beta_X > 0$) and negative charge development at the thiophenoxy sulfur atom ($\rho_Z > 0$) in the transition state (TS). However, the Hammett (Fig. 1: log k_2 *vs* σ_X) and Brönsted [Fig. 2: log k_2 *vs* pK_a(X)] plots are biphasic concave downwards for substituent X variations in the nucleophiles with a break point at X = H, while the Hammett plots (log k_2 *vs* σ_Z) for substituent Z variation in the leaving

Table 1. Second-Order Rate Constants ($k_2 \times 10^4$/M^{-1}s^{-1}) and Selectivity Parameters[a] of the Reactions of **1** (*O,O*-Diethyl Z-*S*-Aryl Phosphorothioates) with X-Benzylamines in DMSO at 85.0 °C

X \ Z	4-MeO	4-Me	H	4-Cl	ρ_Z
4-MeO	2.01 ± 0.01	3.49 ± 0.01	5.14 ± 0.01	7.42 ± 0.01	1.07 ± 0.08
4-Me	1.55 ± 0.01	3.14 ± 0.01	4.86 ± 0.01	7.32 ± 0.04	1.26 ± 0.11
H	1.07 ± 0.01	2.08 ± 0.01	3.87 ± 0.01	5.27 ± 0.01	1.33 ± 0.12
4-Cl	0.133 ± 0.001	0.532 ± 0.001	1.63 ± 0.01	3.63 ± 0.03	2.73 ± 0.22
3-Cl	0.0280 ± 0.0001	0.217 ± 0.001	0.933 ± 0.001	2.84 ± 0.01	3.77 ± 0.32
$-\rho_X$[b]	1.01 ± 0.01	0.86 ± 0.03	0.47 ± 0.02	0.58 ± 0.04	ρ_{XZ} = 0.91 ± 0.09[b]
β_X[b]	1.86 ± 0.08	1.41 ± 0.10	0.77 ± 0.06	0.87 ± 0.09	
$-\rho_X$[c]	4.24 ± 0.06	2.65 ± 0.02	1.67 ± 0.01	0.72 ± 0.01	ρ_{XZ} = 6.56 ± 0.21[c]
β_X[c]	4.21 ± 0.10	2.63 ± 0.04	1.66 ± 0.02	0.72 ± 0.01	

[a] The σ values were taken from Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. The pK_a values of the X-benzylammonium ions in water were taken from Blackwell, L. F.; Fischer, A. Miller, I. J.; Topsom, R. D.; Vaughan, J. *J. Chem. Soc.* **1964**, 3588. [b] X = (4-MeO, 4-Me, H). [c] X = (H, 4-Cl, 3-Cl)

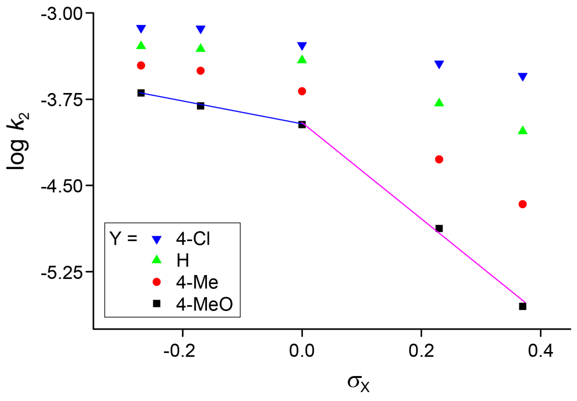


Figure 1. The Hammett plots (log k_2 *vs* σ_X) of the reactions of **1** (*O,O*-diethyl Z-*S*-aryl phosphorothioates) with X-benzylamines in DMSO at 85.0 °C.

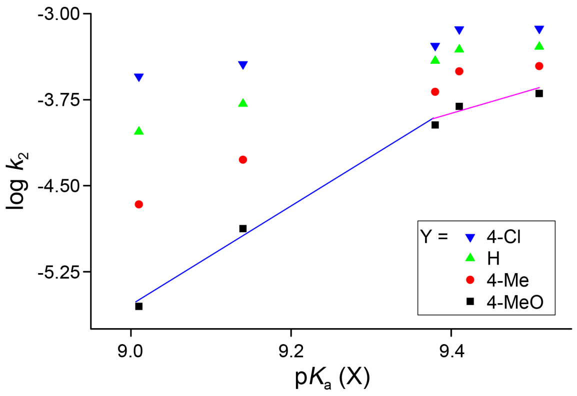


Figure 2. The Brönsted plots [log k_2 *vs* pK_a(X)] of the reactions of **1** (*O,O*-diethyl Z-*S*-aryl phosphorothioates) with X-benzylamines in DMSO at 85.0 °C.

group are linear. The magnitudes of ρ_X (= −0.72 to −4.24) and β_X (= 0.72-4.21) values for the weakly basic benzylamines (X = H, 4-Cl, 3-Cl) are greater than those (ρ_X = −0.47 to −1.01 and β_X = 0.77-1.86) for the strongly basic benzylamines (X = 4-MeO, 4-Me, H). The signs of the cross-interaction constants are positive for both the strongly (ρ_{XZ} = +0.91) and weakly basic nucleophiles (ρ_{XZ} = +6.56).

In the benzylaminolysis of **2**, the Hammett and Brönsted plots for substituent X variations in the nucleophiles were biphasic concave downwards with a maximum point at X = H, and the unusual positive ρ_X and negative β_X values were obtained for the strongly basic benzylamines, suggesting strong interaction between X and Z with the strongly basic benzylamines.[3] The signs of the cross-interaction constants were negative for both the strongly (ρ_{XZ} = −0.03) and weakly basic nucleophiles (ρ_{XZ} = −2.35).[3]

The benzylaminolyses ($C_6H_5CH_2NH_2$) of **1** and **2** give the rate ratio of k_{BnA}(**1**)/k_{BnA}(**2**) = 1.18 × 10^{-4}/2.30 × 10^{-4} = 0.51 in DMSO at 55.0 °C.[7] The pyridinolyses (C_5H_5N) of diethyl [**1'**: $(EtO)_2P(=O)Cl$] and diphenyl [**2'**: $(PhO)_2P(=O)Cl$] chlorophosphates gave the rate ratio of k_{Pyr}(**1'**)/k_{Pyr}(**2'**) = 52.8 × 10^{-3}/266 × 10^{-3} = 0.20 in MeCN at 35.0 °C.[2a,g] In contrast, the anilinolysis ($C_6H_5NH_2$) of **1'** and **2'** gave the rate ratio of k_{An}(**1'**)/k_{An}(**2'**) = 2.82 × 10^{-3}/0.891 × 10^{-3} = 3.2 in MeCN at 55.0 °C.[1a,g] The rate ratios of the aminolyses do not show systematic consistency, i.e., the benzylaminolysis and pyridinolysis rates of substrates (**2** and **2'**) with two phenoxy ligands are faster than with two ethoxy ligands (**1** and **1'**), while the anilinolysis rate shows opposite trend. This implies that the dominant factor to decide the aminolysis reactivity is not the same but different depending upon the kind of the nucleophile: benzylamine, pyridine, or aniline. The difference between **1** and **1'** (**2** and **2'**) is the leaving group, thiophenoxide (**1** and **2**) and chloride (**1'** and **2'**). Taking into account the greater basicity of benzylamine compared to those of pyridine and aniline,[8] and the greater polarity of DMSO compared to that of MeCN,[9] the mentioned second-order rate constants of the aminolyses (benzylaminolysis, pyridinolysis, and anilinolysis) suggest that the leaving group of thiophenoxide is much poorer than chloride.

The CICs (ρ_{XZ}) are determined, where X and Z represent the substituents in the nucleophile and leaving group, respectively, eqs. (2).[10] According to eq. (2b), the ρ_{XZ} values can be obtained from the slopes of the plots of ρ_X *vs* σ_Z and ρ_Z *vs* σ_X for the strongly (Fig. 3(a) for X = 4-MeO, 4-Me, H) and weakly basic nucleophiles (Fig. 3(b) for X = H, 4-Cl, 3-Cl).[11]

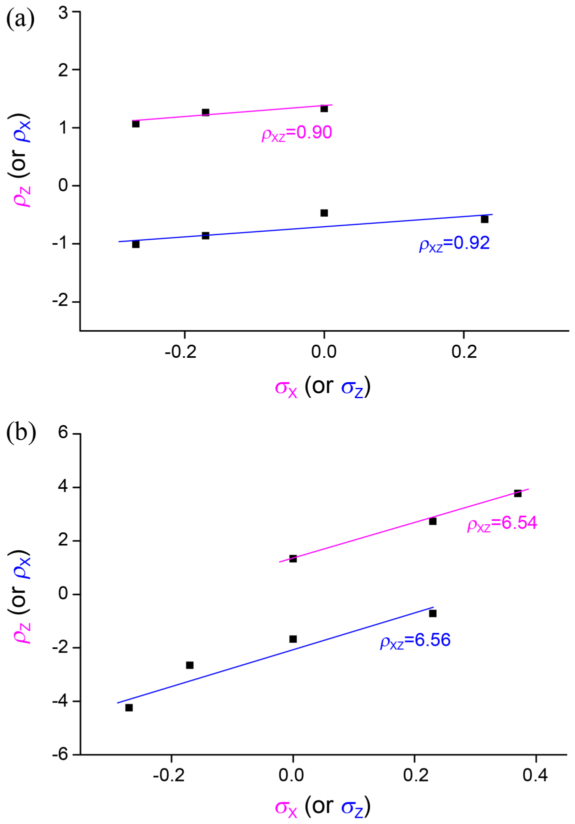


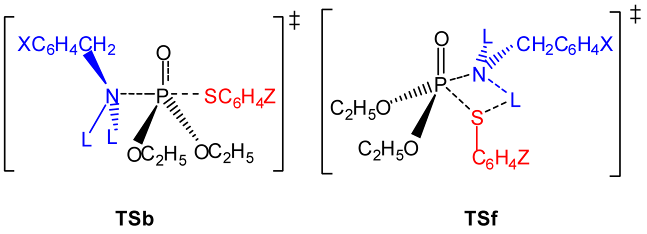
Figure 3. Determination of ρ_{XZ} (= $\partial\rho_X/\partial\sigma_Z = \partial\rho_Z/\partial\sigma_X$) by plotting ρ_Z (or ρ_X) against σ_X (or σ_Z) for the reactions of **1** (*O,O*-diethyl Z-*S*-aryl phosphorothioates) with X-benzylamines in DMSO at 85.0 °C. The obtained ρ_{XZ} values by multiple regressions are: (a) ρ_{XZ} = 0.91 ± 0.09 (r = 0.917) for X = (4-MeO, 4-Me, H) and (b) ρ_{XZ} = 6.56 ± 0.21 (r = 0.936) for X = (H, 4-Cl, 3-Cl).

$$\log(k_{XZ}/k_{HH}) = \rho_X\sigma_X + \rho_Z\sigma_Z + \rho_{XZ}\sigma_X\sigma_Z \tag{2a}$$

$$\rho_{XZ} = \partial\rho_X/\partial\sigma_Z = \partial\rho_Z/\partial\sigma_X \tag{2b}$$

The sign and magnitude of the CICs have made it possible to correctly interpret the reaction mechanism and degree of tightness of the TS, respectively. In general, the ρ_{XZ} has a negative value (or sometimes a small positive value) in a concerted S_N2 and a stepwise mechanism with a rate-limiting bond formation. However, it has a positive value for a stepwise mechanism with a rate-limiting leaving group departure from the intermediate. The magnitude of ρ_{XZ} is inversely proportional to the distance between the nucleophile and leaving group in the TS.[10]

In general, the nonlinear free energy correlation of a concave upward plot is diagnostic of a change in the reaction mechanism, such as parallel reactions where the reaction path is changed depending on the substituents, while nonlinear free energy correlation of the concave downward plot is diagnostic of a rate-limiting step change from bond breaking with less basic nucleophiles to bond formation with more basic nucleophiles.[12] However, these statements are not an iron rule. In the present work, the sign of the CICs, ρ_{XZ}, is positive for both electron-donating and -withdrawing substituent X, indicating that the reaction proceeds through a stepwise mechanism with a rate-limiting leaving group departure from the intermediate regardless of the kinds of substituent X in the nucleophiles. These results imply that biphasic concave downward Hammett and Brönsted plots with the break region (curvature or break point) are not always ascribed to a change in a rate-limiting step from the breakdown to the formation of an intermediate, as the basicity of nucleophile increases. The authors also indicated that biphasic concave upward Hammett and Brönsted plots of the pyridinolysis of dimethyl and diethyl chlorothionophosphate can be diagnostic of a change in the attacking direction of the nucleophile depending on the substituents from backside to frontside.[2g]



Scheme 2. Backside attack TSb and frontside attack TSf.

The magnitude of ρ_{XZ} (= 6.56; exceptionally great value) with the weakly basic nucleophiles is much greater than that (ρ_{XZ} = 0.91) with the strongly basic nucleophiles. The exceptionally great magnitude of ρ_{XZ} = 6.56 value implies that the nucleophile and leaving group are in close enough proximity to interact strongly. This is in agreement with the TSf (Scheme 2) involving a frontside nucleophilic attack with a hydrogen bonded, four-center-type TSf.[13] The authors propose a stepwise mechanism with a rate-limiting leaving group departure from the intermediate with a dominant backside nucleophilic attack towards the leaving group (TSb) for the strongly basic benzylamines.[14]

Experimental Section

Materials. GR grade dimethyl sulfoxide was dried over 4Å molecular sieve and then used after three distillations under reduced pressure. The X-benzylamine nucleophiles, GR grade, were used after recrystallization (4-methylbenzylamine; mp 12-13 °C) or distillation. The substrates were synthesize as previously mentioned way.[3] Equivalent amount of substituted thiophenol and triethylamine solution (solvent; MeCN) was added drop by drop to diethyl chlorophosphate solution (solvent; MeCN) with a vigorous stirring in an ice bath condition. The reaction was allowed for 8-10 hr. Solvent was evaporated under reduced pressure and ethyl ether was added. Insoluble triethylammonium chloride was removed by filtration. The product was isolated by column chromatography after evaporation of ether under reduced pressure. Different proportions of ethyl acetate and *n*-hexane mixture were used as chromatographic eluent to isolate substituted products. Product was finally isolated by removing solvent under vacuum using oil diffusion pump. The analytical data of the substrates are given bellow:

$(C_2H_5O)_2P(=O)SC_6H_4(4\text{-}OCH_3)$. Colorless oily liquid; ^{1}H NMR (200 MHz, $CDCl_3$), δ 1.31 (t, 6H), 3.81 (s, 3H), 4.08-4.28 (m, 4H), 6.84-6.92 (d, 2H, J = 8.4 Hz), 7.43-7.51 (d, 2H, J = 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 15.98-16.05 (CH_3, aliphatic, 2C, d, J = 1.76 Hz), 55.33 (OCH_3, 1C, s), 63.90-63.96 (CH_2, 2C, d, J = 6.0 Hz), 114.93-160.48 (Aromatic, 6C, d); ^{31}P NMR (162 MHz, $CDCl_3$), δ 29.04 (1P, s); ν_{max} (KBr Disk), 3093-2914 (C-H, str. aromatic), 2838 (C-H, str. aliphatic region), 1595, 1496, 1295 (P-O-Ph), 1253 (P=O str.), 644 (C-S str.); *m/z* 276 (M^+).

$(C_2H_5O)_2P(=O)SC_6H_4(4\text{-}CH_3)$. Colorless oily liquid; ^{1}H NMR (200 MHz, $CDCl_3$), δ 1.31 (t, 6H), 2.35 (s, 3H), 4.10-4.28 (m, 4H), 7.13-7.17 (d, 2H, J = 8.4 Hz.), 7.42-7.47 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 15.88-15.95 (CH_3, aliphatic, 2C, d, J = 7.5 Hz), 21.09 (CH_3, 1C, s), 63.86-63.92 (CH_2, 2C, d, J = 6.1 Hz), 122.67-139.21 (Aromatic, 6C, d); ^{31}P NMR (162 MHz, $CDCl_3$), δ 28.75 (1P, s); *m/z* 260 (M^+).

$(C_2H_5O)_2P(=O)SC_6H_5$. Colorless oily liquid; ^{1}H NMR (200 MHz, $CDCl_3$), δ 1.27-1.34 (t, 6H), 4.11-4.28 (m, 4H), 7.32-7.36 (m, arom., 3H) 7.54-7.60 (m, arom., 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 15.90-15.97 (CH_3, aliphatic, 2C, d, J = 6.9 Hz), 63.98-64.04 (CH_2, 2C, d, J = 6.0 Hz), 125.09 (Aromatic, 1C, d), 129.11 (Aromatic, 4C, d), 134.49 (Aromatic, 2C, d); ^{31}P NMR (162 MHz, $CDCl_3$), δ 28.29 (1P, s); *m/z* 246 (M^+).

$(C_2H_5O)_2P(=O)SC_6H_4(4\text{-}Cl)$. Colorless oily liquid; ^{1}H NMR (200 MHz, $CDCl_3$), δ 1.28-1.36 (t, alph., 6H), 4.15-4.25 (m, alph., 4H), 7.31-7.35 (d, 2H, J = 8.4 Hz), 7.48-7.53 (d, 2H, J = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 15.96-16.03 (CH_3, aliphatic, 2C, d, J = 6.8 Hz), 64.18-64.24 (CH_2, 2C, d, J = 6.1 Hz), 125.05-135.75 (Aromatic, 6C, d); ^{31}P NMR (162 MHz, $CDCl_3$), δ 27.59 (1P, s); *m/z* 280 (M^+).

Kinetic Procedure. Rates were measured conductometrically at 85.0 °C using a computer controlled conductivity bridge constructed in this lab. Pseudo-first-order rate constants, k_{obsd}, were measured by using curve-fitting method in ORIGIN program as previously described.[1-3] Pseudo-first-order rate constants were determined with large excess of benzylamine; [Substrate] = 1×10^{-3} M and [X-BnA] = 0.10-0.25 M. Pseudo-first-order rate constants were reproducible within ± 3%.

Product Analysis. Diethyl 4-chloro-*S*-phenyl phosphorothioate (0.05 M) was reacted with 4-methylbenzylamine (0.5 M) in DMSO at 85.0 °C. After more than 15 half-lives, product was isolated by solvent extraction process using ethylacetate (50 mL) and water (5 mL) mixture with several attempts. Finally, the product was isolated by column chromatography using 25% ethylacetate/*n*-hexane. The analytical data of the product gave the following results:

$(C_2H_5O)_2P(=O)NHCH_2C_6H_4(4\text{-}CH_3)$. Colorless oily liquid; ^{1}H NMR (200 MHz, $CDCl_3$), δ 1.27-1.34 (t, 6H), 2.07 (s, 1H), 2.34 (s, 3H), 4.00 (s, 2H), 3.95-4.10 (q, 4H), 7.12-7.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 16.12 (d, J = 6.8 Hz, CH_3, 2C), 20.89 (CH_3, 1C, d, J = 31.8 Hz), 44.95 (CH_2, 1C, s), 62.48 (CH_2, 2C, d, J = 5.3 Hz), 127.23-137.01 (m, 6C, aromatic); ^{31}P NMR (162 MHz, $CDCl_3$), δ 14.12 (1P, s); *m/z* 257 (M^+).

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7. The k_2(**1**) of 1.18×10^{-4} M^{-1} s^{-1} at 55.0 °C was calculated by extrapolation in the Arrhenius plot (r = 0.999) with empirical kinetic data: k_2 = 2.71 (75.0 °C), 3.87 (85.0 °C), and 5.67×10^{-4} M^{-1} s^{-1} (95.0 °C). Enthalpy of activation, $\Delta H^{\ddagger}$ = 8.7 ± 0.3 kcal mol^{-1}, and entropy of activation, $\Delta S^{\ddagger} = -50 \pm 1$ cal mol^{-1} K^{-1}, were obtained.
8. The basicity of benzylamine [pK_a = 10.16 (DMSO), 16.76 (MeCN), 9.34 (H_2O)] is much greater (ΔpK_a = 4-7) than those of pyridine [pK_a = 3.45 (DMSO), 12.33 (MeCN), 5.17 (H_2O)] and aniline

[pK_a = 3.82 (DMSO), 10.56 (MeCN), 4.58 (H_2O)]. The pK_a values of amines in three solvents (DMSO, MeCN, and water) are collected from: (a) Coetzee, J. F.; Padmanabhan, G. R. *J. Am. Chem. Soc.* **1965**, *87*, 5005. (b) Kolthoff, I. M.; Chantooni, M. K., Jr.; Bhowmik, S. *J. Am. Chem. Soc.* **1968**, *90*, 23. (c) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 556. (d) Crampton, M. R.; Robotham, I. A. *J. Chem. Res. (S)* **1997**, 22.

9. $\Delta\varepsilon_r$ (dielectric constant) = 46.45 (DMSO) − 35.94 (MeCN) = 10.51.
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11. As seen in Fig. 3, the twelve k_2 values [(four of Z-substituted leaving groups) × (three of X-substituted nucleophiles) for both the strongly and weakly basic nucleophiles] are used to determine the ρ_{XZ} values, respectively. Although the multiple correlation coefficients do not show satisfactory results, the trends of ρ_{XZ} values are manifest. In general, more than 20 points are employed to calculate the CIC in order to minimize the experimental error.
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13. Primary normal deuterium kinetic isotope effects (DKIEs: k_H/k_D > 1) involving deuterated benzylamines [$XC_6H_4CH_2ND_2$] are essential to substantiate a hydrogen bonded, four-center-type TSf. The values of k_H/k_D = 1.11 with X = 4-Cl and Z = H, and k_H/k_D = 1.28 with X = 4-Cl and Z = 4-Cl are obtained.
14. Secondary inverse DKIE of k_H/k_D = 0.71 is obtained with X = Z = 4-MeO.