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

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Kinetic studies of the reactions of O,O-diphenyl Z-s-aryl phosphorothioates with X-benzylamines have been carried out in dimethyl sulfoxide at 55.0 °C. The Hammett (log k vs σX) and Brönsted [log k vs pKα(X)] plots for substituent X variations in the nucleophiles are biphasic concave downwards with a maximum point at X = H, and the unusual positive ρX and negative βk values are observed for the strongly basic benzylamines. 

**Key Words**: Phosphoryl transfer reaction, Benzylaminolysis, Deuterium kinetic isotope effect, Nonlinear bifasic free energy correlation

**Introduction**

In previous work, this lab reported the variety of phosphoryl and thiophosphoryl transfer reactions: anilinolyses, pyridinolyses, and theoretical studies. The studied substrates were dominantly R,R,P(=O or S)Cl-type with the Cl leaving group in MeCN. Besides the Cl leaving group, the phenoxy (OC6H4H2Z; in MeCN and DMSO), iso-thiocyanate (NCS; in MeCN), and thio-oxydine (NHC6H4H2Z; in DMSO) leaving groups were employed to understand the leaving group mobility and leaving group effects on the reaction mechanism. The study on the benzylaminolysis for phosphoryl transfer reaction in this first time in this lab. The basicity of benzylamine [pKα = 10.16 (DMSO), 16.76 (MeCN), 9.34 (H2O)] is much greater (ΔpKα = 4-7) than those of pyridine [pKα = 3.45 (DMSO), 12.33 (MeCN), 5.17 (H2O)] and aniline [pKα = 3.82 (DMSO), 10.56 (MeCN), 4.58 (H2O)]. The kinetic studies of the reactions of O,O-diphenyl Z-s-aryl phosphorothioates with X-benzylamines have been carried out in DMSO at 55.0 ± 0.1 °C (Scheme 1) to gain further information into the aminolysis mechanism and stereo-chemistry on the basis of the sign and magnitude of the cross-interaction constants (CICs) and deuterium kinetic isotope effects (DKIEs; kobs/k0) involving deuterated benzylamines (XCH2CH2ND2).

**Results and Discussion**

The pseudo-first-order rate constants observed (kobsd) for all reactions obeyed eq. (1) with negligible k0 (= 0) in DMSO. The clean second-order rate constants (k2) obtained by curve fitting the slope of the plot kobsd against at least five concentrations of benzylamine are summarized in Tables 1 together with selectivity parameters (ρX, βk, ρZ, and ρXZ). 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.

\[ k_{obsd} = k_0 + k_2 [XCH2CH2NH2] \] (1)

The Brönsted βk values are obtained by correlating log k2 (DMSO) with pKα(H2O). The βk values listed in Table 1 seem to be less reliable since the pKα values used are not those determined in DMSO, but rather in water. Using the pKα values for the anilinium ions determined in DMSO, an approximate straight line is obtained when they are plotted against those determined in water. Spillane and coworkers reported that the βk value for the reactions of N-phenyl sulfamoyl chloride (PhNHSO2Cl) with X-anilines in DMSO is similar when determined using the pKα values of anilines.

![Scheme 1](image-url)
The degree of steric hindrance would thus be much greater as the predominant factor to determine the anilinolysis rates of less steric congestion compared to the phenyl ring of the attacking axis in the TBP-5C TS, would experience much greater basicity of benzylamine compared to pyridine. The second-order rate constant of the studied substrate was 1.10 × 10^{-2} in MeCN at 35.0 °C, while that with benzylic (C_{6}H_{5}CH_{2}NHz) is 2.30 × 10^{-4} M^{-1}s^{-1} in DMSO at 55.0 °C. Taking into account (i) the greater basicity of benzylamine compared to pyridine (ΔpK_{b} = 4.7), (ii) the greater polarity of DMSO compared to MeCN (Δp(σ(dielectric constant)) = 46.45(DMSO) − 35.94(MeCN) = 10.51), and (iii) the higher reaction temperature increases with a more electron-withdrawing substituent Z in the leaving groups, which is consistent with a typical nucleophilic leaving groups show linear free energy correlations. The rate of benzylaminolysis compared to pyridinolysis (ΔpK_{b}) are better than 0.978. According to the Hammett (Fig. 1; log k_{2} vs σ_{Γ}) plots for substituent X variations in the nucleophiles are biphasic concave downwards with a maximum point at X = H. Thus, the unusual positive ρ_{X} and negative β_{X} values are obtained for the strongly basic benzylamines. These results suggest an atypical nucleophilic substitution reaction with negative charge development at the nucleophilic nitrogen atom in the TS. The Hammett (Fig. 3; log k_{2} vs σ_{Z}) plots for substituent Z variations in the leaving groups show linear free energy correlations. The rate increases with a more electron-withdrawing substituent Z in the leaving groups, which is consistent with a typical nucleophilic substitution reaction with negative charge development.

### Table 1. Second-Order Rate Constants (k_{2} × 10^{6}(M^{-1}s^{-1})) and Selectivity Parameters^a of the Reactions of O,O-Diphenyl Z-S-Aryl Phosphorothioates with X-Benzylamines in DMSO at 55.0 °C

<table>
<thead>
<tr>
<th>X \ Z</th>
<th>4-Me</th>
<th>H</th>
<th>4-Cl</th>
<th>3-Cl</th>
<th>ρ_{X}</th>
<th>β_{X}</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-MeO</td>
<td>1.40</td>
<td>2.03</td>
<td>5.22</td>
<td>8.03</td>
<td>1.46 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>4-Me</td>
<td>1.46</td>
<td>2.08</td>
<td>5.61</td>
<td>8.51</td>
<td>1.49 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>1.59</td>
<td>2.30</td>
<td>6.16</td>
<td>8.92</td>
<td>1.46 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>4-Cl</td>
<td>0.494</td>
<td>0.734</td>
<td>1.30</td>
<td>1.74</td>
<td>1.02 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>3-Cl</td>
<td>0.313</td>
<td>0.404</td>
<td>0.546</td>
<td>0.636</td>
<td>0.57 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>−ρ_{X}^{</td>
<td>a</td>
<td>}</td>
<td>−0.21 ± 0.01</td>
<td>−0.21 ± 0.01</td>
<td>−0.26 ± 0.01</td>
<td>−0.16 ± 0.01</td>
</tr>
<tr>
<td>−β_{X}^{</td>
<td>b</td>
<td>}</td>
<td>−0.36 ± 0.02</td>
<td>−0.34 ± 0.02</td>
<td>−0.49 ± 0.02</td>
<td>−0.33 ± 0.01</td>
</tr>
<tr>
<td>−ρ_{X}^{</td>
<td>c</td>
<td>}</td>
<td>1.94 ± 0.06</td>
<td>2.05 ± 0.02</td>
<td>2.85 ± 0.02</td>
<td>3.10 ± 0.01</td>
</tr>
<tr>
<td>−β_{X}^{</td>
<td>d</td>
<td>}</td>
<td>1.93 ± 0.04</td>
<td>2.04 ± 0.01</td>
<td>2.84 ± 0.01</td>
<td>3.08 ± 0.03</td>
</tr>
</tbody>
</table>

^aThe σ values were taken from Hansch, C.; Leo, A.; Taft, R. W. Chem. Rev. 1991, 91, 165. The pK_{b} 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. \( X = (4-\text{MeO}, 4-\text{Me}, \text{H}) \).^b Correlation coefficients (r) are better than 0.978. \( r ≥ 0.802 \). \( r ≥ 0.994 \). \( r ≥ 0.997 \). \( r ≥ 0.992 \). \( r = 0.986 \). \( r = 0.996 \).

![Figure 1](image-url)
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The CICs ($\rho_{XZ}$) are determined, where $X$ and $Z$ represent the substituents in the nucleophile and leaving group, respectively (eqs. 2).

According to eq. (2b), the $\rho_{XZ}$ values can be obtained from the slopes of the plots of $\rho_{X}$ vs $\sigma_{Z}$ and $\rho_{Z}$ vs $\sigma_{X}$ for the strongly (Fig. 4(a); $X = 4$-MeO, 4-Me, H) and weakly basic nucleophiles (Fig. 4(b); $X = H, 4$-Cl, 3-Cl), respectively. 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 $\rho_{XZ}$ has a negative value (or sometimes a small positive value) in a concerted S$_{N}$2 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 $\rho_{XZ}$ is inversely proportional to the distance between the nucleophile and leaving group in the TS.

The negative sign of $\rho_{XZ}$ values suggests that the reaction proceeds through S$_{N}$2 mechanism, regardless of the nature of the substituents, electron-donating or -withdrawing. At a glance, the interaction between X and Z seems to be much greater with the weakly basic nucleophiles ($X = H, 4$-Cl, 3-Cl) compared to with the strongly basic nucleophiles ($X = 4$-MeO, 4-Me, H) considering the magnitude of $\rho_{XZ} = -2.35$ for the weakly basic nucleophiles and $\rho_{XZ} = -0.03$ for the strongly basic benzylamines. On the contrary, however, the interaction between X and Z for the strongly basic benzylamines is really much greater than for the weakly basic benzylamines since the unusual positive $\rho_{X}$ values are ascribed to the strong interaction between X and Z (vide infra). The large magnitudes of $\rho_{XZ} = -2.35$ and positive $\rho_{X}$ values imply that the nucleophile and leaving group are in close enough proximity to interact strongly. This is in agreement with the TS involving a frontside nucleophilic attack. The large magnitudes of the $\rho_{XZ}$ values ([|$\rho_{XZ}$| $\geq$ 0.5]) were obtained due to the frontside nucleophilic attack as follows: (i) the reactions of aryl bis(4-methoxyphenyl)
phosphates with the weakly basic pyridines in MeCN ($\rho_{KZ} = –1.98$);\(^{38}\) (ii) the anilinolysis of anilino thioethers in MeOH ($\rho_{KZ} = –1.70$);\(^{39}\) (iii) the pyridinolysis of Z-N-aryl-P,P-di-phenyl phosphinic amides in DMSO with poor leaving groups ($\rho_{KZ} = –1.54$);\(^{38}\) (iv) the benzylaminolysis of Z-aryl cyclopropane carboxylates in MeCN ($\rho_{KZ} = +1.06$);\(^{38}\) (v) the benzylaminolysis of Z-aryl 2-furoates in MeCN ($\rho_{KZ} = +1.19$);\(^{38}\) (vi) the benzylaminolysis of Z-thiophenyl acetates in MeCN ($\rho_{KZ} = +0.90$);\(^{38}\) (vii) the anilinolysis of cumyl aresulphonates in MeCN ($\rho_{KZ} = –0.75$);\(^{38}\) (viii) the anilinolysis of 1-phenylethyl aresulphonates in MeOH ($\rho_{KZ} = –0.56$);\(^{38}\) (iv) the anilinolysis of 2-phenylethyl aresulphonates in MeOH ($\rho_{KZ} = –0.45$).\(^{38}\)

The DKIEs can be only secondary inverse ($k_{d}/k_{o} < 1$) in a normal $S_{N}2$ reaction, since the NH(D) vibrational frequencies invariably increase upon going to the TS, given the increase in steric hindrance in the bond formation step; the greater the bond formation, the greater the steric congestion occurs, and the smaller the $k_{d}/k_{o}$ value becomes.\(^{9}\) In contrast, when partial deprotonation of the benzylamine occurs in a rate-limiting step by hydrogen bonding, the DKIEs are primary normal ($k_{d}/k_{o} > 1$); the greater the extent of the hydrogen bond that occurs, the greater the $k_{d}/k_{o}$ value becomes.\(^{9}\) The DKIEs, $k_{d}/k_{o}$, involving deuterated benzylamines are summarized in Table 2. In the present work, the obtained primary normal DKIEs ($k_{d}/k_{o} = 1.02-2.28 > 1$) imply the partial deprotonation of the benzylamine, i.e., hydrogen bonding, in the TS. The real primary normal DKIE due to the hydrogen bond should be greater than the observed value, since the other hydrogen (deuterium) atom in the N-H(D) moiety, not involved in the hydrogen bond, yields the secondary inverse DKIE ($k_{d}/k_{o} < 1$) due to the steric congestion.

The authors herein propose the reaction mechanism for both the strongly and weakly basic benzylamines: (i) a concerted $S_{N}2$ mechanism on the basis of the negative sign of $\rho_{KZ}$; (ii) involving a frontside nucleophilic attack on the basis of the positive sign of $\rho_{K}$ with the strongly basic benzylamines and great magnitude of $\rho_{KZ}$ with the weakly basic benzylamines; (iii) with a hydrogen bonded, four-center-type TS(P) on the basis of the primary normal DKIEs. A hydrogen bonded, four-center-type TS(C) was reported for the benzylaminolyses\(^{31}\) and anilinolyses\(^{12}\) of various substrates containing carbonyl (and thio-carbonyl) carbon reaction center on the basis of the primary normal DKIEs.

### Experimental Section

**Materials.** The substrates were prepared as described previously.\(^{25}\) GR grade dimethyl sulfoxide was dried over 4 Å 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, recrystallized in ice bath) or distillation. For preparation of deuterated benzylamine, X-benzylamines (2 g) were taken with 15 mL ethyl ether and 10 mL of $D_{2}O$. The mixture was stirring for 24 hrs at room temperature. The deuterated benzyamines were isolated with ether and dried over anhydrous MgSO$_4$. Finally, X-benzylamines were isolated by solvent evaporation under reduced pressure and identified by $^{1}H$-NMR.

**Kinetic Procedure.** Rates were measured conductometrically at 55.0 °C using a computer controlled conductivity bridge constructed in this lab. Pseudo-first-order rate constants, $k_{dms}$, were measured by using curve-fitting method in

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**Table 2. Deuterium Kinetic Isotope Effects ($k_{d}/k_{o}$) of the Reactions of $O,O'$-Diphenyl Z-$S$-Aryl Phosphorothioates with X-Benzylamines in DMSO at 55.0 °C**

<table>
<thead>
<tr>
<th>X</th>
<th>Z</th>
<th>$k_{d}/k_{o}$</th>
<th>$k_{d}/k_{o}$</th>
<th>$k_{d}/k_{o}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-MeO</td>
<td>H</td>
<td>2.03 ± 0.01</td>
<td>1.44 ± 0.01</td>
<td>1.41 ± 0.01</td>
</tr>
<tr>
<td>H</td>
<td>2.30 ± 0.01</td>
<td>1.01 ± 0.01</td>
<td>2.28 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>4-Cl</td>
<td>H</td>
<td>0.734 ± 0.012</td>
<td>0.719 ± 0.009</td>
<td>1.02 ± 0.02</td>
</tr>
</tbody>
</table>

$^{a}$Standard error $\pm (1/k_{d})(\Delta k_{d})^2 + (k_{d}/k_{o})^2(\Delta k_{o})^2$. From Crumpler, T. B.; Yeh, J. H., *Chemical Computations and Errors*; John Wiley: New York, 1940; p 178.
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ORIGIN program. Pseudo-first-order rate constants were determined with large excess of benzylamine; [Substrate] = 5 × 10^{-3} M and [X-BnA] = 0.10-0.25 M. Pseudo-first-order rate constants were reproducible within ± 3%.

**Product Analysis.** Diphenyl 3-chloro-S-phenyl and 4-methyl-S-phenyl phosphorothioate (0.05 M) were reacted with 4-methoxybenzylamine and 4-chlorobenzylamine (0.5 M), respectively, in DMSO at 55.0 °C. After more than 15 half-lives, product was isolated by solvent extraction process using ethylacetate (50 mL) and water (5 mL) mixture. Product and other reactants were isolated from ethylacetate fraction. Finally the product was isolated by column chromatography using 20% ethylacetate/n-hexane. Analytical data of the products gave the following results:

(C_{2}H_{5})_{2}P(=O)NHCH_{2}CH_{2}(4-OCH_{3})): Brown solid (silica gel, 20% ethylacetate/n-hexane); mp 58-60 °C; Anal. Found: C, 58.4; H, 5.1; N, 5.4. Caled. for C_{12}H_{14}NPO_{3}Cl: C, 61.1; H, 4.6; N, 3.8. 1H NMR (200 MHz, CDCl_{3}), δ 3.4 (s, 1H), 3.839 (s, 2H, 7.22-7.301 (m, 14H); 13C NMR (50 MHz, CDCl_{3}), δ 113.84-169.039 (C=C, aromatic, 18C, s/m), 55.274 (CH_{2}, 1C, m), 45.222 (OCH_{3}, 1C, m); 31P NMR (126 MHz, CDCl_{3}), δ 3.845 (1P, s); ν_{max} (nujol mull), 3277 (N-H, str. amide), 3180 (C-H, str. aromatic) max K, m), 45.222

(C_{2}H_{5})_{2}P(=O)NHCH_{2}CH_{2}(4-Cl): Brown jelly (silica gel, 20% ethylacetate/n-hexane); Anal. Found: C, 58.4; H, 5.1; N, 5.4. Caled. for C_{12}H_{14}NPO_{3}Cl: C, 61.1; H, 4.6; N, 3.8. 1H NMR (200 MHz, CDCl_{3}), δ 3.4 (s, 1H), 3.839 (s, 2H, 7.22-7.301 (m, 14H); 13C NMR (50 MHz, CDCl_{3}), δ 113.84-169.039 (C=C, aromatic, 18C, s/m), 55.274 (CH_{2}, 1C, m), 45.222 (OCH_{3}, 1C, m); 31P NMR (126 MHz, CDCl_{3}), δ 3.845 (1P, s); ν_{max} (nujol mull), 3277 (N-H, str. amide), 3180 (C-H, str. aromatic) max

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References and Notes
