

Kinetics and Mechanism of the Aminolysis of Dimethyl Thiophosphinic Chloride with Anilines

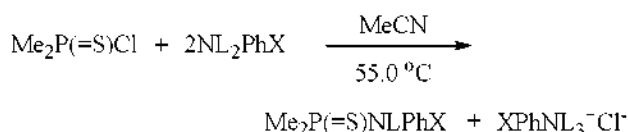
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Continuing our experimental and theoretical studies on phosphoryl and thiophosphoryl transfer reactions,¹ nucleophilic substitution reactions of dimethyl thiophosphinic chloride with anilines are studied kinetically. To clarify the (thio)phosphoryl transfer mechanism, as well as to compare the reactivity, selectivity parameters, and deuterium kinetic isotope effects (DKIEs) of dimethyl phosphinic chloride [Me₂P(=O)Cl; **2**],¹¹ diphenyl thiophosphinic chloride [Ph₂P(=S)Cl; **3**],^{1e} and diphenyl phosphinic chloride [Ph₂P(=O)Cl; **4**],^{1d} we investigate the aminolysis of dimethyl thiophosphinic chloride [Me₂P(=S)Cl; **1**] with substituted anilines (XC₆H₄NH₂) and deuterated anilines (XC₆H₄ND₂) in acetonitrile at 55.0 °C.



L = H or D, X = 4-MeO, 4-Me, 3-Me, H, 3-MeO, 4-Cl, 3-Cl

The second-order rate constants (k_{H} and k_{D}) for the reactions were obtained as the slope of k_{obsd} (pseudo-first-order rate constant) against at least five concentrations of aniline nucleophiles [XC₆H₄NH₂(D₂)] in eq 1.

$$k_{\text{obsd}} = k_0 + k_{\text{H/D}}[\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)] \quad (1)$$

The intercept (k_0) was negligible in all cases. No third-order kinetics was observed and no complications were found in the determination of k_{obsd} . The k_{H} values are summarized in Table 1, together with k_{D} values involving deuterated anilines. The

Table 1. Second-Order Rate Constants, k_{H} and k_{D} ($\times 10^3/\text{M}^{-1}\text{s}^{-1}$), of the Reactions of Dimethyl Thiophosphinic Chloride (**1**) with XC₆H₄NH₂ and XC₆H₄ND₂ in Acetonitrile at 55.0 °C

X	k_{H}	k_{D}	$k_{\text{H}}/k_{\text{D}}$
4-MeO	95.6 ± 0.9 ^a	101 ± 2	0.945 ± 0.014 ^b
4-Me	35.0 ± 1.0	37.9 ± 0.6	0.953 ± 0.030
3-Me	16.2 ± 0.2	17.8 ± 0.3	0.910 ± 0.019
H	9.79 ± 0.26	11.1 ± 0.1	0.882 ± 0.025
3-MeO	3.97 ± 0.11	4.58 ± 0.12	0.867 ± 0.033
4-Cl	1.47 ± 0.04	1.80 ± 0.07	0.817 ± 0.038
3-Cl	0.407 ± 0.003	0.550 ± 0.008	0.740 ± 0.012

^aStandard deviation ^bStandard error $\{= 1/k_{\text{D}}[(\Delta k_{\text{H}})^2 + (k_{\text{H}}/k_{\text{D}})^2 \times (\Delta k_{\text{D}})^2]\}^{1/2}$

rate increases with a more electron-donating substituent X in the nucleophile which is consistent with a typical nucleophilic substitution reaction with negative charge development at the reaction center P in the transition state (TS).

As shown in Figure 1, the reactivity of the P=O system is greater than that of its P=S counterpart [$k_{\text{H}}(\mathbf{2})/k_{\text{H}}(\mathbf{1}) \approx 800$ and $k_{\text{H}}(\mathbf{4})/k_{\text{H}}(\mathbf{3}) \approx 3$]. It is well known that the P=O systems are generally more reactive than their P=S counterparts for several reasons, the so-called "thio effect", which is mainly the electronegativity difference between O and S and favors O over S.³ The natural bond order (NBO) charges⁴ of the reaction center P in the gas phase are 1.180 (**1**), 1.793 (**2**),¹¹ 1.236 (**3**),^{1e} and 1.844 (**4**).^{1d} which are consistent with the inductive effects of Ph ($\sigma_{\text{I}} = +0.12$)⁵ and Me ($\sigma_{\text{I}} = -0.01$)⁵ ligands. Solely considering the positive charge of the reaction center P atom in the P=S (and P=O) system, the aminolysis rate of **1** (and **2**) should be slower than that of **3** (and **4**), *i.e.*, $k_{\text{H}}(\mathbf{1})/k_{\text{H}}(\mathbf{3}) < 1$ [and $k_{\text{H}}(\mathbf{2})/k_{\text{H}}(\mathbf{4}) < 1$]. However, the observed rate ratios of $k_{\text{H}}(\mathbf{1})/k_{\text{H}}(\mathbf{3}) = 16$ and $k_{\text{H}}(\mathbf{2})/k_{\text{H}}(\mathbf{4}) = 4.520$ are completely opposite to expectations from the inductive effects of the ligands, strongly suggesting that the inductive effects of the ligands do not play an important role to decide the reactivity in each reaction system, P=S or P=O system.⁶

The values of second-order rate constants (k_{H}), selectivity parameters (ρ_{X} and β_{X} ; see Figure 2), and DKIEs ($k_{\text{H}}/k_{\text{D}}$) of

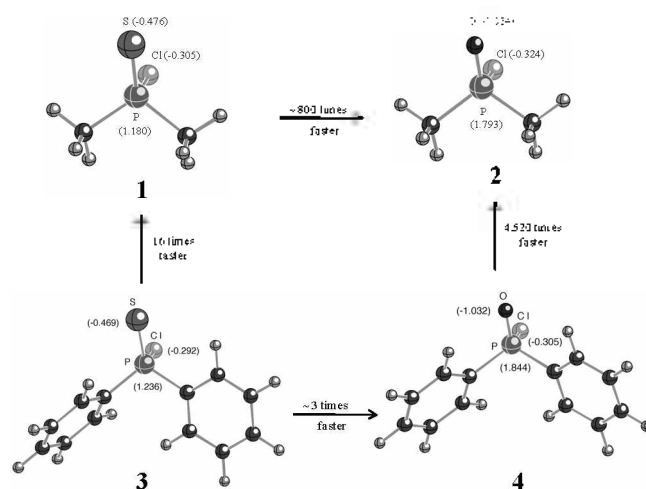


Figure 1. The B3LYP/6-311+G(d,p)¹ geometries and NBO charges of **1**, **2**,¹¹ **3**,^{1e} and **4**^{1d} in the gas phase. The aminolysis (C₆H₅NH₂) rate ratios in acetonitrile at 55.0 °C are displayed next to the arrows.

Table 2. The k_H ($\times 10^4/M^{-1}s^{-1}$), ρ_X , β_X , and k_H/k_D Values of the Reactions of $Me_2P(=S)Cl$ (**1**), $Me_2P(=O)Cl$ (**2**), $Ph_2P(=S)Cl$ (**3**), and $Ph_2P(=O)Cl$ (**4**) with X-Anilines in Acetonitrile at 55.0 °C

Substrate	k_H^a	$-\rho_X^b$	β_X^c	k_H/k_D	ref.
1	97.9	3.60 ^d /3.45 ^e	1.28 ^f /1.22 ^g	0.740 - 0.945	This work
2 ^h	78,200 ⁱ	4.59/4.42	1.62/1.56	0.703 - 0.899	1i
3	6.01	3.97/3.94	1.40/1.40	1.00 - 1.10	1e
4	17.3	4.78/4.56	1.69/1.62	1.42 - 1.82	1d

^aWhen X = H ^bThe σ values were taken from ref. 7 ^cThe pK_a values in water were taken from ref. 8 ^dCalculated from k_H values. Correlation coefficient (r) = 0.999 ^eCalculated from k_D values. r = 0.999 ^fCalculated from k_H values. r = 0.997 ^gCalculated from k_D values. r = 0.997 ^hThe values of ρ_X , β_X , and k_H/k_D are at 15.0 °C ⁱThe k_H value of $7.82 M^{-1} s^{-1}$ at 55.0 °C was calculated by extrapolation in the Arrhenius plot (r = 0.999) with empirical kinetic data: k_H = 0.776 (0.0 °C), 1.01 (5.0 °C) and $1.61 M^{-1} s^{-1}$ (15.0 °C) from ref. 1i

the reactions of **1**, **2**,¹ⁱ **3**,^{1e} and **4**^{1d} with X-anilines in acetonitrile are summarized in Table 2. The observed rate ratios of $k_H(\mathbf{1})/k_H(\mathbf{3}) = 16$ and $k_H(\mathbf{2})/k_H(\mathbf{4}) = 4.520$ can be rationalized by the degree of steric hindrance. Two phenyl groups are bonded to the reaction center P atom in **3** (and **4**) while two methyl groups are bonded in **1** (and **2**). As a result, the steric hindrance in **3** (and **4**) would be much greater than that in **1** (and **2**) when the aniline nucleophile attacks opposite

the Cl leaving group, *i.e.*, backside nucleophilic attack.

The DKIEs can only be secondary inverse ($k_H/k_D < 1.0$) in a normal S_N2 reaction, since the N-H(D) vibrational frequencies invariably increase on going to the TS because of an increase in steric congestion in the bond-making process, and the greater the extent of bond formation occurs, the smaller the k_H/k_D value becomes.¹⁰ In contrast, when partial deprotonation of the aniline occurs in rate-limiting step by hydrogen bonding, the k_H/k_D values would be greater than unity.¹¹

A backside nucleophilic attack concerted mechanism with a late, product-like TS (in-line type TS I) in the anilinolysis of Y-aryl phenyl chlorophosphates [(YPhO)(PhO)P(=O)Cl] in acetonitrile at 55.0 °C was proposed based on large ρ_X (and β_X), large negative cross-interaction constant¹² ($\rho_{XY} = -1.31$), and the secondary inverse DKIEs ($k_H/k_D = 0.61 - 0.87$).^{1a} In contrast, a partial participation of frontside attack concerted mechanism through a hydrogen-bonded four-center type TS II was suggested for the anilinolysis of Y-aryl phenyl chlorothiophosphates [(YPhO)(PhO)P(=S)Cl] in acetonitrile at 55.0 °C based on several reasons, mainly the primary normal DKIEs ($k_H/k_D = 1.11 - 1.33$) and $\rho_{XY} = -0.22$.^{1c} In the anilinolysis of **3** in acetonitrile at 55.0 °C,^{1e} a partial frontside attack concerted mechanism through a hydrogen-bonded four-center type TS II was suggested on the basis of relatively small value of primary normal DKIEs, $k_H/k_D = 1.00 - 1.10$, the same as in Y-aryl phenyl chlorothiophosphates. In the anilinolysis of **4** in acetonitrile at 55.0 °C,^{1d} the relatively large primary normal k_H/k_D values, $k_H/k_D = 1.42 - 1.82$, imply that the reaction proceeds predominantly through TS II. In the anilinolysis of **2** in acetonitrile at 15.0 °C,¹ⁱ the large secondary inverse DKIEs, $k_H/k_D = 0.703 - 0.899$, suggest that the reaction proceeds mainly through TS I.

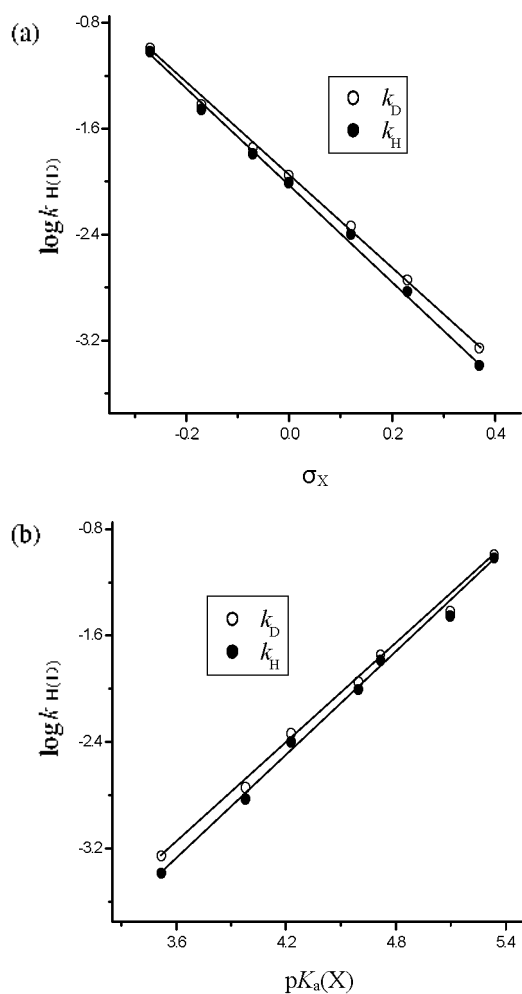
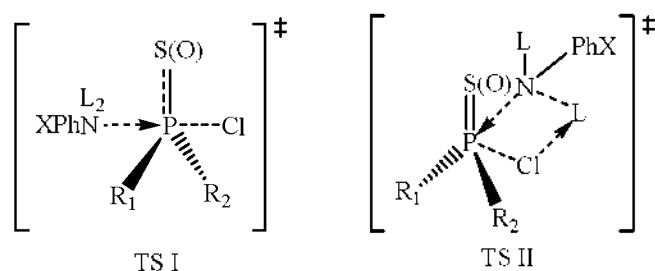


Figure 2. The Hammett (a) and Brønsted (b) plots of the reactions of dimethyl thiophosphinic chloride with $XC_6H_4NH_2$ (\bullet) and $XC_6H_4ND_2$ (\circ) in acetonitrile at 55.0 °C. The σ and pK_a values of $XC_6H_4ND_2$ are assumed to be the same as the σ and pK_a values of $XC_6H_4NH_2$.



In the present work, the DKIEs, $k_H/k_D = 0.740 - 0.945$, are large secondary inverse similar to the anilinolysis of its P=O counterpart, **2**. Thus, a backside nucleophilic attack concerted

mechanism through TS 1 is proposed for the anilinolysis of **1**. We can say that the steric effect is the major factor to determine not only the reactivity but also the direction of the nucleophilic attack, *i.e.*, two large phenyl ligands lead to a partial participation of frontside nucleophilic attack whereas two small methyl ligands lead to backside attack, especially because of the relatively large size of aniline nucleophile.

When the backside nucleophilic attack is major direction, which leads to the secondary inverse DKIEs, $k_H/k_D < 1$, more bond formation will result in smaller k_H/k_D value. The observed sequence of the k_H/k_D values of $X = 4\text{-MeO} > 4\text{-Me} > 3\text{-Me} > \text{H} > 3\text{-MeO} > 4\text{-Cl} > 3\text{-Cl}$ indicates that the weaker nucleophile approaches closer to the reaction center P in the TS compared to the stronger nucleophile, the same tendency as in **2**.

The magnitudes of Hammett ρ_X and Brønsted β_X values are both large, suggesting extensive bond formation in the TS. The larger magnitudes of ρ_X and β_X values of P=O systems (**2** and **4**) compared to P=S systems (**1** and **3**) suggest that P=O system has a later, more product-like TS than P=S system. The magnitudes of ρ_X and β_X values with deuterated anilines ($\text{XC}_6\text{H}_4\text{ND}_2$) are somewhat smaller than those with anilines ($\text{XC}_6\text{H}_4\text{NH}_2$), suggesting less sensitivity to substituent effect of deuterated anilines than of anilines.

Summary

The aminolysis of dimethyl thiophosphinic chloride with substituted anilines and deuterated anilines is investigated kinetically in acetonitrile at 55.0 °C. When substituents in the nucleophiles were varied, the rate changes were consistent with the nature of a typical nucleophilic substitution reaction. Structure-reactivity relationship between **1**, **2**, **3**, and **4** was discussed based on NBO charges and steric effects. Large Hammett ρ_X ($\rho_{\text{inc}} = -3.60$) and Brønsted β_X ($\beta_{\text{inc}} = 1.28$) values suggest extensive bond formation in the transition state. The relatively large secondary inverse DKIEs ($k_H/k_D = 0.740 - 0.945$) involving deuterated aniline nucleophiles indicate that the aniline nucleophile attacks backside toward the reaction center P atom through trigonal bipyramidal pentacoordinate TS.

Experimental Section

Materials. Dimethyl thiophosphinic chloride, 97% (substrate), and HPLC grade acetonitrile (water content is less than 0.005%) were used for kinetic studies without further purification. Anilines were redistilled or recrystallized before use as previously described.¹ Deuterated anilines were prepared by heating anilines with D₂O (99.9 atom % D), and one drop of HCl catalyst at 90 °C for 72 hrs and, after numerous attempts, were more than 98% deuterated, as confirmed by ¹H-NMR.^{1a-i}

Kinetic Measurements. Rates were measured conductometrically using a computer controlled conductivity bridge constructed in this laboratory as described previously.¹ The pseudo-first-order rate constants were determined with large excess of nucleophiles. [substrate] = 5×10^{-4} M and [An] =

0.01 - 0.05 M. The pseudo-first-order rate constant values were the average of three runs, which were reproducible within $\pm 3\%$.

Product Analysis. Dimethyl thiophosphinic chloride was reacted with excess amount of 4-methyl aniline for more than 15 half-lives in acetonitrile at 55.0 °C. The products were isolated by a work-up process with diethyl ether and dilute HCl. The MgSO₄ was added and kept for two hours. The products finally were isolated by solvent evaporation under reduced pressure after filtration. The products were passed through column chromatography (30% ethyl acetate and n-hexane). The analytical data are as follows.

(CH₃)₂P(=S)NHC₆H₄-4-CH₃. Brown solid; mp 122-124 °C; ¹H NMR (400MHz, CDCl₃) δ 1.88-2.01 (6H, m, CH₃), 2.24-2.34 (3H, m, CH₃), 4.41 (1H, s, NH), 6.89-7.10 (4H, m, aromatic); ¹³C NMR (100 MHz, CDCl₃) δ 20.6 (s, CH₃), 22.9, 23.6 (ss, CH₃), 120.7, 120.8, 130.0, 132.8, 137.4 (C=C, aromatic); ³¹P NMR (162 MHz, CDCl₃) δ 62.3 (1P, s, P=S); m/z, 199 (M⁺); found: C 54.2, H 7.3, N 6.8; C₉H₁₄NPS requires C 54.2, H 7.1, N 7.0%.

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