

Anilinolysis of Dimethyl Isothiocyanophosphate in Acetonitrile

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Received April 1, 2012, Accepted May 6, 2012**Key Words** : Phosphoryl transfer reaction, Anilinolysis, Dimethyl isothiocyanophosphate, Deuterium kinetic isotope effect

To extend the kinetic studies on the phosphoryl transfer reactions involving a leaving group of isothiocyanate,¹ the nucleophilic substitution reactions of dimethyl isothiocyanophosphate (**1**) with substituted anilines (XC₆H₄NH₂) and deuterated anilines (XC₆H₄ND₂) are investigated kinetically in acetonitrile (MeCN) at 55.0 ± 0.1 °C (Scheme 1). The purpose of this work is to gain further information into the leaving group ability, deuterium kinetic isotope effects (DKIEs), and mechanism, as well as to compare with the kinetic results of the anilinolyses of diethyl isothiocyanophosphate [**2**: (EtO)₂P(=O)NCS],^{1a} and their counterparts with a leaving group of chloride: dimethyl [**1'**: (MeO)₂P(=O)Cl] and diethyl [**2'**: (EtO)₂P(=O)Cl] chlorophosphates.²

Results and Discussion

The observed pseudo-first-order rate constants (*k*_{obsd}) were found to follow Eq. (1) for all the reactions under pseudo-first-order conditions with a large excess of aniline nucleophile. The *k*₀ values were negligible (*k*₀ ≈ 0) in MeCN. The second-order rate constants (*k*_H and *k*_D) were determined for at least five concentrations of anilines. The linear plots of Eq. (1) suggest that there are no base-catalysis or noticeable side reactions and that the overall reaction is described by Scheme 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 *k*_H and *k*_D values with X-anilines and deuterated X-anilines, respectively, are summarized in Table 1, together with the DKIEs (*k*_H/*k*_D) and Hammett ρ_{X(H and D)} and Brønsted β_{X(H and D)} coefficients. The p*K*_a(X) values of the X-anilines in water were used to obtain the Brønsted β_X values in MeCN, and this procedure was justified experimentally and theoretically.³ The values of p*K*_a(X) and σ_X of the deuterated



Scheme 1. The anilinolysis of dimethyl isothiocyanophosphate (**1**) in MeCN at 55.0 °C.

Table 1. The Second-Order Rate Constants (*k*_{H(D)} × 10³ M⁻¹ s⁻¹), Selectivity Parameters (ρ_X and β_X),^a and DKIEs (*k*_H/*k*_D) of the Reactions of Dimethyl Isothiocyanophosphate (**1**) with XC₆H₄NH₂(D₂) in MeCN at 55.0 °C

| X | <i>k</i> _H × 10 ³ | <i>k</i> _D × 10 ³ | <i>k</i> _H / <i>k</i> _D |
|--------------------------|---|---|---|
| 4-MeO | 406 ± 1 ^b | 378 ± 1 | 1.07 ± 0.01 ^g |
| 4-Me | 140 ± 1 | 114 ± 2 | 1.23 ± 0.02 |
| 3-Me | 38.3 ± 0.2 | 29.7 ± 0.3 | 1.29 ± 0.01 |
| H | 15.1 ± 0.3 | 11.2 ± 0.5 | 1.35 ± 0.07 |
| 4-F | 9.46 ± 0.01 | 6.80 ± 0.01 | 1.39 ± 0.01 |
| 3-MeO | 4.24 ± 0.01 | 2.86 ± 0.07 | 1.48 ± 0.04 |
| 4-Cl | 1.39 ± 0.01 | 0.913 ± 0.009 | 1.52 ± 0.02 |
| 3-Cl | 0.363 ± 0.002 | 0.166 ± 0.001 | 2.19 ± 0.01 |
| -ρ _{X(H and D)} | 4.83 ± 0.06 ^c | 5.24 ± 0.05 ^e | |
| β _{X(H and D)} | 1.71 ± 0.11 ^d | 1.85 ± 0.09 ^f | |

^aThe σ values were taken from ref. 5. The p*K*_a values of X-anilines in water were taken from ref. 6. ^bStandard deviation. ^cCorrelation coefficient, r = 0.998. ^dr = 0.995. ^er = 0.999. ^fr = 0.997. ^gStandard error {= 1/*k*_D [(Δ*k*_H)² + (*k*_H/*k*_D)² × (Δ*k*_D)²]^{1/2}} from ref. 7.

X-anilines are assumed to be identical to those of the X-anilines. Perrin and coworkers reported that the basicities of β-deuterated analogs of benzylamine, *N,N*-dimethylaniline and methylamine increase roughly by 0.02 p*K*_a units per deuterium, and that these effects are additive.⁴ Thus, the p*K*_a(X) values of deuterated X-anilines may be slightly greater than those of X-anilines, however, the difference is too small to be taken into account.

The anilinolysis rate increases with a more electron-donating substituent X in the nucleophile which is consistent with a typical nucleophilic substitution reaction with positive charge development at the nucleophilic reaction center N atom in the transition state (TS). The Hammett (Fig. 1; log *k*_{H(D)} vs σ_X) and Brønsted [Fig. 2; log *k*_{H(D)} vs p*K*_a(X)] plots for substituent X variations in the nucleophiles give considerably large magnitudes of ρ_{X(H)} = -4.83 (ρ_{X(D)} = -5.24) and β_{X(H)} = 1.71 (β_{X(D)} = 1.85). The magnitudes of selectivity parameters with the deuterated anilines are slightly greater than those with the anilines. The DKIEs are primary normal (*k*_H/*k*_D > 1) and the values of DKIEs invariably increase as the nucleophile becomes weaker. The remarkably large value of *k*_H/*k*_D = 2.19 with X = 3-Cl is the largest one, observed for the phosphoryl transfer reactions in this lab.⁸

The second-order rate constants (*k*_H) with unsubstituted

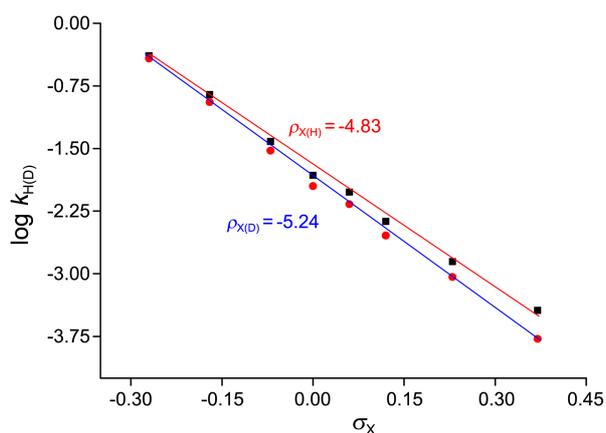


Figure 1. The Hammett plots ($\log k_{\text{H(D)}}$ vs σ_{X}) of the reactions of dimethyl isothiocyano-phosphate (**1**) with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN at 55.0 °C.

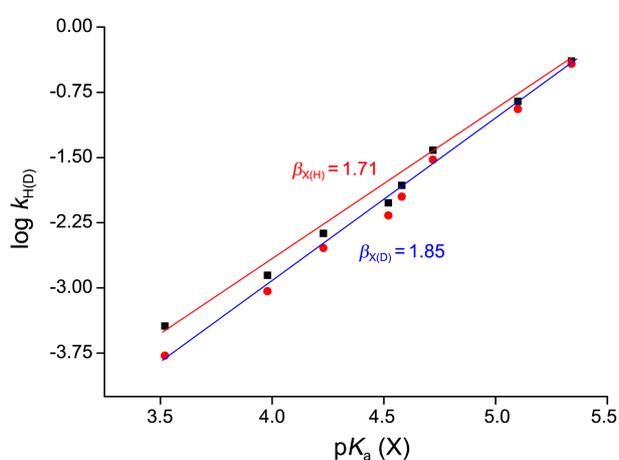
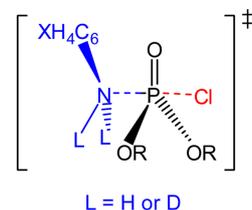


Figure 2. The Brønsted plots [$\log k_{\text{H(D)}}$ vs $\text{p}K_{\text{a}}(\text{X})$] of the reactions of dimethyl isothiocyano-phosphate (**1**) with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN at 55.0 °C.

aniline, natural bond order (NBO) charges at the reaction center P atom in the gas phase [B3LYP/6-311+G(d,p) level of theory],⁹ Brønsted coefficients ($\beta_{\text{X(H)}}$), and DKIEs ($k_{\text{H}}/k_{\text{D}}$) of the reactions of **1**, **2**, **1'**, and **2'** with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN at 55.0 °C are summarized in Table 2. The magnitude of the NBO charge of the reaction center P atom in the substrate does not correlate with the rate, suggesting that the inductive effects of the two ligands do not play any role to determine the anilinolysis rate. The rate (with $\text{C}_6\text{H}_5\text{NH}_2$) of **1** (and **1'**) with the two methoxy ligands is faster than that of **2** (and **2'**) with the two ethoxy ligands: $k(\mathbf{1})/k(\mathbf{2}) = 17.7$ and

$k(\mathbf{1}')/k(\mathbf{2}') = 1.5$. These suggest that the steric effects of the two ligands play an important role to determine the anilinolysis rate and that the rate is inversely proportional to the size of the two ligands. It is well known that the chloride (Cl^-) is a better leaving group compared to isothiocyanate (NCS^-).¹ The rate ratio of $k(\mathbf{2}')/k(\mathbf{2}) = 3.3$ is consistent with expectation for the leaving group abilities of chloride and isothiocyanate. However, the rate ratio of $k(\mathbf{1}')/k(\mathbf{1}) = 0.28$ is pretty unusual. The anilinolysis of **1** exhibits linear free energy relationship for substituent X variations in the nucleophiles while that of **2** exhibits discrete biphasic free energy correlations.^{1a} The $\beta_{\text{X}} (= 1.71)$ ¹⁰ value of **1** and that ($\beta_{\text{X}} = 1.45$) of **2** with the strongly basic anilines are relatively large. The $\beta_{\text{X}} (= 0.92)$ value of **2** with the weakly basic anilines and those of **2** ($\beta_{\text{X}} = 0.96$) and **3** ($\beta_{\text{X}} = 1.06$) are comparable. The DKIEs of **1** are primary normal ($k_{\text{H}}/k_{\text{D}} = 1.07$ -2.19) and those of **2** with the weakly basic anilines are partially primary normal ($k_{\text{H}}/k_{\text{D}} = 0.71$ -1.58). The DKIEs of **2** with the strongly basic anilines ($k_{\text{H}}/k_{\text{D}} = 0.74$ -0.87), **1'** ($k_{\text{H}}/k_{\text{D}} = 0.80$ -0.98), and **2'** ($k_{\text{H}}/k_{\text{D}} = 0.71$ -0.92) are secondary inverse.

The DKIEs are one of the strong tools to clarify the reaction mechanism. The DKIEs have provided a useful means to determine the TS structures in the nucleophilic substitution reactions, and how the reactants, especially through changes in substituents, alter the TS structures. Incorporation of deuterium in the nucleophile has an advantage in that the α -DKIEs reflect only the degree of bond formation. The DKIEs can only be secondary inverse ($k_{\text{H}}/k_{\text{D}} < 1.0$) in a normal $\text{S}_{\text{N}}2$ reaction, since the N–H(D) vibrational frequencies invariably increase upon going to the TS because of an increase in steric congestion in the bond-making process.¹¹ The greater the degree of the steric congestion in the TS, the value of $k_{\text{H}}/k_{\text{D}}$ becomes smaller. In contrast, when partial deprotonation of the aniline occurs in a rate-limiting step by hydrogen bonding, the $k_{\text{H}}/k_{\text{D}}$ values are greater than unity, primary normal ($k_{\text{H}}/k_{\text{D}} > 1.0$).¹² The greater the extent of the hydrogen bond, the value of $k_{\text{H}}/k_{\text{D}}$ becomes greater.



Backside attack TSb

Table 2. Summary of the Second-Order Rate Constants ($k_{\text{H}} \times 10^3/\text{M}^{-1} \text{s}^{-1}$) with $\text{C}_6\text{H}_5\text{NH}_2$, NBO Charges at the Reaction Center P Atom, Brønsted Coefficients ($\beta_{\text{X(H)}}$), and DKIEs ($k_{\text{H}}/k_{\text{D}}$) for the Reactions of **1**, **2**, **1'**, and **2'** with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN at 55.0 °C

| substrate | $k_{\text{H}} \times 10^3$ ^a | charge at P | $\beta_{\text{X(H)}}$ | $k_{\text{H}}/k_{\text{D}}$ |
|--|---|-------------|------------------------|----------------------------------|
| 1 : (MeO) ₂ P(=O)NCS | 15.1 | 2.444 | 1.71 | 1.07-2.19 |
| 2 : (EtO) ₂ P(=O)NCS | 0.854 | 2.454 | 1.45/0.92 ^b | 0.74-0.87/0.71-1.58 ^b |
| 1' : (MeO) ₂ P(=O)Cl | 4.28 | 2.226 | 0.96 | 0.80-0.98 |
| 2' : (EtO) ₂ P(=O)Cl | 2.82 | 2.236 | 1.06 | 0.71-0.92 |

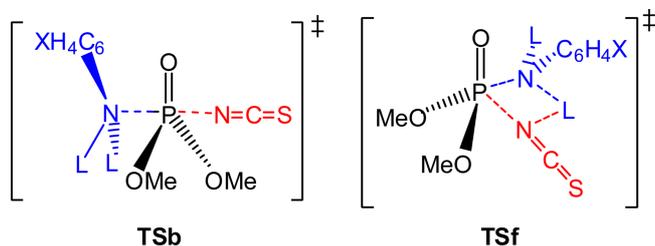
^aThe values with unsubstituted aniline. ^bStrongly/weakly basic anilines.

The authors accordingly proposed that the anilinolyse of **1**' and **2**' proceed through a concerted mechanism with a backside nucleophilic attack TSb on the basis of the secondary inverse DKIEs and good leaving group ability of chloride.

The authors proposed the mechanism for the anilinolysis of **2** as follows: (i) for the strongly basic anilines, a stepwise mechanism with a rate-limiting leaving group departure from the intermediate involving a predominant backside attack TSb (Scheme 2) based on the large β_X value and secondary inverse DKIEs; (ii) for the weakly basic anilines, a concerted mechanism (or a stepwise process with a rate-limiting bond formation) on the basis of the small β_X value and the TS variation from a dominant backside attack TSb with X = (4-F, 3-MeO) to a dominant frontside attack involving a hydrogen bonded, four-center-type TSf (Scheme 2)¹³ with X = (4-Cl, 3-Cl) on the basis of the secondary inverse DKIEs ($k_H/k_D = 0.71$ with X = 4-F and 0.83 with X = 3-MeO) and primary normal DKIEs ($k_H/k_D = 1.15$ with 4-Cl and 1.58 with 3-Cl).

The change of the leaving group from chloride to that of a lower leaving ability, isothiocyanate, can cause a change in mechanism from a concerted to a stepwise process with a rate-limiting breakdown of the trigonal bipyramidal pentacoordinate (TBP-5C) intermediate. This is in accord with the well established trend of the mechanistic change depending on the leaving group ability: the lower the leaving ability of the leaving group, the greater is the tendency for a stepwise mechanism with a rate-limiting expulsion of the leaving group from the intermediate.¹⁴ In the present work, thus, the authors propose a stepwise mechanism with a rate-limiting leaving group departure from the intermediate involving a hydrogen bonded, four-center-type TSf (Scheme 2) on the basis of the large β_X value and primary normal DKIEs.

Activation parameters, enthalpy and entropy of activation, are determined as shown in Table 3. The enthalpy of activation is relatively low and entropy of activation is relatively large negative value. The relatively low of activation enthalpy



Scheme 2. Backside attack TSb and frontside attack involving a hydrogen bonded, four-center-type TSf (L = H or D).

Table 3. Activation Parameters^a of the Reactions of Dimethyl Isothiocyanophosphate (**1**) with C₆H₅NH₂ in MeCN

| <i>t</i> /°C | $k_H \times 10^3/M^{-1} s^{-1}$ | $\Delta H^\ddagger/kcal mol^{-1}$ | $-\Delta S^\ddagger/cal mol^{-1} K^{-1}$ |
|--------------|---------------------------------|-----------------------------------|--|
| 45.0 | 10.6 ± 0.7 | | |
| 55.0 | 15.1 ± 0.3 | 6.9 | 46 |
| 65.0 | 21.4 ± 0.3 | | |

^aSee 'Supporting Information'.

and large negative value of activation entropy are typical for the aminolyses of P=O systems.

In summary, the nucleophilic substitution reactions of dimethyl isothiocyanophosphate (**1**) with substituted anilines (XC₆H₄NH₂) and deuterated anilines (XC₆H₄ND₂) are investigated kinetically in acetonitrile at 55.0 °C. The magnitudes of the selectivity parameters are considerably large. The DKIEs are primary normal ($k_H/k_D = 1.07$ -2.19). These are interpreted to indicate a stepwise mechanism with rate-limiting expulsion of the isothiocyanate leaving group from an intermediate. A predominant frontside nucleophilic attack involving a hydrogen bonded, four-center-type TSf is proposed on the basis of the primary normal DKIEs.

Experimental Section

Materials. The substrate of dimethyl isothiocyanophosphate was synthesized as previously described.¹⁵ HPLC grade acetonitrile (water content is less than 0.005%) was used for kinetic studies without further purification. Anilines were redistilled or recrystallized before use as previously described.^{1,2} Deuterated anilines were synthesized by heating anilines and deuterium oxide (99.9 atom %D) and one drop of HCl as catalyst at 90 °C for 72 hours, and after numerous attempts, anilines were deuterated more than 98%, as confirmed by ¹H NMR.

Kinetic Procedure. Rates were measured conductometrically at 55.0 °C. The conductivity bridge used in this work was a self-made computer automated A/D converter conductivity bridge. Pseudo-first-order rate constants, k_{obsd} were measured by curve fitting analysis in origin program with a large excess of anilines, [substrate] = 5×10^{-3} M and [X-aniline] = (0.1-0.3) M. Second-order rate constants, k_2 , were obtained from the slope of a plot of k_{obsd} vs. [X-aniline] with five concentrations of anilines. The pseudo-first-order rate constant values (k_{obsd}) were the average of at least three runs that were reproducible within ± 3%.

Product Analysis. Dimethyl isothiocyanophosphate was reacted with excess aniline for more than 15 half-lives at 55.0 °C in MeCN. Acetonitrile was evaporated under reduced pressure. The product mixture was treated with ether by a work-up process with dilute HCl and dried over anhydrous MgSO₄. Then the product was isolated through column chromatography (30% ethyl acetate/*n*-hexane) and then dried under reduced pressure. The analytical and spectroscopic data of the product gave the following results (see Supporting Information):

(CH₃O)₂P(=O)NHC₆H₅: Light yellow liquid; ¹H-NMR (400 MHz, MeCN-*d*₃) δ 3.61-3.73 (aliphatic, 6H, m), 6.59 (aliphatic, 1H, s), 7.19-7.22 (aromatic, 5H, m); ¹³C-NMR (100 MHz, MeCN-*d*₃) δ 53.95-54.01 (aliphatic, 2C, m), 118.39-141.29 (aromatic, 6C, m); ³¹P-NMR (162 MHz, MeCN-*d*₃) δ 15.38 (P=O, 1P, s); GC-MS for C₈H₁₂NO₃P (EI, *m/z*) 201 (M⁺).

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References and Notes

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