Anilinolysis of Bis(N,N-dimethylamino) Phosphinic Chloride

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Kinetics and Mechanism of the Anilinolysis of Bis(*N*,*N*-dimethylamino) Phosphinic Chloride in Acetonitrile
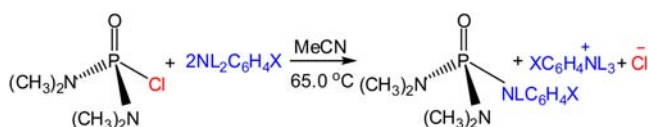
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The nucleophilic substitution reactions of bis(*N*,*N*-dimethylamino) phosphinic chloride (**3**) with substituted anilines ($XC_6H_4NH_2$) and deuterated anilines ($XC_6H_4ND_2$) are investigated kinetically in acetonitrile at 65.0 °C. The anilinolysis rate of **3** is rather slow to be rationalized by the conventional stereoelectronic effects. The magnitudes of ρ_X ($= -6.42$) and β_X ($= 2.27$) values are exceptionally great. The deuterium kinetic isotope effects (DKIEs; k_H/k_D) are secondary inverse ($k_H/k_D = 0.69$-0.96). A concerted S_N2 mechanism involving a backside attack is proposed on the basis of secondary inverse DKIEs and the variation trend of the k_H/k_D values with X. The anilinolyses of six phosphinic chlorides in MeCN are briefly reviewed by means of DKIEs, steric effects of the two ligands, positive charge of the reaction center phosphorus atom, and selectivity parameters to obtain systematic information on phosphoryl transfer reaction mechanism.

Key Words : Phosphoryl transfer reaction, Anilinolysis, Bis(*N*,*N*-dimethylamino) phosphinic chloride, Deuterium kinetic isotope effect

Introduction

The kinetics and mechanism of the anilinolyses of various substrates in acetonitrile (MeCN) have been extensively investigated in this lab by means of the deuterium kinetic isotope effects (DKIEs; k_H/k_D) involving deuterated anilines ($XC_6H_4ND_2$), selectivity parameters (ρ_X, β_X, ρ_Y, ρ_{XY}), positive charge at the reaction center P atom, and steric effects of the two ligands.[1] In the present work, the nucleophilic substitution reactions of bis(*N*,*N*-dimethylamino) phosphinic chloride (**3**) with $XC_6H_4NH_2(D_2)$ in MeCN at 65.0 ± 0.1 °C (Scheme 1) are studied kinetically to gain further systematic information into the phosphoryl transfer reaction mechanism as well as to compare with the relevant anilinolyses of phosphinic chloride systems ($R_1R_2P(=O)Cl$-type): dimethyl [**1:** $Me_2P(=O)Cl$],[1i] diethyl [**2:** $Et_2P(=O)Cl$],[1l] bicyclohexyl [**4:** $cHex_2P(=O)Cl$],[1o] methyl phenyl [**5:** $MePhP(=O)Cl$],[1i] and diphenyl [**6:** $Ph_2P(=O)Cl$][1d] phosphinic chlorides. The studied substrate of **3** with the two ligands of $N(CH_3)_2$ is the first one in this lab where the ligand with nitrogen atom is bonding to the reaction center phosphorus atom. The numbering of the substrates of each group follows the sequence of the summations of the Taft's
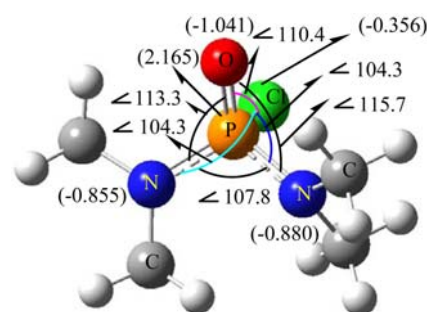

Figure 1. The B3LYP/6-311+G(d,p) geometry of bis(*N*,*N*-dimethylamino) phosphinic chloride (**3**) in the gas phase.

steric constants of the two ligands.[2]

The B3LYP/6-311+G(d,p) geometry, bond angles, and natural bond order (NBO) charges of **3** in the gas phase[3] are shown in Figure 1. The MO theoretical structure shows that the oxygen, two nitrogens, and chlorine have somewhat distorted tetrahedral geometry with the phosphorus atom at the center. The ground state (GS) structure of **3** does not have symmetry plane although it has two same ligands.

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 ($k_0 \approx 0$) in MeCN. The second-order rate constants ($k_{H(D)}$) were determined for at least five concentrations of anilines. The linear plots of eq. (1) suggest that there is no base-catalysis or noticeable side reaction and that the overall reaction is described by Scheme 1.

Scheme 1. The reaction system of the reactions of bis(*N*,*N*-dimethylamino) phosphinic chloride (**3**) with $XC_6H_4NH_2(D_2)$ in MeCN at 65.0 °C.

$$k_{obsd} = k_0 + k_{H(D)}[XC_6H_4NH_2(D_2)] \qquad (1)$$

The second-order rate constants of k_H and k_D values are summarized in Table 1, together with the DKIEs (k_H/k_D) and the Hammett ρ_X and Brönsted β_X selectivity parameters. The pK_a(X) values of the X-anilines in water were used to obtain the Brönsted β_X values in MeCN, and this procedure was justified experimentally and theoretically.[7] The values of pK_a(X) and σ_X of the deuterated 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 pK_a units per deuterium, and that these effects are additive.[8] Thus, the pK_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. Figures 2 and 3 show the Hammett (log $k_{H(D)}$ *vs* σ_X) and Brönsted [log $k_{H(D)}$ *vs* pK_a(X)] plots for substituent X variations in the nucleophiles, respectively. The rates are faster with stronger nucleophiles ($\rho_X < 0$ and $\beta_X > 0$) which are compatible with typical nucleophilic substitution reactions with positive charge development at the nucleophile N atom in the transition state (TS). The magnitudes of the selectivity parameters are exceptionally great, and the $\rho_{X(H)}$ (= −6.42) and $\beta_{X(H)}$ (= 2.27) values with anilines are slightly greater than those ($\rho_{X(D)}$ = −6.15 and $\beta_{X(D)}$ = 2.22) with deuterated anilines, suggesting less sensitivity to substituent effects of the deuterated anilines compared to the anilines. The observed DKIEs are secondary inverse (k_H/k_D <1) and the values of DKIEs invariably decrease as the nucleophile changes from the strongly to weakly basic: e.g., X = 4-MeO (k_H/k_D = 0.955) to X = 3-Cl (k_H/k_D = 0.686).

The second-order rate constants (k_H) with unsubstituted aniline at 55.0 °C, summations of the Taft's steric constants of the two ligands [$\Sigma E_S = E_S(R_1) + E_S(R_2)$],[2] NBO charges at the reaction center P atom [B3LYP/6-311+G(d,p) level of

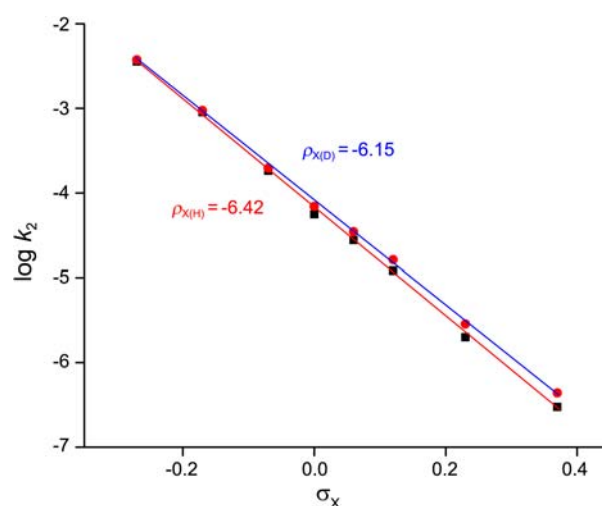**Figure 2.** The Hammett plots (log $k_{H(D)}$ *vs* σ_X) of the reactions of bis(*N,N*-dimethylamino) phosphinic chloride (**3**) with $XC_6H_4NH_2(D_2)$ in MeCN at 65.0 °C.

Figure 3. The Brönsted plots [log $k_{H(D)}$ *vs* pK_a(X)] of the reactions of bis(*N,N*-dimethylamino) phosphinic chloride (**3**) with $XC_6H_4NH_2(D_2)$ in MeCN at 65.0 °C.

theory] in the gas phase,[3] Brönsted coefficients ($\beta_{X(H \text{ and } D)}$), and DKIEs ($k_H/k_D$) of the reactions of **1-6** with $XC_6H_4NH_2(D_2)$ in MeCN are summarized in Table 2. Solely considering the magnitudes of the positive charges at the reaction center P atom, the sequence of the anilinolysis rate should be **3** >> **4** > **6** > **5** > **2** > **1**. However, the observed sequence of the rate, **1** >> **2** > **5** >> **6** >> **3** > **4**, giving the relative rate ratio of 832,000(**1**)[1i]:20,100(**2**)[1l]:14,700(**5**)[1i]:184(**6**)[1d]:3.4(**3**):1(**4**),[1o] is completely contrary to expectations for the electronic influence of the two ligands. It is evident that the positive charge at the reaction center P atom is not major factor to determine the anilinolysis rate of the phosphinic chloride systems.[11]

When **3** and **4** are *not* considered, the sequence of the anilinolysis rates of the phosphinic chlorides, **1** >> **2** > **5** >> **6**, is inversely proportional to the size of the two ligands; Ph,Ph(**6**) > Ph,Me(**5**) > Et,Et(**2**) > Me,Me(**1**).[12] The greater

Table 1. The Second-Order Rate Constants ($k_{H(D)} \times 10^5$/M^{-1} s^{-1}), Selectivity Parameters (ρ_X and β_X),[a] and DKIEs (k_H/k_D) of the Reactions of Bis(*N,N*-dimethylamino) Phosphinic Chloride (**3**) with $XC_6H_4NH_2(D_2)$ in MeCN at 65.0 °C
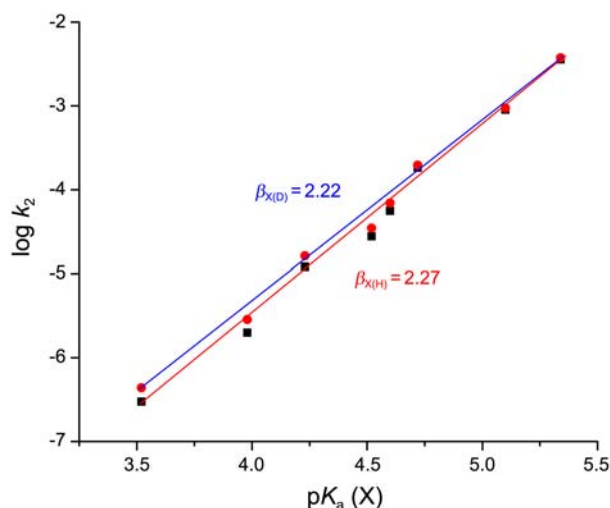
X	$k_H \times 10^5$	$k_D \times 10^5$	k_H/k_D
4-MeO	357 ± 2^b	374 ± 2	0.955 ± 0.007^g
4-Me	89.7 ± 0.1	93.9 ± 0.3	0.955 ± 0.006
3-Me	18.2 ± 0.1	19.6 ± 0.3	0.929 ± 0.015
H	5.59 ± 0.05	6.90 ± 0.01	0.810 ± 0.007
4-F	2.77 ± 0.01	3.48 ± 0.02	0.796 ± 0.005
3-MeO	1.21 ± 0.01	1.63 ± 0.02	0.742 ± 0.011
4-Cl	0.200 ± 0.001	0.286 ± 0.002	0.699 ± 0.006
3-Cl	0.0299 ± 0.0001	0.0436 ± 0.0004	0.686 ± 0.007
$-\rho_{X(H \text{ and } D)}$	6.42 ± 0.04^c	6.15 ± 0.04^e	
$\beta_{X(H \text{ and } D)}$	2.27 ± 0.13^d	2.22 ± 0.11^f	

[a]The σ values were taken from ref. 4. The pK_a values of X-anilines in water were taken from ref. 5. [b]Standard deviation. [c]Correlation coefficient, r = 0.999. [d]r = 0.996. [e]r = 0.999. [f]r = 0.997. [g]Standard error {= 1/$k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}$} from ref. 6.

Table 2. Summary of the Second-Order Rate Constants ($k_H \times 10^3/M^{-1}\ s^{-1}$) with $C_6H_5NH_2$ at 55.0 °C, Summations of the Taft's Steric Constants (ΣE_S), NBO Charges at the Reaction Center P Atom, Brönsted Coefficients ($\beta_{X(H\ and\ D)}$), and DKIEs (k_H/k_D) of the Reactions of **1-6** with $XC_6H_4NH_2(D_2)$ in MeCN

Substrate	$k_H \times 10^3$	$-\Sigma E_S$	charge at P	$\beta_{X(H)}/\beta_{X(D)}$[e]	k_H/k_D	ref
1: $Me_2P(=O)Cl$	7,820[a]	0.00	1.793	1.62/1.56[f]	0.703-0.899[f]	1i
2: $Et_2P(=O)Cl$	189[b]	0.14	1.817	0.56/0.52[g]	0.828-0.974[g]	1l
3: $(Me_2N)_2P(=O)Cl$	0.0318[c]	0.94[d]	2.165	2.27/2.22[h]	0.686-0.955[h]	this work
4: $cHex_2P(=O)Cl$	0.00940	1.58	1.863	0.67/0.56[i]	0.673-1.10[i]	1o
5: $MePhP(=O)Cl$	138	2.48	1.821	0.88/0.8[i]	1.62-2.10[i]	1i
6: $Ph_2P(=O)Cl$	1.73	4.96	1.844	1.69/1.62[j]	1.42-1.82[j]	1d

[a]The value of $k_H = 7,820 \times 10^{-3}\ M^{-1}\ s^{-1}$ at 55.0 °C was obtained by extrapolation in the Arrhenius plot (r = 0.999) with kinetic data: $k_H = 776$, 1,010, and $1,610 \times 10^{-3}\ M^{-1}\ s^{-1}$ at 0.0, 5.0, and 15.0 °C, respectively, from ref. 1i. [b]The value of $k_H = 189 \times 10^{-3}\ M^{-1}\ s^{-1}$ at 55.0 °C was obtained by extrapolation in the Arrhenius plot (r = 0.999) with kinetic data: $k_H = 117$, 162, and $211 \times 10^{-3}\ M^{-1}\ s^{-1}$ at 40.0, 50.0, and 60.0 °C, respectively, from ref. 1l. [c]Empirical kinetic value. See ref. 9. [d]The value of $E_S(i\text{-Pr}) = -0.47$ is employed. See ref. 10. [e]$\beta_{X(H)}/\beta_{X(D)}$ indicates that the values are calculated from k_H and k_D values, respectively. [f]Values at 15.0 °C. [g]Values at 50.0 °C. [h]Values at 65.0 °C. [i]Values at 60.0 °C. [j]Values at 55.0 °C.

the size of the two ligands, the anilinolysis rate becomes slower, i.e., the relative rate ratio of 4,520(**1**)[1i]:109(**2**)[1l]:80(**5**)[1i]:1(**6**).[1d] These results indicate that: (i) the steric effects of the two ligands are predominant factor to determine the anilinolysis rates of phosphinic chlorides in MeCN;[13] (ii) in the case of **3** and **4**, the anilinolysis rates are exceptionally slow to be substantiated by the conventional stereoelectronic effects, suggesting that additional factor plays an important role to determine the reactivity. Further systematic works are essential to clarify additional factor(s).[14]

The DKIEs can be only secondary inverse ($k_H/k_D < 1$) in a normal S_N2 reaction, since the NH(D) vibrational frequencies invariably increase upon going to the TS (in-line-type TSb in Scheme 2; backside nucleophilic attack), 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_H/k_D value becomes.[15] In contrast, when partial deprotonation of the aniline occurs in a rate-limiting step by hydrogen bonding (hydrogen-bonded, four-center-type TSf in Scheme 2; frontside nucleophilic attack), the DKIEs are primary normal ($k_H/k_D > 1$); the greater the extent of the hydrogen bond that occurs, the greater the k_H/k_D value becomes.[16] When the reaction proceeds simultaneously through both pathways, backside (TSb) and frontside (TSf) attack, the observed DKIEs are the sum of both effects, primary normal and secondary inverse, and the obtained value of k_H/k_D can be greater or lesser than the unity depending on the proportion of the two pathways. Thus, the DKIEs can be one of the strong tools to substantiate the TS structure. Herein, it should be noted that the real primary normal DKIE due to TSf is greater than the

observed value, since the observed value is the sum of: (i) the primary normal DKIE ($k_H/k_D > 1$) because of the partial deprotonation of one of the two N–H(D) bonds, TS II; (ii) the secondary inverse DKIE ($k_H/k_D < 1$) because of the steric hindrance that increases the out-of-plane bending vibrational frequencies of the other N–H(D) bond; (iii) lowering of the k_H/k_D value because of the nonlinear and asymmetrical structure of N···H(D)···Cl; (iv) lowering of the k_H/k_D value because of the heavy atom (N and Cl) contribution of the reaction-coordinate motion.[15,16]

Thus, the attacking direction of the aniline nucleophile is manifested by the magnitude of the DKIEs. The attacking direction of aniline nucleophile can be *semi*-quantitatively divided into three groups on the basis of the magnitudes of the k_H/k_D values: (i) predominant backside attack when $k_H/k_D < 1$; (ii) backside and frontside attacks when the k_H/k_D values change from less than unity to greater than unity; (iii) predominant frontside attack when $k_H/k_D > 1.1$. There is no doubt that two small methyl (and ethyl) ligands in **1** (and **2**) enable predominant backside attack TSb (Scheme 2) of the aniline nucleophile, resulting in secondary inverse DKIEs: k_H/k_D(**1**) = 0.703-0.899 and k_H/k_D(**2**) = 0.828-0.947.[1i,l] In the present work of **3**, the DKIEs are secondary inverse [k_H/k_D(**3**) = 0.686-0.955] due to dominant backside attack TSb. In **4**, the DKIEs [k_H/k_D(**4**) = 0.672-1.10] are invariably changing from secondary inverse (backside attack TSb) to primary normal (frontside attack TSf involving the hydrogen bonded, four-center-type; Scheme 2) as the anilines become stronger, implying that the fraction of a frontside attack increases as the aniline becomes more basic.[1o] In **5** and **6**, the DKIEs are primary normal due to predominant frontside attack TSf: k_H/k_D(**5**) = 1.62-2.10[17] and k_H/k_D(**6**) = 1.42-1.82.[1d,i] These results explicitly show the relation between the size of the two ligands and the attacking direction of the aniline nucleophile: the greater the size of the two ligands, the steric hindrance becomes greater, and the frontside attack becomes more favorable. The variation trends of DKIEs with X are the same for **1-6**, and the magnitude of the k_H/k_D value increases with a stronger nucleophile. However there is no correlation between the k_H/k_D and β_X values.

The authors proposed that: the anilinolyses of **1** and **2**
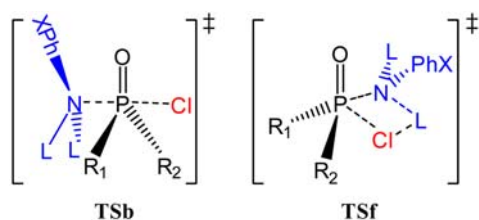
Scheme 2. Backside attack TSb and frontside attack TSf (L = H or D).

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proceed through a concerted mechanism involving a predominant backside attack TSb on the basis of the secondary inverse DKIEs; the anilinolysis of **4** proceed through a concerted S_N2 mechanism on the basis of both secondary inverse and primary normal DKIEs and the fraction of a frontside attack increases as the aniline becomes more basic; the anilinolyses of **5** and **6** proceed through a concerted mechanism involving a predominant frontside attack with a hydrogen-bonded, four-center-type TSf on the basis of the considerably large primary normal DKIEs. In the present work, thus, a concerted mechanism involving a backside nucleophilic attack is proposed on the basis of the secondary inverse DKIEs and the variation trends of the k_H/k_D values with X. The smaller k_H/k_D value (greater secondary inverse DKIE) with a weaker nucleophile indicates that the steric congestion in the TS becomes greater and that the degree of bond formation becomes greater, resulting in later TS.

Experimental Section

Materials. Bis(*N,N*-dimethylamino) phosphinic chloride, commercially available, was used without further purification. 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] Deuterated anilines were synthesized by heating anilines and deuterium oxide (99.9 atom % D) and one drop of HCl as catalyst at 85 °C for 72 hours, and after numerous attempts, anilines were deuterated more than 98%, as confirmed by ^{1}H NMR.

Kinetic Procedure. Rates were measured conductometrically as previously described.[1] 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] = 5×10^4 M and [X-aniline] = (0.1-0.3) M. Second-order rate constants, $k_{H(D)}$, were obtained from the slope of a plot of k_{obsd} *vs* [X-aniline] with at least five concentrations of anilines. The k_{obsd} values were at least average of three runs, which were reproducible within ± 3%.

Product Analysis. Bis(*N,N*-dimethylamino) phosphinic chloride was reacted with excess aniline for more than 15 half-lives at 65.0 °C in MeCN. The aniline hydrochloride salt was separated by filtration. Acetonitrile was removed under reduced pressure. The product was isolated through column chromatography (60% ethyl acetate/*n*-hexane) after treatment with ether and dilute HCl, then dried under reduced pressure. The analytical data are summarized as follows:

[N(CH$_3$)$_2$]$_2$P(=O)NHC$_6$H$_5$. White solid crystal, mp 152-153 °C; ^{1}H-NMR (400 MHz, CDCl$_3$ & TMS) δ 2.66 (aliphatic, 12H, d, *J* = 8.0 Hz), 4.74 (aliphatic, 1H, s), 6.89-7.32 (aromatic, 5H, m,); ^{13}C-NMR (100 MHz, CDCl$_3$ & TMS) δ 36.90 (aliphatic, 4C, s), 117.63-140.93 (aromatic, 6C, m); ^{31}P-NMR (162 MHz, CDCl$_3$ & TMS) δ 21.48 (1P, s, P=O); GC-MS (EI, *m/z*) 227 (M$^+$).

References and Notes

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9. The second-order rate constants are 3.18 (± 0.02) (55.0 °C), 4.27 (± 0.04) (60.0 °C), and 5.59 (± 0.05) × 10^{-5}/M^{-1} s^{-1} (65.0 °C), giving the activation parameters of ΔH = 11.8 kcal/mol and ΔS = –43 eu for the reaction of **3** with aniline (C$_6$H$_5$NH$_2$) in MeCN at 55.0 °C.

10. The E_S value of N(CH$_3$)$_2$ is not available and the value of *i*-Pr (E_S = –0.47) is introduced.

11. Note that the magnitude of the positive charge (2.165) of the reaction center P atom of **3** is greater (*ca.* ~0.30-0.37) than those (1.793-1.863) of other substrates due to the two NMe$_2$ ligands.

12. The sensitivity coefficient of δ, according to the Taft eq. of log k_H = $\delta\Sigma E_S$ + C, for the anilinolysis of **1**, **5**, and **6** is 0.737 (strongly dependent upon the steric hindrance of the two ligands; r = 0.999) while δ = 0.572 (roughly linear; r = 0.895) for the anilinolysis of **1**, **2**, **5**, and **6**. This means that the anilinolysis rate of **2** is not

quantitatively but qualitatively dependent upon the steric effects of the two ligands. See refs. 1i,l.

13. In general, the anilinolysis rates of P=O and P=S systems are predominantly dependent upon the steric effects over the inductive effects of the two ligands. See refs. 1c,e-g,i,l,m,n,p.

14. The steric effects of $N(CH_3)_2$ and cHex ligands on the anilinolysis rate could be much greater (TS destabilization) than the reference reaction of Taft's equation. Another plausible factor could be exceptional ground state stabilization.

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17. The value of $k_H/k_D = 2.10$ for the reaction of **5** with 4-methoxy aniline is the largest one observed for the anilinolyses of the studied P=O and P=S substrates in this lab.