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Transition State Variation in the Anilinolysis of *O*-Aryl Phenyl Phosphonochloridothioates in Acetonitrile

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The nucleophilic substitution reactions of Y-*O*-aryl phenyl phosphonochloridothioates with substituted anilines ($XC_6H_4NH_2$) and deuterated anilines ($XC_6H_4ND_2$) are kinetically investigated in acetonitrile at 55.0 °C. The deuterium kinetic isotope effects (DKIEs) invariably increase from an extremely large secondary inverse ($k_H/k_D = 0.439$; min) to a primary normal ($k_H/k_D = 1.34$; max) as both substituents of nucleophile (X) and substrate (Y) change from electron-donating to electron-withdrawing. These results are opposite to the DKIEs on Y-*O*-aryl methyl phosphonochloridothioates, and can be rationalized by the gradual transition state (TS) variation from backside to frontside attack. The trigonal bipyramidal pentacoordinate TS is proposed for a backside attack, while the hydrogen-bonded, four-center-type TS is proposed for a frontside attack. The negative values of the cross-interaction constants ($\rho_{XY(H)} = -0.38$ for $XC_6H_4NH_2$ and $\rho_{XY(D)} = -0.29$ for $XC_6H_4ND_2$) indicate that the reactions proceed by a concerted S_N2 mechanism.

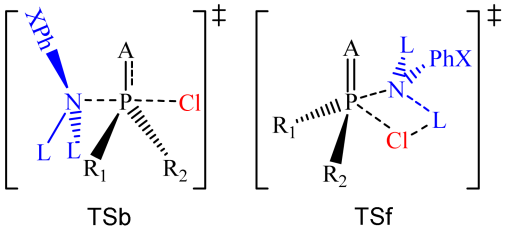
Key Words : Phosphoryl transfer reaction, Deuterium kinetic isotope effect, Cross-interaction constant, *O*-Aryl phenyl phosphonochloridothioates, Transition state variation

Introduction

Phosphoryl transfer reactions are important because of analogy to the numerous enzyme-catalyzed reactions at phosphorus. A considerable amount of work has been focused on the two types of phosphoryl transfer reaction mechanisms, stepwise ($A_N + D_N$) through a trigonal bipyramidal pentacoordinate (TBP-5C) intermediate, and concerted (A_ND_N) through a single pentacoordinate transition state (TS).[1] The attacking direction of the nucleophile can be backside and/or frontside, depending on the substrate, nucleophile, leaving group, and reaction condition.[2]

In previous work, this lab reported upon various types of phosphoryl and thiophosphoryl transfer reactions: anilinolyses,[3] pyridinolyses,[4] and theoretical studies.[5] The kinetics and mechanism of the anilinolyses of $R_1R_2P(=O \text{ or } =S)Cl$-type substrates in MeCN were investigated by means of the deuterium kinetic isotope effects (DKIEs) involving deuterated anilines ($XC_6H_4ND_2$), selectivity parameters (ρ_X, β_X, ρ_Y, ρ_{XY}), and steric effects of the two ligands (R_1 and R_2).

The DKIEs can be only secondary inverse ($k_H/k_D < 1$) in a normal S_N2 reaction, since the N–H(D) vibrational frequencies invariably increase upon going to the TS (in-line-type TSb in Scheme 1; 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.[6] 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 1; 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.[7] When the reaction proceeds



Scheme 1. Proposed TS structures (A = O or S; L = H or D).

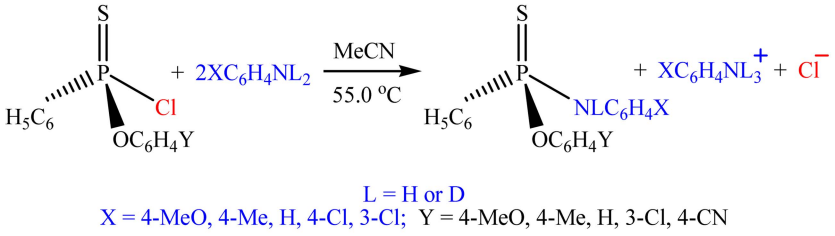
simultaneously through both pathways, backside (TSb) and frontside (TSf) attack, the observed DKIEs are the sum of both effects, primary normal and secondary inverse, and the obtained value of k_H/k_D can be greater or lesser than the unity depending on the proportion of the two pathways.

The cross-interaction constant (CIC; ρ_{XY}), eqs. (1), is negative in a normal S_N2 reaction (or in a stepwise reaction with a rate-limiting bond formation), and positive in a stepwise reaction with a rate-limiting leaving group expulsion from the intermediate.[8] The magnitude of the CIC is inversely proportional to the distance between X and Y through the reaction center; the tighter the TS, the greater the magnitude of the CIC. Here, X and Y denote the substituents of the nucleophile and substrate, respectively.[8]

$$\log (k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \quad (1a)$$

$$\rho_{XY} = \partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X \quad (1b)$$

In the present work, the DKIEs and reaction mechanism for the reactions of Y-*O*-aryl phenyl phosphonochloridothioates with $XC_6H_4NH_2(D_2)$ in MeCN at 55.0 ± 0.1 °C (Scheme 2) are examined to gain further information on the phosphoryl transfer reaction mechanism. The anilinolyses of



Scheme 2. The studied reaction system.

select R_1R_2P(=O or S)Cl-type substrates in MeCN are compared on the basis of DKIEs and selectivity parameters to obtain systematic information on the DKIEs and mechanism for phosphoryl transfer reactions.

Results and Discussion

The observed pseudo-first-order rate constants (k_{obsd}) were found to follow eq. (2) for all of the reactions under pseudo-first-order conditions with a large excess of the aniline nucleophile. The k_0 values were negligible ($k_0 = 0$) in MeCN. The linear plots of eq. (2) suggest that there is no any base-catalysis or noticeable side reactions and that the overall reactions follow the route given by Scheme 1.

$$k_{obsd} = k_0 + k_{H(D)}[\,XC_6H_4NH_2(D_2)] \quad (2)$$

The second-order rate constants (k_H and k_D) in MeCN at 55.0 °C are summarized in Table 1, together with selectivity parameters, $\rho_{X(H\text{ and }D)}$, $\beta_{X(H\text{ and }D)}$, $\rho_{Y(H\text{ and }D)}$, and $\rho_{XY(H\text{ and }D)}$ (= $\partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X$; Fig. 1). The p$K_a$ values of the anilines in water were used to obtain the Brönsted β_X values in MeCN and were justified experimentally and theoretically.[11] The pK_a and σ values of the deuterated anilines are assumed to be identical to those of the anilines.[12] The rates are faster with a stronger nucleophile ($\rho_X < 0$ and $\beta_X > 0$) and a stronger electron-acceptor substituent in the substrate ($\rho_Y > 0$) which are compatible with typical nucleophilic substitution reactions with negative charge development at the reaction center P atom of the substrate and with positive charge development at the nucleophile N atom in the TS. The magnitudes of the ρ_X values are considerably greater than those of the ρ_Y values. The magnitudes of the $\rho_{X(D)}$ (= –3.93 to –4.18) and $\beta_{X(D)}$ (= 1.38-1.47) values with deuterated anilines are somewhat larger than those ($\rho_{X(H)}$ = –3.47 to –3.79 and $\beta_{X(H)}$ = 1.22-1.33) with anilines, while the magnitudes of the ρ_Y values show opposite tendencies ($\rho_{Y(D)}$ = 0.27-0.42 < $\rho_{Y(H)}$ = 0.38-0.64). The signs of the CICs are all negative for both anilines and deuterated anilines, and the magnitudes of the CICs with anilines ($\rho_{XY(H)}$ = –0.38) and deuterated anilines ($\rho_{XY(D)}$ = –0.29) are comparable.

The DKIEs (k_H/k_D) summarized in Table 2 invariably increase from an extremely large secondary inverse (k_H/k_D = 0.439; min when X = Y = 4-MeO) to a primary normal (k_H/k_D = 1.34; max when X = 3-Cl and Y = 4-CN) as both substituents of the nucleophile (X) and substrate (Y) change from electron-donating to electron-withdrawing. Two kinds of substrates are reported, dimethyl chlorothiophosphate [$(MeO)_2P$(=S)Cl][3g] and Y-*O*-aryl methyl phosphonochloridothioates [(YC_6H_4O)MeP(=S)Cl],[3k] simultaneously with both DKIEs, apparent primary normal (k_H/k_D > 1) and secondary inverse (k_H/k_D < 1). However, the substituent effects of X and/or Y on the DKIEs do not show the same

Table 1. Second-Order Rate Constants (k_2 × $10^4/M^{-1}s^{-1}$) and Selectivity Parameters[a] of the Reactions of (YC_6H_4O)PhP(=S)Cl with $XC_6H_4NH_2(D_2)$ in MeCN at 55.0 °C

X \ Y		4-MeO	4-Me	H	3-Cl	4-CN	$\rho_{Y(H)}/\rho_{Y(D)}$[b]
4-MeO	k_H	148 ± 1	159 ± 2	190 ± 6	361 ± 10	557 ± 6	0.64 ± 0.03/
	k_D	337 ± 3	343 ± 1	357 ± 6	537 ± 1	825 ± 5	0.42 ± 0.05
4-Me	k_H	41.0 ± 0.2	43.3 ± 0.1	54.3 ± 0.2	92.4 ± 0.3	135 ± 1	0.58 ± 0.02/
	k_D	48.1 ± 1.4	50.1 ± 0.1	61.5 ± 1.2	102 ± 2	147 ± 2	0.54 ± 0.02
H	k_H	12.1 ± 0.3	12.9 ± 0.2	15.0 ± 0.1	24.6 ± 0.7	41.8 ± 0.1	0.58 ± 0.04/
	k_D	11.7 ± 0.1	12.3 ± 0.2	13.7 ± 0.1	22.1 ± 0.4	36.7 ± 0.2	0.54 ± 0.04
4-Cl	k_H	2.06 ± 0.01	2.14 ± 0.01	2.43 ± 0.06	3.79 ± 0.01	5.30 ± 0.20	0.46 ± 0.02/
	k_D	1.97 ± 0.01	2.00 ± 0.05	2.16 ± 0.05	3.34 ± 0.02	4.57 ± 0.07	0.41 ± 0.03
3-Cl	k_H	0.764 ± 0.022	0.815 ± 0.011	0.986 ± 0.017	1.27 ± 0.04	1.77 ± 0.01	0.38 ± 0.02/
	k_D	0.724 ± 0.001	0.757 ± 0.010	0.867 ± 0.006	0.984 ± 0.008	1.33 ± 0.01	0.27 ± 0.02
$-\rho_{X(H)}$		3.47 ± 0.09	3.48 ± 0.10	3.50 ± 0.09	3.72 ± 0.10	3.79 ± 0.10	$\rho_{XY(H)}$ = –0.38
$-\rho_{X(D)}$		3.93 ± 0.21	3.93 ± 0.21	3.92 ± 0.19	4.09 ± 0.15	4.18 ± 0.14	$\rho_{XY(D)}$ = –0.29
$\beta_{X(H)}$		1.22 ± 0.12	1.22 ± 0.13	1.23 ± 0.13	1.31 ± 0.13	1.33 ± 0.13	
$\beta_{X(D)}$		1.38 ± 0.24	1.38 ± 0.24	1.38 ± 0.22	1.44 ± 0.18	1.47 ± 0.18	

[a]The σ values were taken from ref. 9. The pK_a values of the X-anilinium ions in water were taken from ref. 10. [b]The subscripts, (H) and (D), indicate that the values are calculated from k_H and k_D, respectively.

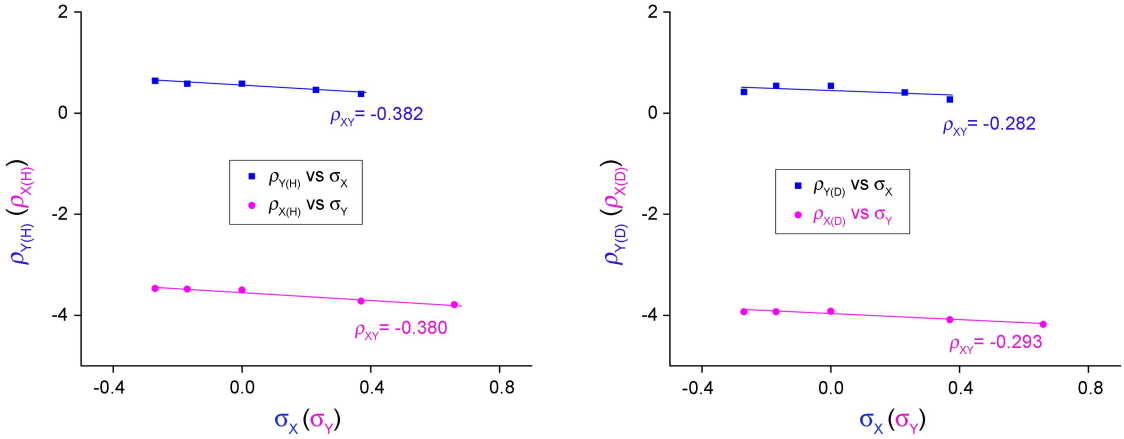


Figure 1. Determination of ρ_{XY} (= $\partial\rho_X/\partial\sigma_Y$ = $\partial\rho_Y/\partial\sigma_X$) by plotting ρ_Y (or ρ_X) against σ_X (or σ_Y) for the reactions of (YC_6H_4O)-PhP(=S)Cl with $XC_6H_4NH_2(D_2)$ in MeCN at 55.0 °C. The obtained values by multiple regressions are $\rho_{XY(H)}$ = –0.38 ± 0.08 (r = 0.993) and $\rho_{XY(D)}$ = –0.29 ± 0.16 (r = 0.979).

Table 2. Deuterium Kinetic Isotope Effects (k_H/k_D) of the Reactions of $(YC_6H_4O)PhP(=S)Cl$ with $XC_6H_4NH_2(D_2)$ in MeCN at 55.0 °C

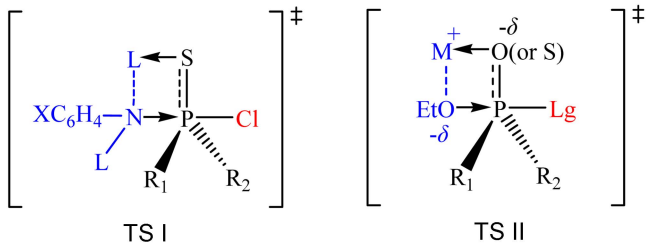
X \ Y	4-MeO	4-Me	H	3-Cl	4-CN
4-MeO	0.439 ± 0.005[a]	0.464 ± 0.006	0.532 ± 0.019	0.672 ± 0.019	0.675 ± 0.016
4-Me	0.852 ± 0.025	0.864 ± 0.003	0.883 ± 0.018	0.906 ± 0.011	0.918 ± 0.013
H	1.03 ± 0.03	1.05 ± 0.02	1.11 ± 0.01	1.11 ± 0.04	1.14 ± 0.01
4-Cl	1.05 ± 0.01	1.07 ± 0.03	1.13 ± 0.04	1.14 ± 0.01	1.16 ± 0.05
3-Cl	1.06 ± 0.03	1.08 ± 0.02	1.14 ± 0.02	1.29 ± 0.04	1.34 ± 0.01

[a]Standard error $\{= 1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}\}$ from ref. 13.

trends as the present work; consider the following points (i) In dimethyl chlorothiophosphate, the DKIEs showed trends opposite to the present results, invariably increasing from secondary inverse to primary normal as X changes from electron-withdrawing to electron-donating: X(k_H/k_D); 3-Cl(0.945) < 4-Cl(0.955) < 3-MeO(0.974) < H(0.991) < 3-Me(1.03) < 4-Me(1.04) < 4-MeO(1.06); (ii) In Y-*O*-aryl methyl phosphonochloridothioates, nonlinear free-energy correlations, biphasic concave downwards Hammett and Brönsted plots with a break region between X = H and 4-Cl, were observed. The DKIEs were distinctly divided into two parts, unprecedented great secondary inverse (k_H/k_D = 0.367-0.567 << 1) for the weakly basic anilines (X = 4-Cl, 3-Cl, 3-NO_2) and primary normal (k_H/k_D = 1.03-1.30) for the strongly basic anilines (X = 4-MeO, 4-Me, H). The primary normal DKIEs became systematically greater with a stronger nucleophile and with a more electron-withdrawing substituent in the substrate: identical trends with respect to Y and opposite with respect to X in the present results. In the case of secondary inverse DKIEs, the variation trends lacked consistency. With respect to X, the DKIEs became systematically greater with a stronger nucleophile for Y = (4-MeO, 4-Me, H), but systematically smaller with a stronger nucleophile for Y = (3-Cl, 4-CN). With respect to Y, the DKIEs became systematically greater with a more electron withdrawing Y for X = (3-Cl, 3-NO_2), but Y(k_H/k_D); 4-MeO(0.490) < 4-Me(0.495) < H(0.504) > 3-Cl(0.462) > 4-CN(0.367) for X = 4-Cl.

It needs to be stressed that the DKIEs obtained that are greater than unity are not ascribed to the secondary normal *β*-type-DKIEs observed when the rate-limiting step is a breakdown of the intermediate. The secondary normal *β*-type-DKIEs were reported for the reactions of: (i) 4-nitrophenyl acetates with deuterated primary and secondary amines in MeCN and chlorobenzene giving k_H/k_D = 0.93-1.00;[14] (ii) phenyl benzoates with deuterated benzylamines in MeCN giving k_H/k_D = 1.03-1.10;[15] (iii) benzhydryl chlorides with deuterated pyrrolidines in MeCN giving k_H/k_D = 1.02-1.11;[16] (iv) phenyl dithiobenzoates with deuterated anilines in MeCN giving k_H/k_D = 1.01-1.02;[17] (v) thiophenyl benzoates with deuterated pyrrolidines and benzylamines in MeCN giving k_H/k_D = 1.02-1.06 and 1.01-1.03, respectively;[18] (vi) 4-nitrophenyl *N*-phenylcarbamates with deuterated benzylamines in MeCN giving k_H/k_D = 1.04-1.12;[19] (vii) phenylacetyl chlorides with deuterated anilines in MeCN giving k_H/k_D = 1.03-1.11;[20] (viii) 2-norbornyl arensufonates with deuterated anilines in MeCN giving k_H/k_D = 1.09-1.11.[21] The obtained order of 1.1 is consistent with the typical value of secondary normal *β*-DKIEs.[22]

In the present work, a concerted mechanism is proposed on the basis of the negative sign of the CICs ($\rho_{XY(H)}$ = –0.38 and $\rho_{XY(D)}$ = –0.29). The DKIEs suggest that the nucleophile attacks the substrate from both the backside (type TSb) and frontside (type TSf), as observed in the anilinolysis of dimethyl chlorothiophosphate[3g] and Y-*O*-aryl methyl phosphonochloridothioates.[3k] Backside nucleophilic attack (in-



Scheme 3. Plausible TS structure.

line-type TSb) would be predominant for a stronger nucleophile and a more electron-donating Y substituent in the substrate. When X = Y = 4-MeO, the steric congestion in the TS is so severe that the secondary inverse DKIE could be as small as 0.439. As X and Y change from electron-donating to electron-withdrawing, the DKIEs gradually increase. These results suggest that the fraction of backside attack gradually decreases, while that of frontside attack gradually increases. When both X and Y are electron-withdrawing groups (X = 3-Cl and Y = 4-CN) frontside attack (a hydrogen-bonded, four-center-type TSf) would be predominant and, as a result, primary normal DKIE is as large as 1.34.

Alternatively, the experimental results can be divided simply into two parts depending only on nucleophiles, and suggest the mechanism as follows: (i) predominant backside attack with a secondary inverse k_H/k_D = 0.439-0.918 for strongly basic anilines (X = 4-MeO and 4-Me); (ii) predominant frontside attack with a primary normal k_H/k_D = 1.03-1.34 for weakly basic anilines (X = H, 4-Cl, and 3-Cl). However, the free energy correlations, Hammett ($\rho_{X(H\text{ and }D)}$ and $\rho_{Y(H\text{ and }D)}$; Figs. S7 and S8), Brönsted ($\beta_{X(H\text{ and }D)}$; Fig. S9), and CIC ($\rho_{XY}$; Fig. 1) plots, show good linearities without break region or point spread over the substituents of X and Y. This stands in contrast to the biphasic concave downwards nonlinear free-energy correlations with a break region between X = H and 4-Cl for the anilinolysis of Y-*O*-aryl methyl phosphonochloridothioates.[3k,23] Thus, in the present work, it may be more reasonable that the fraction of backside and frontside attacks of the aniline nucleophile changes gradually with variation in the substituents of X and Y.

It is worthy of note that another plausible TS structure with $k_H/k_D > 1$ could be TS I in Scheme 3, taking into account a four-membered TS II in the ethanolyses of the phosphinates, paraxon, and parathion with alkali metal ions by Buncel[24] and Um.[25] However, positive charge development on the hydrogen (deuterium) atom of the N–H(D) moiety in the TS I would be much smaller than that on M^+ ions, so that a hydrogen bond involving the acceptor P=S, as in the TS I, is not feasible. Most of all, the obtained DKIEs of k_H/k_D = 0.439-1.34 cannot be rationalized by the TS I. Thus, the TS I can be safely ruled out to substantiate the observed primary normal DKIEs of $k_H/k_D > 1$.

In summary, the nucleophilic substitution reactions of Y-*O*-aryl phenyl phosphono-chloridothioates with $XC_6H_4NH_2(D_2)$ in MeCN at 55.0 °C are kinetically investigated. Surprising substituent effects of X and Y on DKIEs (k_H/k_D) are observed. The DKIEs systematically increase from extremely large secondary inverse (k_H/k_D = 0.439) to primary normal (k_H/k_D = 1.34) as both substituents of the nucleophile and substrate change from electron-donating to electron-withdrawing, rationalized by a gradual TS variation from backside to frontside nucleophilic attack. The trigonal bipyramidal pentacoordinate TS is proposed for a backside attack, while a hydrogen-bonded, four-center-type TS for a frontside attack. A concerted S_N2 mechanism is proposed for the studied reaction systems on the basis of the negative values of the cross-interaction constants.

Experimental Section

Materials. The substrates were prepared as previously described.[4f] HPLC grade acetonitrile was used for the kinetic studies without further purification. Anilines were redistilled or recrystallized prior to use. Deuterated anilines were prepared by heating anilines with D_2O at 85 °C for 72 h with one drop of HCl added as a catalyst. After numerous attempts, the anilines were deuterated more than 98%, as confirmed by ^1H NMR.

Kinetic Procedure. Rates were measured conductometrically in MeCN at 55.0 °C. A self-made computer connected automatic A/D converter conductivity bridge was used in this work. Pseudo-first-order rate constants (k_{obsd}) were determined as previously described[3] with a large excess of anilines: [Substrate] = 3×10^{-3} M and [X-Aniline] = 0.1-0.5 M.

Product Analysis. *O*-(4-Methoxyphenyl) phenyl phosphonochloridothioate was treated with excess 4-methylaniline for more than 15 half-lives at 55.0 °C in acetonitrile. The 4-methylaniline hydrochloride salt was separated by filtration. Acetonitrile was evaporated under reduced pressure. The remaining product was isolated with ether by a work-up process with water-ether system and dried over anhydrous $MgSO_4$. Then the product was isolated by evaporating the solvent under reduced pressure after filtration. The physical constants are as follows:

[(4-CH_3O-C_6H_4O)(C_6H_5)P(=S)(NHC_6H_4-4-CH_3)]: Reddish brown gelatinous substance; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 14.3, 7.4 Hz, 2H), 7.51-7.44 (m, 3H), 7.10 (dd, J = 6.9, 3.3 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 6.84-6.78 (m, 4H), 5.68 (d, J = 8.8 Hz, 1H, N-H), 3.76 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8 (d, J = 2.3 Hz), 143.5 (d, J = 9.9 Hz), 137.1 (d, J = 3.8 Hz), 133.3 (d, $J_{P\text{-}C}$ = 146.3 Hz), 131.9 (d, J = 3.8 Hz), 131.6 (s), 130.7 (d, J = 11.4 Hz), 129.7 (s), 128.6 (d, J = 15.1 Hz), 122.6 (d, J = 3.7 Hz), 118.0 (d, J = 6.8 Hz), 114.4 (d, J = 1.5 Hz), 55.5 (s, OCH_3), 20.6 (s, CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ 73.43 (s, 1P); IR (KBr, cm^{-1}) 3251 (-NH-), 3000 (C-H, aromatic), 1503 (C=C, Ar) 1440 (P-C, Ar), 1373, 1193 (P-O-C_6H_4), 832 (P=S); GCMS: *m/z* 369 (M^+); Anal. Calcd for $C_{20}H_{20}O_2NPS$: C, 65.02; H, 5.46; S, 8.68, N, 3.79. Found: C, 65.09; H, 5.60; S, 8.81, N, 3.65.

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