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P–S Bond Scission by Bis(cyclopentadienyl)molybdenum(IV) Dichloride, Cp_2MoCl_2(aq): First Documented Example of an Organometallic Complex Hydrolyzing Thiophosphinates

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Thiophosphinate hydrolysis involving P–S bond scission is desirable for the degradation of organophosphate neurotoxins, and we report the first case for such a hydrolytic process by an organometallic compound. The metallocene, bis(cyclopentadienyl)molybdenum(IV) dichloride, Cp_2MoCl_2 ($Cp = \eta^5$-C_5H_5), hydrolyzes a variety of thioaryl diphenylphosphinates in an aqueous THF solution. P–S scission of *p*-methoxythiophenyl diphenylphosphinate has a 500-fold rate of acceleration in the presence of Cp_2MoCl_2(aq) with activation parameters of 20(3) kcal mol^{-1} and –15(3) cal mol^{-1} K^{-1} for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, respectively. These activation parameters and the rate acceleration are consistent with an intermolecular hydrolytic process in which the Cp_2Mo serves as a Lewis acid to activate the phosphinate for nucleophilic attack. Furthermore, $\rho = 2.3$ (25 °C) which indicates a single nonconcerted mechanism in which the rate determining step is the nucleophilic attack on the activated phosphinate.

Introduction

The degradation of organophosphate toxins is a national security goal because of the threat of chemical warfare agents and the 1997 Chemical Weapons Convention treaty.[1] Nerve agents such as fluorophosphonates are readily hydrolyzed in alkaline solution through P−F cleavage, whereas P−S bond cleavage for nerve agents such as VX is more difficult.[2] Alkaline hydrolysis of VX in 0.1 M aqueous NaOH results in both P−S (87%) and P−O (13%) cleavage.[3] However, P−O cleavage yields a phosphonothioate ion that is nearly as toxic as the parent VX molecule.[4] Therefore, there is a major incentive to find reactions that cleave the P−S bond of phosphonothioates through perhydrolytic[5,6] and aqueous[7] pathways. The high toxicity of organophosphorus neurotoxins necessitates the use of model compounds such as phosphinates [$R_2P(O)\cdot OR'$], thiophosphinates [$R_2P(O)\cdot SR'$], phosphonothioate [$RP(O)\cdot(OR')SR''$], and thiophosphate esters [$R_2P(S)\cdot OR'$]. In studies with model compounds, oxone[8] and micellar iodoso- and iodoxybenzoates[9] degraded organophosphorus molecules, and selective P−S fission was seen for phosphonothioate degradation.

We report the first case of thiophosphinate hydrolysis by an organometallic compound, which may open up a new class of reagents for the degradation of organophosphorus neurotoxins. The metallocene bis(cyclopentadienyl)molybdenum(IV) dichloride[10] (Cp_2MoCl_2: $Cp = \eta^5$-C_5H_5) was chosen because of its water solubility and aqueous properties.[11] Structurally, Cp_2MoCl_2 resembles a clamshell where

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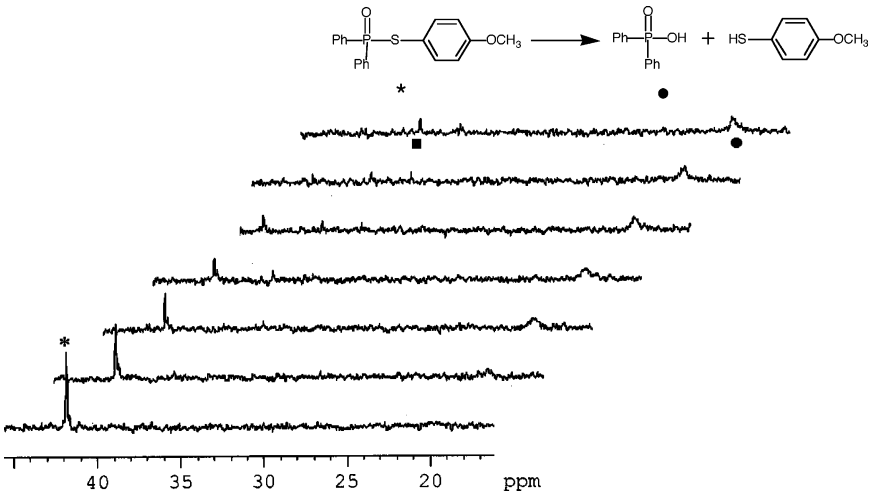

Figure 1. ^{31}P NMR stacked plot of the hydrolysis of **I** by Cp_2MoCl_2., monitoring the P−S scission of **I** (4 mM) by Cp_2MoCl_2 (33 mM) in a D_2O/THF (1:2) solution at 30 °C with 41 mM MOPS at pH 5.0. Each spectrum is separated by a seven minute time interval. The asterisked signal at 41.9 ppm (*) is the starting material (**I**), while the signal at 21.0 ppm (●) is the diphenylphosphoric acid product. A trace signal at 38.5 (■) is attributable to an adduct formed between Cp_2MoCl_2 and diphenylphosphoric acid.

both cyclopentadienyl ligands flank a pseudotetrahedral Mo(IV) coordinated to two chlorides.[12] In water, the cyclopentadienyl rings remain bound to the tetrahedral Mo(IV) center even at neutral pH. Meanwhile, both chlorides rapidly hydrolyze off ($\tau_{1/2} \approx 20$ min) to form aquated species with pK_a values at 5.5 and 8.5.[11] These aqueous properties and the diamagnetic d^2 molybdenum center make this metallocene amenable for observing phosphinate hydrolysis with NMR methods.

The Cp_2MoCl_2(aq) complex has been found to hydrolyze activated[13] and inactivated[14] phosphate esters with rate accelerations of 10^7 to 10^8. It was postulated that the mechanism proceeds through intramolecular attack on the phosphate by a Cp_2Mo-bound hydroxide. We also showed that the same metallocene hydrolyzes the thiophosphate ester parathion through nucleophilic attack by a water solvent molecule at the α carbon of the ethyl group.[15] The Cp_2Mo center serves as a coordinating Lewis acid that activates the thiophosphate for this intermolecular process with up to a 10^3 rate acceleration. Herein, we extend the well-known Cp_2Mo[16] coordination chemistry toward aqueous P−S scission transformation for the long-term goal of determining which factors promote phosphonothioate hydrolysis.

Materials and Methods

^{31}P and ^{1}H NMR spectra were obtained on a Bruker Avance-300 at 121 and 300 MHz, respectively, and the phosphorus spectra were acquired using inverse-gated decoupling with a delay of ~4 T_1. The Cp_2MoCl_2 compound was obtained from Strem Chemical Co. (Newburyport, MA), and all reagents for the synthesis of the thiol phosphinates were purchased from Aldrich (Milwaukee, WI) and used without further purification. The thioaryl diphenylphosphinates were prepared according to the procedure of Blasko and co-workers.[8] Manipulations with Cp_2MoCl_2 were done in an Innovative Technology System One Glovebox or with standard Schlenk techniques. All solvents used in the hydrolysis studies were purged with N_2 for >10 min, and the reported pH readings in D_2O are uncorrected. Stock solutions of Cp_2MoCl_2 in D_2O containing 41 mM MOPS were made and adjusted to pH 4.5 with concentrated HCl or NaOH prior to kinetic measurements. The hydrolysis reactions, which were followed by ^{31}P NMR, were initiated by adding a degassed THF solution of the thioaryl diphenylphosphinate to the aqueous Cp_2MoCl_2 so that their final concentrations were 4 and 33 mM, respectively.

After it sat for more than a week, the reaction of Cp_2MoCl_2 with *p*-methoxythiophenyl diphenylphosphinate (**I**) in the NMR tube yielded yellow needles that were washed with a 1:1 ether/hexane mixture. The compound $Cp_2Mo(S\text{-}C_6H_4\text{-}OCH_3)_2$ crystallizes in the monoclinic space group *C*2/*c* with $a = 21.983(2)$ Å, $b = 6.8325(5)$ Å, $c = 13.883(1)$ Å, $\beta = 96.509(2)°$, and $Z = 4$ at 153(2) K. Data collection was done on a Bruker SMART APEX CCD diffractometer with 13991 reflections (crystal size = 0.27 × 0.22 × 0.18 mm). The structure was solved by direct methods with the SHELXTL package (Sheldrick, G. M. SHELXTL-97, version 5.10; Bruker AXS, Madison, WI 53719). The final refinement converged to $R = 4.13\%$. Further details on the crystallographic collection are included in the Supporting Information material.

Results and Discussion

We set out to see if the molybdocene complex could promote P−S cleavage of thiophosphinates, such as **I**, to yield diphenylphosphonic acid and *p*-methoxythiophenol. The addition of THF to buffered (pH 4.5) aqueous solutions of Cp_2MoCl_2 (33 mM) solubilized the diphenylarylthiophosphinate (4 mM), which was monitored with ^{31}P NMR spectroscopy. Figure 1 clearly shows the disappearance of the starting thiophosphinate (41.8 ppm) and the appearance of a new upfield peak at 21.0 ppm that was diphenylphosphonic acid as identified through authentic addition. In addition, a signal at 38.5 ppm is seen in trace amounts which increases when we add a 1:1 adduct of diphenylphosphonic acid and Cp_2MoCl_2(aq).

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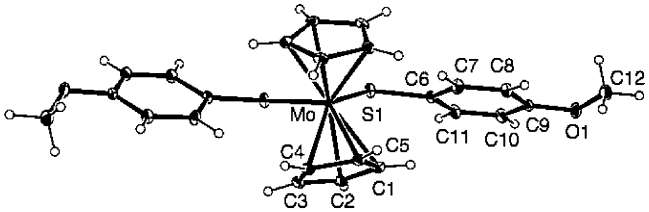
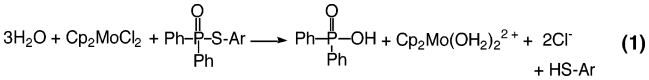


Figure 2. Crystal structure of $Cp_2Mo(S\text{-}C_6H_4\text{-}p\text{-}OCH_3)_2$ (**II**). Thermal ellipsoids represent 30% probabilities. Crystals were formed from the reaction of **I** with Cp_2MoCl_2 that was left in the NMR tube to settle for more than a week. Major geometrical parameters of **II** are as follows: Mo−S1 = 2.4775(6) Å, average Mo−C = 2.32(5) Å, and S−Mo−S = 77.72(3)°.

Therefore, both peaks, at 21.0 and 38.5 ppm, indicate the appearance of diphenylphosphonic acid as one of the products in the reaction of **I** with Cp_2MoCl_2. As was the case with phosphate triester hydrolysis (parathion and paraoxon) by Cp_2MoCl_2(aq),[15] we were unable to unequivocally establish from NMR alone the presence of a putative Cp_2Mo-phosphinate intermediate. The other major product is *p*-methoxythiophenol, which was confirmed (^{1}H NMR) with authentic addition to the final product mixture. The net reaction for this process at pH 4.5 can then be summarized with eq 1.



(1)

The thiophenol product in eq 1 coordinates to Cp_2Mo and precipitates nicely in the NMR tube to form X-ray quality crystals of a bis(*p*-methoxythiophenol) adduct (**II**). X-ray diffraction reveals that single crystals of **II** are composed of well-separated and discrete $Cp_2Mo(S\text{-}C_6H_4\text{-}p\text{-}OCH_3)_2$ molecules in which the Mo(IV) ion adopts the familiar "clamshell" geometry found in other Cp_2MoL_n complexes.[17] This geometry is unexceptional with regard to the average Mo−C bond distance (2.32(5) Å), and the Mo−S distance (2.4775(6) Å) is similar to that of other Cp_2Mo derivatives containing S-bonded ligands.[18] Even the S−Mo−S angle of 77.72(3)° is within the predicted L−M−L angle of ∼78° calculated for bent d^2 Cp_2ML_2 complexes.[19] The orientation of the two phenyl rings lie almost in the S−Mo−S plane (Figure 2) with a dihedral angle of 38.4°, which is consistent with the crystal structure of the $Cp_2Ti(SPh)_2$ complex in which the two phenyl rings point in almost opposite directions with one ring above and the other below the S−Ti−S plane.[20] Furthermore, Calhorda and co-workers have also seen a similar phenyl orientation relative to the metallocene equatorial plane in a $Cp_2Mo(NH_3)(SC_6H_5)^+$ structure in which extended HMO and steric energy calculations were used to account for the thiophenyl geometry.[21]

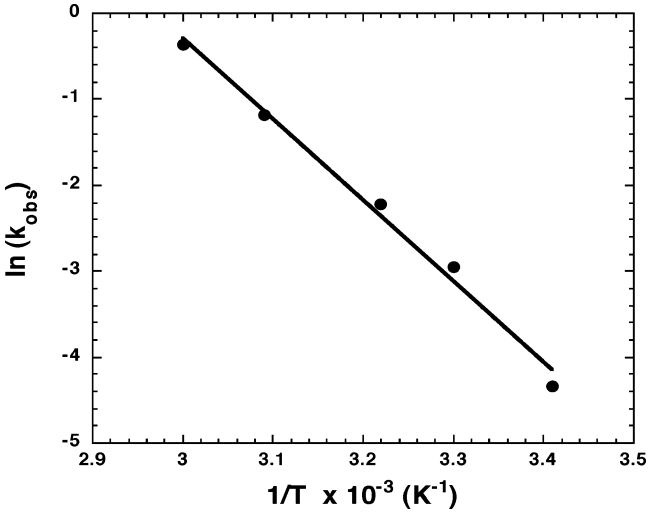


Figure 3. Arrhenius plot of the hydrolysis of **I** by Cp_2MoCl_2. Activation energy parameters were measured as $\Delta H^{\ddagger}$ = 20(3) kcal/mol and $\Delta S^{\ddagger}$ = 15(3) eu in the conditions described in the Experimental Section.

The disappearance of **I** followed first-order kinetics with a rate constant of 0.30 h^{-1} (50 °C) at pH 4.5. When the identical reaction was carried out in the absence of Cp_2MoCl_2, the rate constant was 6.0×10^{-4} h^{-1}, which represents a 500-fold rate acceleration with the molybdocene compound. The reaction was first order in **I**, and solubility issues in an aqueous THF solution precluded the determination of the reaction order of the Cp_2MoCl_2(aq) concentration. The rates of hydrolysis by Cp_2MoCl_2 reach a maximum at pH 6 and then drop in the alkaline range. It is interesting to note that this rate acceleration is close to the $\sim 10^3$ rate acceleration observed when the phosphate triester, parathion, is hydrolyzed by Cp_2MoCl_2(aq).[15]

The well-behaved kinetics of thiophosphinate hydrolysis prompted us to look at its temperature and leaving group dependencies to gain insight into the transition state for this process. The Arrhenius plot (Figure 3) of the hydrolysis of **I** by Cp_2MoCl_2 gives a $\Delta S^{\ddagger}$ value of −15(3) eu in the 20−60 °C temperature range, indicative of an ordered transition state consistent with an intermolecular process.

Prior measurements of alkylthiol dialkylphosphinate hydrolysis in alkaline solution yielded a $\Delta S^{\ddagger}$ value of −41 to −49 eu.[22] The higher $\Delta S^{\ddagger}$ value for the Cp_2Mo-promoted process is consistent with the notion that the cyclopentadienyl ligand provides a more disordered transition state (i.e., free rotation about the centroid−Mo bond) than a simple hydroxide attack on the thiophosphinate functionality. This implies that coordination of the Cp_2Mo fragment to the phosphinate is part of the transition state.

In previous studies of Cp_2MoCl_2-promoted hydrolysis of activated phosphate diesters, the $\Delta S^{\ddagger}$ was measured to be

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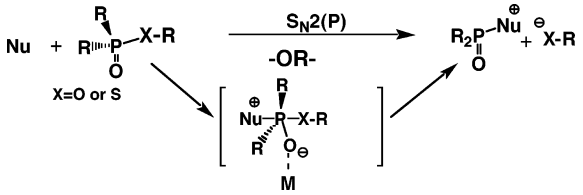
Scheme 1



0.0 eu,[13] which was attributable to an intramolecular process. Moreover, phosphate hydrolysis reactions promoted by metal complexes have yielded rate accelerations of $>10^7$ and 10^2 for intramolecular and intermolecular processes, respectively.[23] The 10^2 rate acceleration and the negative $\Delta S^{\ddagger}$ for the Cp_2MoCl_2-promoted hydrolysis of **I** is consistent with a bimolecular process in which the Cp_2Mo serves to activate the thiol phosphinate for nucleophilic attack. Molecular orbital calculations have suggested that the P═O group exists primarily in the dipolar form with a highly negative charge on the phosphinyl oxygen atom.[24] Coordination of the Cp_2Mo^{2+} group to the phosphinyl oxygen would increase the electrophilicity at the phosphorus atom for nucleophilic attack.

The thiophenolate leaving group prompted us to make several aryl derivatives of **I** at the para position which would allow us to probe the sensitivity of the P−S scission toward electronic effects as well as reveal possible mechanistic pathways. A number of hydrolysis studies have already been done with thioaryl phosphinates[22,25] and aryl phosphinates.[26] A mechanism involving direct displacement ($S_N2(P)$) results in a large rate difference between the phosphinate and thiophosphinate hydrolysis, and the rates themselves would correlate with Hammett's σ^-. Alternatively, in a reaction that goes through an intermediate, the rate determining step for both substrates would be the formation of the intermediate (Scheme 1) because the leaving groups are less basic than hydroxide. This leads to a relatively small difference in the rates of thiophosphinates and phosphinates, and the rates of hydrolysis correlate with the Hammett's σ constants.[25]

In Figure 4, there is linear free energy relationship between the Hammett's σ constant for the substituent on the leaving group and the rate of hydrolysis.

Besides indicating a single mechanism for the P−S scission process, the correlation with σ ($R = 0.993$) instead of σ^- (see Supporting Information) is consistent with a process which goes through an intermediate as shown in Scheme 1 where M = $MoCp_2$. With the exception of aryl dimethylphosphinate, all prior phosphinate and thiophosphinate hydrolysis studies under alkaline conditions correlate

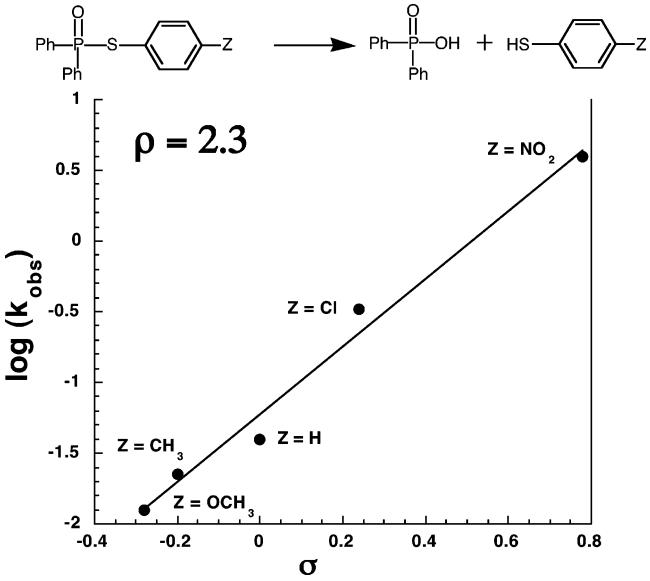
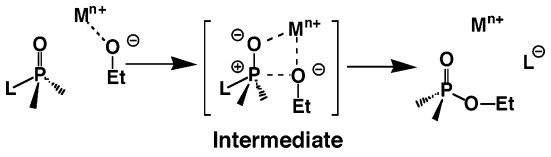


Figure 4. Linear free-energy relationship of thiophophosphinate hydrolysis by Cp_2MoCl_2. Hydrolysis reactions were carried out at 20 °C under the conditions described in the Experimental Section. The ρ value was measured to be 2.3.

Scheme 2



with σ constants.[25,26] Thiophosphinate hydrolysis studies by hydroxide give a ρ (25 °C) value of 1.46.[25] Cook and coworkers have listed an array of ρ values (25 °C) for the alkaline hydrolysis of phosphinates and thiol phosphinates in various solvents (no metal ions), and the highest value recorded is 2.2 for a phosphinate.[25] The measured ρ in thiol phosphinate hydrolysis by Cp_2MoCl_2 has a value of 2.3 (25 °C) in Figure 4. This indicates that, in the organometallic system, the hydrolytic process is more sensitive to electronic effects, which may result from the unique role of the metal in promoting the P−S fission process.

Dunn and Buncel have proposed a mechanism for the metal ion-catalyzed nucleophilic displacement of *p*-nitrophenyl diphenylphosphinate by ethoxide, which resembles the intermediate pathway depicted in Scheme 2 (R = 4-nitrobenzene, X = O, and nucleophile = ethoxide).[27] In their proposal, monovalent metal ions (K^+, Na^+, and Li^+) serve two roles, association of the phosphinyl oxygen that enhances the phosphorus nucleophilicity and formation of metal−ethoxide ion pairs that catalyzes the ethoxide nucleophilic attack on the phosphinate. By microscopic reversibility it is possible that the metal ion could coordinate to a leaving group, which in this case would be a tight ion pair between an oxophilic alkali metal ion and the oxygen atom of ethoxide.

This mechanism prompts us to ask if Cp_2Mo coordination to the sulfur leaving group plays a part in the P−S scission chemistry especially in light of the fact that compound **II**

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was one of the main products in the hydrolysis reaction and that Cp_2Mo coordination to sulfur-containing molecules is well-known.[18] Various ortho-substituted thiophenyl diphenylphosphinates were made to sterically encumber possible Cp_2Mo coordination to the sulfur leaving group. These derivatives were 2-methylthiophenyl and 2,6-dimethylthiophenyl diphenylphosphinate, and their rates of hydrolysis by Cp_2MoCl_2 were measured relative to *p*-methylthiophenyl diphenylphosphinate. The measured first-order hydrolysis rates shows a drop of 2−3 in the rates of P−S scission by Cp_2MoCl_2 when 2-methylthiophenyl and 2,6-dimethylthiophenyl diphenylphosphinate were hydrolyzed.

This drop in P−S scission rates with sterically encumbered leaving groups becomes insignificant in light of the fact that 2-methylthiophenyl diphenylphosphinate by itself undergoes P−S cleavage 2−3 times slower than the *p*-methylthiophenyl derivative. The drop in the rate of hydrolysis may be an inherit property caused by the steric hindrance of the five-coordinate phosphorus intermediate of the ortho-substituted thiol phosphinates.[28] This suggests that metal coordination to the leaving group (Scheme 2) either does not take place or plays a minor role in P−S hydrolysis. Consistent with this notion is the recent report by Tyler and co-workers who showed that the hydrolysis of carboxylic esters by $(MeCp)_2Mo(OH)(OH_2)^{2+}$ displayed no Mo(IV) coordination to the alkoxide leaving group.[29] The Mo−S bond strength in Cp_2Mo complexes is reported to be 20−25 kcal/mol weaker than the corresponding Mo−O bond;[30] this further underscores the fact that the Mo(IV) coordination to the sulfur leaving group is not critical to the hydrolysis of thiol phosphinates. Instead, the key pathway for the thiophosphinate hydrolysis proceeds through Scheme 1 where M = $MoCp_2$.

Conclusion

We have shown the first case of an organometallic complex that hydrolyzes thiol phosphinates through P−S scission. Kinetics data are consistent with a mechanism that involves intermolecular nucleophilic attack to form a five-coordinate intermediate, which is the rate determining step, followed by expulsion of the thiophenolate leaving group. This mechanistic hypothesis is in accordance with the prior phosphinate hydrolysis studies in alkaline solution. The rate accelerations of the thiophosphinates by Cp_2MoCl_2 are proposed to come from the binding of the phosphinyl oxygen to the Mo(IV) center to increase the electrophilicity of the phosphorus center for nucleophilic attack. These initial findings lead us to examine the hydrolysis of phosphonothioates that have both thiolate and alkoxide leaving groups, as means to see the viability of Cp_2MoCl_2 and its derivatives as reagents to degrade organophosphorus neurotoxins.

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Supporting Information Available: X-ray crystallographic files in CIF format for the structure determination of $Cp_2Mo(S\text{-}C_6H_4\text{-}pOCH_3)_2$ (**II**) and a graph of the absence of a correlation of the rate of hydrolysis with σ^-. This material is available free of charge via the Internet at http://pubs.acs.org.

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