

DFT Studies on Hydrolyses of Dimethylchlorothiophosphate

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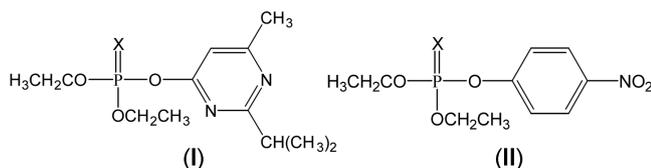
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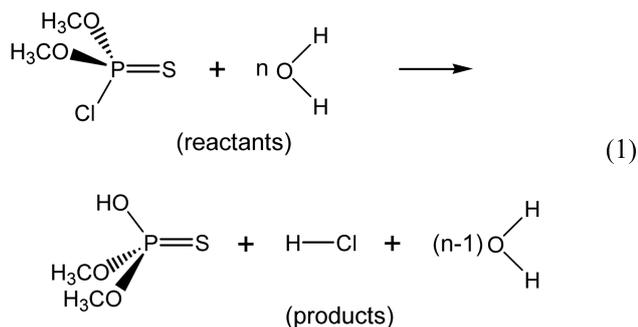
Received May 17, 2006

Key Words : Density functional theory, Hydrolyses, Dimethylchlorothiophosphate

Many thiophosphates are widely used as substrate analogues in studies of enzymatic reactions as well as organic insecticides in agricultural pest control. These organophosphorus compounds yield toxic metabolites by several reactions before hydrolysis occurs.¹ Therefore, the rates of hydrolyses of these compounds are important for green chemistry.^{1c} More sluggish degradations of thiophosphate pesticides are often observed as compared with the corresponding phosphate compound: for example, the hydrolysis rate of diazinon (I, X=S) is slower than that of the diazoxon (I, X=O), where the sulfur atom is replaced by oxygen atom, by about 10 times at pH of 7.4, corresponding to the difference in the free energy of activation by about 1.1 kcal/mol at 20 °C. However, an inverse thio effect ($k_S/k_O > 1$) was found occasionally for the hydrolyses of organophosphorus compounds including parathion (II, X=S) and paraoxon (II, X=O),³ and it was rationalized by the higher electronegativity of oxygen as compared to sulfur.⁴ Although, the differential electronic structure including the bond order and charge localization of P=O and P=S bond are discussed in detail,⁵ the relative bond order and charge localization are varied for the phosphorothioates and the origin of differential reactivity of those compounds is not clear.



Although the mechanism of phosphoryl-transfer reactions have been extensively discussed both experimentally as well as theoretically, theoretical studies on the thiophosphoryl-transfer



reactions are very scarce.⁶ In the present work, we examine the mechanism of the hydrolysis of thiophosphates (eq. 1), and compare with the results of hydrolysis of chlorophosphates,⁷ which we have successfully reproduced the relative reactivity for the different halides as leaving groups.

Computational Method

All calculations were performed using the Gaussian 98⁸ on the PC cluster implemented with the Linda parallel program. All structures were fully optimized at the density functional theory (DFT) of Becke's 3-parameter hybrid method using the correlation functional of Lee, Yang, and Parr (B3LYP)⁹ at the 6-31G(d) level.

Gas phase transition state structures were located by the Bery optimization algorithm using the "Opt=CalcAll" option which requests that second derivatives are computed at every point in the optimization,¹⁰ and the structures exhibited only one imaginary frequency. For the reactions in water, we used Onsager's self-consistence reaction field (SCRf) method¹¹ with dielectric constant of 78.5. Cavity radii were adjusted consistently since the transition structures in water were different from that of the gas phase. The Gibbs free energies of activation were estimated using equation (2), where the energies were corrected for basis set superposition error (BSSE)^{12,13} and entropic effects in solution as described in previous report.⁷

$$\begin{aligned} \Delta G^\ddagger &= \Delta H_{\text{Onsager}}^\ddagger - \alpha T \cdot \Delta S^\ddagger + \beta \text{BSSE} \\ &= \Delta H_{\text{Onsager}}^\ddagger - T(0.54 \Delta S^\ddagger + 0.48) + \beta \text{BSSE} \end{aligned} \quad (2)$$

Natural bond orbital (NBO) analyses were applied to calculate the proximate $\sigma-\sigma^*$ (including $n-\pi^*$, $n-\sigma^*$ etc.) charge-transfer energies and electrostatic interaction energies.¹⁴

Results and Discussion

Figures 1 and 2 show potential energy profile and some stationary structures for the hydrolysis of chlorothiophosphate (PSCl) with one water molecule in the gas phase. The energy profile and structures are very similar to that for the hydrolysis of chlorophosphate (POCl), except slightly higher first barrier (TS1) by 2.6 kcal/mol in PSCl.

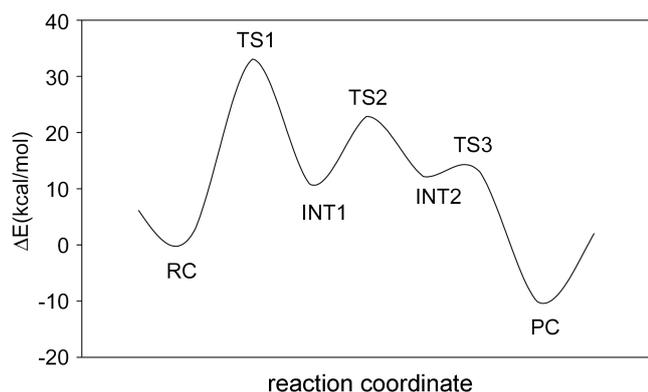


Figure 1. Potential energy profile ((B3LYP/6-31G(d)) for the hydrolysis of chlorothiophosphate (PSCl) with one water molecule in the gas phase. RC, TS, INT and PC refer to reactant complex, transition state, intermediate and product complex, respectively. The relative energies of the stationary structure are 0.0(RC), 32.41(TS1), 11.18(INT1), 22.99(TS2), 11.11(INT2), 12.93(TS3), and -10.08 (PC) kcal/mol.

The first step involves a nucleophilic attack by water to form a four membered cyclic transition state (TS1) followed by P-SH rotation (TS2) and H-Cl leaving (TS3) steps as shown in the hydrolysis of POCl.

In the reaction field, structures for the hydrolysis with one water are close to those of the gas phase, but we found two transition structures for the hydrolysis with two water molecules, which are termed TS_{cyc} and TS_{lin} as shown in Figure 3.

The former corresponds to the bifunctional catalysis,¹⁵ and the latter corresponds to the general base catalyst. Overall structures are very similar to those of POCl. Activation energies relative to the separated reactants in the reaction field are summarized at Table 1. Additional or catalytic water molecule lowered the barrier substantially as found in hydrolysis of POCl. The reaction mechanism in the reaction field is purely one step concerted $S_N2(P)$ as found in the hydrolysis of POCl.⁷ The linear transition structure (TS_{lin}) is quite different from that of the cyclic transition structure due to the fact that more polar TS is substantially stabilized compared to the less polar cyclic transition structure. However, the magnitude of barrier of *ca.* 6 kcal/mol for the

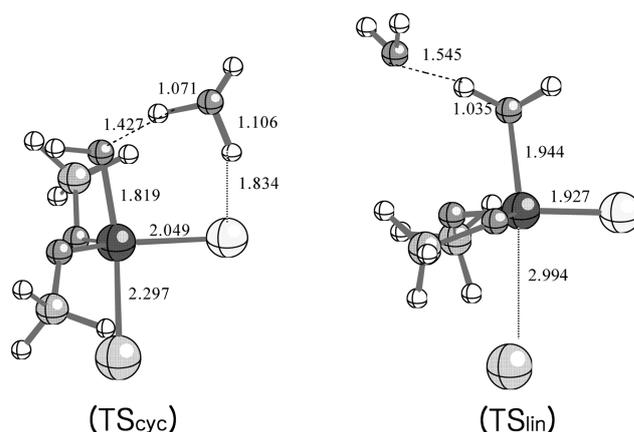


Figure 3. Transition structures for the hydrolysis of chlorothiophosphate with two water molecules in the reaction field. Only selected bond lengths in Å are displayed. Central atom is phosphorus and chlorine atom is pointing downward.

hydrolysis of PSCl through the path with linear TS seems to be too small comparing those of Diazinon and Diazoxon^{2b} which are about 12-14 kcal/mol at pH of 3.1 and 10.4. Therefore it is necessary to correct entropic effect and basis set superposition error to bring up to these experimental range of magnitude.

We summarized activation parameters of some reactions using strategy adopted in our previous work (eqn. (2)) at

Table 1. Electronic energies (Hartrees) of reactants and transition states and activation energies (kcal/mol) relative to the separated reactants in the reaction field

Reaction	E(B3LYP/6-31G(d))		ΔE^\ddagger
	separated reactants	TS1	
$(CH_3O)_2PSCl + H_2O$	-1506.48374	-1506.43613	29.87
$(CH_3O)_2PSCl + 2H_2O$ (cyclic TS)	-1582.89573	-1582.87607	12.34
$(CH_3O)_2PSCl + 2H_2O$ (linear TS)	-1582.89573	-1582.88651	5.78
$(CH_3O)_2POCl + 2H_2O$ (linear TS)	-1259.94048	-1259.93664	2.41

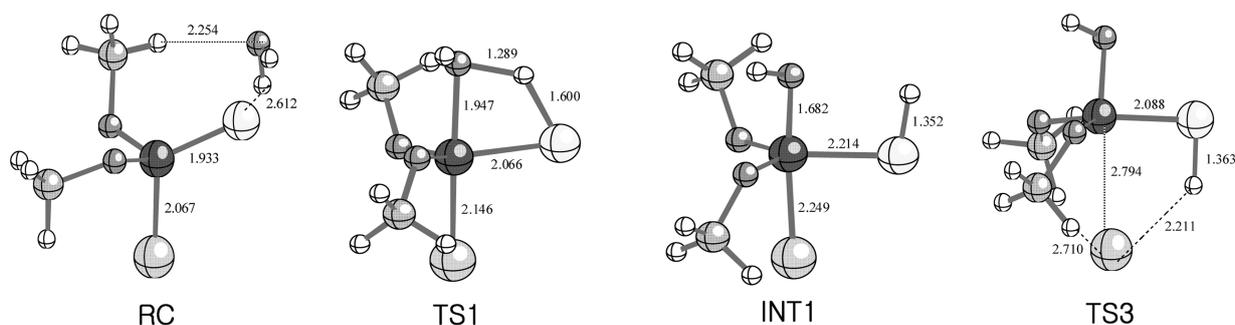


Figure 2. Some stationary structures for the hydrolysis of chlorothiophosphate with one water molecule in the gas phase. Only selected bond lengths in Å are displayed. Central atom is phosphorus and chlorine atom is pointing downward. The structure of TS2 is not displayed, but the structure is very close to that of INT1 with different torsional angle of Cl-P-S-H.

Table 2. Estimated activation parameters (B3LYP/6-31G(d), kcal/mol) for the hydrolysis of (CH₃O)₂PSCl and (CH₃O)₂POCl in the reaction field at 298 K

	(CH ₃ O) ₂ PSCl		(CH ₃ O) ₂ POCl	
	H ₂ O	2H ₂ O (cyclic)	2H ₂ O (linear)	2H ₂ O (linear)
$\Delta H_{\text{nsager}}^{\ddagger}$	29.18	12.44	8.43	4.98
ΔS^{\ddagger}	-39.33	-75.01	-67.98	-65.99
BSSE	7.77	12.29	8.84	8.22
ΔG^{\ddagger}	$\beta=1$	43.14	36.66	28.07
	$\beta=0.5$	39.26	30.52	23.65

Table 2.

Gibbs free energy of activation with correction of well known 50% BSSE ($\beta = 0.5$)¹³ shows good estimation of relative reactivity of PSCl to the POCl. The magnitude of Gibbs free energy of activation can be compared with estimated values of diazinon (27.0 kcal/mol at 20 °C) and diazoxon (25.9 kcal/mol) from the reported rate constant^{2b} using transition state theory. Without the experimental Gibbs free energy of activation for the hydrolysis reaction of PSCl, the value is reasonable quantity, and the corrections of entropy in the solution and BSSE with suitable scaling factor seem to be essential in discussion of reactivity. As found in the hydrolysis of the POCl,⁷ additional water molecule acts as a purely general base catalyst, and the reaction is subjected to the third order kinetics in the reaction field. The third order kinetics are well discussed in many solvolytic reactions.¹⁶ Since the potential energy profiles and transition state structures are almost the same for the hydrolysis of POCl and PSCl in the reaction field, the different reactivity of those compounds can be rationalized by examining the orbital interaction between nucleophile and substrate. The simplest way is to examine the energy levels of frontier molecular orbital (FMO) of reactants,¹⁷ *i.e.*, water, POCl and PSCl etc. However the calculated LUMO energy of PSCl (-0.75 eV) is lower than that of the POCl (-0.05 eV),¹⁸ which contradicts the simple FMO theory that the lower the LUMO level of substrate, the faster is the reaction rate in the nucleophilic substitution reaction. Therefore the reaction should be examined with interactions between all molecular orbitals. To take all molecular orbitals into account, we performed the NBO analysis¹⁴ for the TSs of the hydrolysis reactions of PSCl and POCl with two water molecules in the reaction field. The TSs are stabilized by the relatively strong proximate charge-transfer interaction ($\Sigma\Delta E_{\sigma-\sigma^*} = -134$ kcal/mol) in the POCl than in the PSCl (-29 kcal/mol).

The electrostatic interaction energies of the POCl and PSCl are -47 kcal/mol and -34 kcal/mol, respectively. Both of the higher stabilization interactions in POCl than in PSCl could be the reasons for the higher reactivity of POCl than of PSCl, and the charge transfer delocalization is the predominant transition state stabilization factor. This is clear by examining the HOMOs of the two transition structures as shown at Figure 4 with FMO diagram. The HOMO of POCl is more delocalized than that of PSCl. However, the

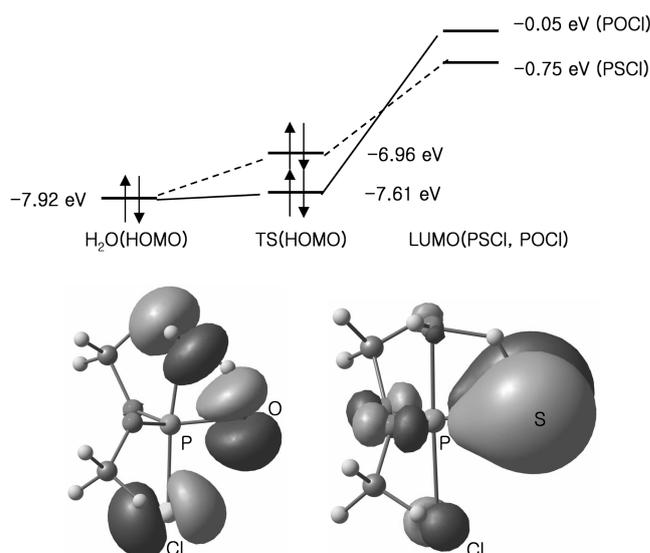


Figure 4. FMO Diagram and HOMOs of POCl (left) and PSCl (right).

differences of other indices such as deformation energies¹⁹ of POCl (50.53 kcal/mol) and PSCl (49.57 kcal/mol) and, the estimated P-Cl force constants (B3LYP/6-31G(d)) at POCl (0.1602 hartrees/Å²) and at PSCl (0.1578 hartrees/Å²), are so small to clarify the relative reactivity of POCl and PSCl.

Acknowledgment. It is gratefully acknowledged that this work was supported by Gyeongsang National University.

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18. Since one of the reviewers pointed out the deficiency of DFT method in the calculation of orbital energy, especially negative LUMO energy here, we confirmed that the order of energy levels and the shape of FMO obtained by DFT are the same as those obtained by Hartree-Fock (HF) method except negative LUMO energy.
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