DFT Study of the Silyl Esters of Thiophosphorus Acids

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Abstract Quantum mechanical DFT calculations of the model methyl and silyl esters of simple thiophosphorus acids are presented which help to predict some structural features and reactivity aspects of these reactants. Their applicability in organophosphorus chemistry is discussed.

Keywords Silyl esters of thiophosphoric acids · Silyl esters of thiophosphinic acids · Structure · Reactivity · DFT calculations

1 Introduction

Phosphorus acids and their esters play an essential role in the chemistry of life. Among them, thiophosphorus acids are of particular importance in organophosphorus chemistry. A change in the rate of hydrolysis has been observed to accompany this sulfur substitution, leading to a phenomenon known as the “thio effect” [1]. The simple replacement of an anionic oxygen by sulfur in the phosphate group (PO-oligonucleotides) not only enhances the resistance to degradation by nucleases [2] but also, in many instances, favorably alters the biological activity [3, 4]. Several phosphorothioate antisense oligonucleotides (PS-ODNs)

constitute a new class of potent drugs directed against various diseases and are currently undergoing clinical evaluation for a number of diseases, including cancer, viral infections, and inflammatory disorders [5–8]. The thiono-thiolo isomerization of O-alkyl esters of thiophosphoric acids to corresponding S-alkyl isomers is one of the most important reactions because of high biological activity of both esters. The isomerization can be effected by both bases (amines, phosphines) and acids [9, 10].

Recent decades have witnessed a dynamic growth in the area of silicon-containing organophosphorus reagents. Their potential in the synthesis of organophosphorus compounds of industrial, biological, medical, and other synthetic uses have been widely recognized and exploited [11, 12].

The silyl ester function plays an important role in organic chemistry especially as a versatile protecting group in multistep synthesis [13]. Phosphorus esters undergo facile transesterification reactions with silyl halides to form the corresponding phosphorus silyl esters and alkyl halides [14, 15]. The silyl esters are cleaved by protic solvents under very mild conditions to yield the phosphorus acids which are often hardly available by any other route [12]. An important application of silyl esters of tetracoordinate phosphorus is connected with their use as precursors of phosphorus acids applied as models for biochemical mechanistic studies [16–21].

Theoretical studies of small phosphate and thiophosphate models is an important step toward a detailed understanding of many biochemical processes at the atomic level [22–26]. We present here theoretical predictions of some structural features and reactivity aspects, in particular, thiono-thiolo isomerization of model silyl esters of oxy- and thio-phosphorus acids, that have never received even a cursory theoretical explication.

This communication is dedicated to Prof. Yitzhak Apeloig on the occasion of receiving 2010 Kipping Award in recognition of his outstanding contribution to silicon chemistry

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2 Experimental

2.1 Gas-Phase Calculations

All the structures were optimized in the gas phase with Kohn-Sham density functional theory (DFT) methods using the hybrid exchange functional of Becke [27] and the Lee, Yang, and Parr correlation functional [28] (B3LYP). Geometry optimizations were done in redundant internal coordinates with default convergence criteria [29]. Frequency calculations were performed to establish the nature of all stationary points and to allow evaluation of thermodynamic quantities such as thermal vibrational contributions to the enthalpy, entropy and Gibbs free energy.

The geometry optimization and frequency calculations were performed using the 6-31+G(d) basis set. Electronic energies were obtained via single-point calculations at the optimized geometries using the 6-311+G(2d,p) basis set and the B3LYP hybrid density functional. This protocol for obtaining the geometry and energy is designated by the abbreviated notation B3LYP/6-311+G(2d,p)//B3LYP/6-31+G(d). Single-point calculations were run with “tight” convergence criteria [30] to ensure high precision for properties sensitive to the use of diffuse basis functions. This method typically yields relative energies within 3 kcal/mol of experimental values [31]. Because of known limitations of density functional theory, the high level CCSD/6-311+G(2d,p)//B3LYP/6-31+G(d) method was also used to determine single-point energies for the simple structures, to verify the reliability of the DFT results for the class of compounds studied [32]. All electronic structure calculations were performed with the Gaussian 03 suite of programs [30].

2.2 Analysis of Softness and Nucleophilicity

Softness and local nucleophilicities of oxygen and sulfur centers were analyzed in terms of the condensed Fukui functions, $f_k^- = q_k(N) - q_k(N-1)$ and $f_k^+ = q_k(N+1) - q_k(N)$ [33]. For a system of N electrons, independent calculations were made for the corresponding $(N-1)^-$, N^- and $(N+1)$ -electron systems using molecular geometry optimized for N -electron species. Natural electron populations $q_k(N)$ required for calculation of the Fukui functions were computed using the NBO theory as implemented in Gaussian 03 at the B3LYP/6-31+G* level [34]. Global softness was calculated as $\sigma = 1/(IP-EA)$, where IP is the vertical ionization potential and EA is the vertical electron affinity of the

Fig. 1 Structures of the model compounds, where $R = H, Me, F, OMe$ and NH_2 ; $R' = H$ and Me

Table 1 B3LYP/6-31+G(d) bond lengths (Å) in silyl esters of thiophosphorus acids $R_2P(X)YSiH_3$, $X, Y = O, S$

R	P=O	P-S(Si)	S-Si	P=S	P-O(Si)	O-Si
H	1.497	2.120	2.185	1.946	1.623	1.696
Me	1.504	2.144	2.181	1.961	1.637	1.693
F	1.473	2.071	2.205	1.911	1.580	1.711
OMe	1.491	2.100	2.186	1.946	1.601	1.696
NH ₂	1.496	2.133	2.181	1.960	1.628	1.695

electrophile/nucleophile. Local softness of atom k was defined as $s_k = \sigma f_k$ [33].

2.3 Solvation Calculations

Solvation effects were treated by single point calculations based on the gas-phase optimized structures using the CPCM polarizable conductor calculation model [35] as implemented in Gaussian 03, using atomic radii optimized for the PBE1PBE/6-31G(d) level of theory (UAKS). In the present work the approximation is made that the gas-phase geometry, entropy, and thermal corrections to the enthalpy do not change upon solvation.

3 Results and Discussion

3.1 Geometries of Model Compounds

As model compounds for this preliminary study we have chosen simple P(IV) phosphorus and thiophosphorus acids and their silyl esters of general formulas (Fig. 1).

We have also calculated the geometries and energies of the corresponding acids and methyl esters. The selected bonding parameters of these model compounds are collected in Table 1.

Calculated bond lengths of phosphorus to oxygen and sulfur agree well with typical values measured by crystallographic methods [36]. Bonding parameters for F- and Me-substituted esters differ considerably from those of the other analogues. When $R = F$ the adjacent $P=X$ and $P-Y(Si)$ bonds to phosphorus are significantly shorter than for the other derivatives. For $R = Me$ the opposite trend is observed. This points to the importance of the inductive effect of the substituents at phosphorus. Surprisingly, the bond lengths for $R = OMe$ and NH_2 are not different from those in the case of $R = H$. This suggests that for these

Scheme 1 Thiono-thiolo rearrangement of thiophosphorus esters

esters the inductive and back-donating (anomeric) effects, which operate in opposite directions, compensate each other. The importance of the anomeric effect in the chemistry of phosphorus esters is well recognized [37]. Wiberg bond orders for ‘P=O’ and ‘P=S’ terminal bonds are in all cases in the range of 1.2–1.35 and 1.48–1.65, respectively. This supports the observation made previously that neither bond is a true double bond but they show rather an intermediate character [38]. Upon exchange of methyls by fluorines at phosphorus the Wiberg bond order of terminal ‘P=O’ bond increases from 1.22 to 1.34 in silyl phosphorothiolate and the bond order of terminal ‘P=S’ bond increases from 1.48 to 1.65 in silyl phosphorothionate. This change confirms that the inductive effect of fluorine enhances the double bond character of these terminal bonds. Detailed analysis of the structural features of these silyl esters will be reported elsewhere.

3.2 Thermodynamics

The P–S–Si bond sequence is much weaker than P–O–Si. The average overall energy of this system is 122 kcal/mol (512 kJ/mol) compared to 194 kcal/mol (813 kJ/mol). The energy difference between P=O and P=S double bonds is 57 kcal/mol (240 kJ/mol). Thus, the energy difference between thiono- and thiolosilyl esters is about 14 kcal/mol (60 kJ/mol) in favor of thiono form [39]. This thermodynamics explains why thiolosilyl esters are so difficult to prepare. The chemistry of derivatives of tetracoordinated phosphorus thioacids containing trimethylsilyl groups attached to phosphorus via a sulfur bridge have recently been developed giving rise to interesting intermediates for the synthesis of useful organothiophosphorus derivatives [40–43].

We have computed the energetics of simple thiono-thiolo isomerization of model esters (Scheme 1). The results are presented in Table 2.

Table 2 B3LYP/6-311+G(2d,p)//B3LYP/6-31+G(d) Gibbs free energies ΔG (kcal/mol) for thiono-thiolo rearrangement of model thiophosphorus esters (Scheme 1)

R	R' = H ^a (MeCN)	R' = CH ₃ ^a (MeCN)	R' = SiH ₃ ^a (MeCN)	R' = SiMe ₃ (MeCN)
H	4.7 (4.0) 3.9 (4.4)	−4.7 (−6.1) −5.0 (−6.9)	12.3 (10.9) 13.6 (12.2)	14.4 (13.4)
Me	4.6 (3.5) 4.3 (4.5)	−6.3 (−6.9) −6.0 (−7.5)	11.1 (10.2) 13.0 (12.0)	13.1 (12.6)
F	1.8 (2.4) 0.9 (4.1)	−7.1 (−8.1) −7.4 (−8.5)	10.0 (9.4) 11.1 (9.7)	11.9 (11.4)
OMe	1.4 (1.4)	−7.1 (−7.9) −7.3 (−8.4)	9.7 (9.0)	12.0 (11.6)
NH ₂	1.9 (1.1)	−7.1 (−8.2)	9.3 (8.3)	11.4 (11.0)

^a In italics are given the CCSD/6-311+G(2d,p)//B3LYP/6-31+G(d) values

Scheme 2 Intermolecular thiono-thiolo isomerizations of silyl esters of thiophosphorus acid

The reliability of DFT results was supported by the CCSD calculations for small model species. The results obtained by both methods are in very good agreement with each other (Table 2). Calculations confirmed the experimental results that alkyl esters are more stable in the thiol form. This is the driving force of the Pishchmuka reaction of thiono esters with alkyl halides. Acids preferentially exist in thiono form as it was observed earlier [38] although the energy difference between two forms is not large and decreases when electron-withdrawing substituents are attached to phosphorus. In contrast to alkyl esters, silyl derivatives are more stable in thiono form by 9–12 kcal/mol (SiH₃); in the case of R' = SiMe₃ the relative energy difference is by 2 kcal/mol larger, in accord with earlier estimations [39].

3.3 Reactivity

Silyl esters of phosphorus show interesting reactivity. Nucleophilic attack on the silicon atom is strongly preferred over the attack on phosphorus. The presence of a silyl group seems to enhance nucleophilicity of the phosphoryl group, and the phosphoryl group increases the electrophilicity of the silicon center. Thus, many reactions of silyl esters of phosphorus are much faster than those of corresponding alkyl esters [13]. One of the important problems in their chemistry is the isomerization and exchange of silyl groups. These processes lead to inversion of configuration and racemization at both silicon and phosphorus centers. Exchange reactions may be catalyzed by silyl halides [44] or by another molecule of the ester [45].

We have calculated the energy barriers of intra- and intermolecular exchange of silyl groups in esters of phosphorus acids (Schemes 2) to compare the feasibility of these reactions. Both reactions have different stereochemical consequences. Intramolecular exchange results in thiono-thiolo isomerization but the configuration at Si and P is preserved (Scheme 1, Fig. 2). Intermolecular process can occur with a ‘symmetrical’ arrangement of phosphorus moieties (Scheme 2, Fig. 3, path A) or with an ‘asymmet-

Fig. 2 Intramolecular silyl group migration in thiophosphorus esters

Fig. 3 Transition states in intermolecular thiono-thiolo symmetrical (**a**) and asymmetrical (**b**) isomerizations of silyl esters of thiophosphorus acids

rical' arrangement (Scheme 2, Fig. 3, path **B**). Exchange according to path **A** results in inversion of configuration at Si and racemization if chiral silyl substituents are used. The configuration at P does not change unless two differently substituted esters are allowed to react. Path **B** results in configuration inversion at Si and in thiono-thiolo isomerization in both ester molecules. The calculation results for both processes are collected in Tables 3 and 4.

To verify the reliability of DFT results the calculations for small model species were performed also with the CCSD method using B3LYP/6-31+G(d) geometries. In the case of reaction barriers, the DFT results are systematically lower than those obtained by the coupled cluster method by ca. 3.5 kcal/mol and ca. 7.5 kcal/mol for $R' = H$ and $R' = Me$, respectively, but only by 1–2 kcal/mol for $R' = SiH_3$ (Table 3). The energy barriers for thiono-thiolo isomerization for each class of compounds are very similar, little dependent of the substituents at phosphorus. Methyl esters show the highest energy barriers, over 50 kcal/mol, which seem to prevent the reaction of this type from occurring under normal conditions. Silyl (SiH_3) esters show barriers even lower than the corresponding acids which suggests that the intramolecular migration of the silyl group is feasible, at least at elevated temperatures. The trimethylsilyl group is accompanied with an increase of the reaction barrier by 5–6 kcal/mol compared to SiH_3 , due to steric reasons. Solvent has little effect on the isomerization barrier.

The barriers for intermolecular silyl group exchange are higher than those for intramolecular migration for all R except $R = H$. The calculated barriers of the reaction **A** are slightly lower (by about 3 kcal/mol) than those of the reaction **B** for all R except $R = F$, where the energy barriers for both reactions are identical. We have not performed coupled cluster calculations because of the computational cost. Based on the differences between two methods shown in Table 3, those barriers are predicted to be about 8 kcal/mol higher than the DFT barriers.

Fig. 4 Exchange of methyl groups in methyl phosphinate $H_2P(O)OMe$

Table 3 B3LYP/6-311+G(2d,p)//B3LYP/6-31+G(d) Gibbs free energy barriers $\Delta G^\ddagger$ (kcal/mol) for intramolecular thiono-thiolo rearrangement of model phosphorus esters, $R_2P(S)OR'$ (Scheme 1, Fig. 2) in the gas phase and in MeCN (values in parentheses)

R	$R' = H^a$	$R' = CH_3^a$	$R' = SiH_3^a$	$R' = SiMe_3$
H	30.0 (30.5) 33.7 (36.6)	50.6 (50.4) 58.0 (57.7)	24.9 (24.5) 26.0 (26.7)	31.8 (31.5)
Me	28.1 (28.7) 31.5 (31.3)	50.8 (51.2) 59.0 (58.8)	22.7 (22.9) 24.5 (23.8)	30.1 (30.6)
F	31.9 (33.5) 35.5 (39.2)	50.4 (48.7) 58.3 (57.7)	27.0 (27.7) 28.7 (29.5)	32.4 (33.0)
OMe		53.5 60.9	24.2 (23.9)	
NH ₂	26.0 (26.5)	52.8 (52.6)	21.7 (20.7)	

^a In italics are given the CCSD/6-311+G(2d,p)//B3LYP/6-31+G(d) values

To compare the energy barriers for the intermolecular exchange of silyl groups with the analogous reaction of methyl esters, the Gibbs free energy barrier for the exchange of methyl groups between two molecules of methyl phosphinate $H_2P(O)OMe$ (Fig. 4) was calculated to be 73 kcal/mol in the gas phase (76 kcal/mol in acetonitrile). Thus, the intermolecular exchange of silyl groups is much more likely than the analogous reaction of alkyl esters.

Solvent effects in all these reactions calculated assuming the polarizable continuum model in acetonitrile are small or negligible. This does not exclude the possibility of specific dipole–dipole interactions as the reactions in question are associated with some charge separation. Moreover, the processes discussed here are not the only ones which may be responsible for the exchange reactions of silyl esters in the condensed phase. The rearrangement may be induced by traces of basic or acidic impurities in the medium. Very effective may be the silyl group exchange catalyzed by residual acid or acid anions which are likely to be present in the mixture since silyl esters of phosphorus are very sensitive to hydrolysis. A theoretical study of these reactions is in progress.

To get deeper insight into the nucleophilicity of sulfur and oxygen in thiophosphinic acids/esters/anions the

Table 4 B3LYP/6-311+G(2d,p)//B3LYP/6-31+G(d) Gibbs free energy barriers $\Delta G^\ddagger$ (kcal/mol) for intermolecular silyl group exchange in model phosphorus esters (Scheme 2, Fig. 3), in the gas phase and in MeCN (in parentheses)

R	$R' = SiH_3$ (A)	$R' = SiH_3$ (B)
H	11.8 (15.4)	14.8 (18.3)
Me	37.8 (39.2)	41.2 (42.5)
F	39.2 (40.5)	39.4 (40.8)

Table 5 Local and global softness of model nucleophiles and electrophiles

Compound	f_k^+	f_s^-	f_o^-	Local softness, s_k			Global softness, σ
	k = C,Si						
		Electrophile	Nucleophile				
		k = C/Si	S	O			
CH_3^+	0.798			1.379			1.728
SiH_3^+	0.908			1.914			2.108
H_2PSO^-		0.756	0.106		2.414	0.338	3.193
Me_2PSO^-		0.719	0.202		2.138	0.599	2.973
F_2PSO^-		0.742	0.089		2.743	0.331	3.697

analysis based on the condensed Fukui functions was performed. Fukui functions, f_k^- and f_k^+ , are the rough measures of the nucleophilicity and electrophilicity power of atom k , respectively [33]. Thiophosphinate anions, R_2PSO^- , $\text{R} = \text{H, Me, F}$, were taken as the model nucleophiles while CH_3^+ and SiH_3^+ were taken as model electrophiles. The values of global and local softness for all atoms of interest (C, Si, O and S) are collected in Table 5.

The results of softness and nucleophilicity analysis support the intuitive feature that sulfur is softer and more nucleophilic than oxygen. However, the present analysis fails to explain why, in the case of silyl cation, the initial attack of the O atom is favorable although the softness difference is smaller for the S atom. Moreover, the global softness of thiophosphinate anions with regard of substituents R increases in order $\text{Me} < \text{H} < \text{F}$, which is intuitively difficult to explain. These weaknesses of the present analysis demonstrate limitations of this simplified approach. It is possible that, in some extreme cases, some other stronger interaction can overwhelm the predictions made from softness alone. Here, the strong ‘oxyphilicity’ of silicon appears to be the dominating factor.

The calculations showed that in contrast to alkyl esters, which are more stable in the thio form, silyl esters of thiophosphorus acids appear in the thiono form which is thermodynamically preferred. The Gibbs free energy barriers of intramolecular migration of the ligand between oxygen and sulfur in thiophosphinates and in thiophosphinic acids increase in order $\text{SiH}_3 < \text{H} \approx \text{SiMe}_3 \ll \text{Me}$. Energy barriers for the intermolecular exchange of ligands are significantly higher compared to intramolecular process and $\text{SiH}_3 \ll \text{Me}$. Thus intramolecular isomerization is more likely than the intermolecular process in the absence of basic or acidic impurities. The energy barriers for the discussed reaction are little dependent on the substituents at phosphorus and on solvation.

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