Selective site controlled nucleophilic attacks in 5-membered ring phosphate esters: unusual C–O *vs.* common P–O bond cleavage†

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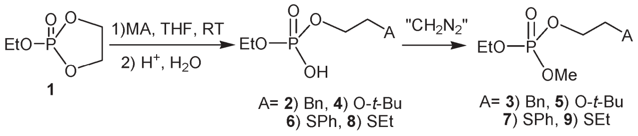
Clean endocyclic C–O bond cleavage has been achieved in the reactions of 5-membered phosphate triesters with various nucleophiles.

Phosphate esters play an important role in many key biochemical processes as a part of nucleotides, nucleic acids and sugar phosphates.[1] Of particular importance are the 5-membered ring systems.[2] Nucleophilic attack on phosphate esters is among the most important reactions in these processes,[3] leading to either the P–O or the C–O bond cleavage.[4,5] Despite the great importance of C–O bond cleavage reactions,[6] the vast majority of the publications report on P–O bond cleavage reactions.[7] While a few examples of C–O bond scission in solution[8] and in the gas phase[9] as well as some theoretical calculations[10] were reported, this process is very rare for 5-membered cyclic phosphate esters.[11] The parent phosphate triesters, 2-alkoxy-1,3,2-dioxaphospholane 2-oxides (commonly named alkyl ethylene phosphates), had been a subject of extensive research mainly in respect to hydrolysis and alcoholysis reactions, from both experimental[12] and theoretical[13] aspects. In his pioneering work Westheimer established that these phospholanes hydrolyze about 10^7 times faster than the corresponding acyclic system and exclusively *via* hydrolytic P–O cleavage, whereas C–O cleavage could not be observed.[14] Recently, we reported that the reactions of 2-ethoxy-1,3,2-dioxaphospholane 2-oxide (**1**) with various Grignard reagents and hydrides proceed exclusively *via* an endocyclic P–O bond cleavage.[15] The cyclic phosphate **1** reacts selectively with only one equivalent of Grignard reagent to form the corresponding phosphonates, while acyclic phosphate triesters and dioxaphosphorinanes undergo multi-substitution under harsh conditions.[16] It is generally accepted that nucleophilic attacks on trialkyl phosphates follow Pearson's theory of hard and soft reagents;[17] hard nucleophiles would attack on the phosphoryl group while softer nucleophiles would attack at the alkyl group.[8a]

In this study we have found unusual and clean endocyclic C–O bond cleavage (Scheme 1) in the reactions of **1** with nucleophiles. The dual electrophilic character of **1** in solution is demonstrated here for the first time. DFT calculations shed more light on the unique reactivity of phospholanes.



Scheme 1 Reaction of **1** with various nucleophiles followed by methylation.

Unexpectedly, in contrast to all other Grignard reagents, which have been examined (Table 1, entries 6–9), the reaction of **1** with benzylmagnesium chloride did not afford any phosphonates, rather a single product was obtained with a ^{31}P NMR signal at −2.49 ppm, which is typical of phosphates. ^{1}H and ^{13}C NMR spectra showed the presence of only two methylene units in the α position to an oxygen atom (two doublets at 66.44 and 63.34 ppm, J_{P-C} = 5.0 and 5.7 Hz, respectively). This and additional spectral data† suggest that the product obtained is ethyl (3-phenyl)propyl phosphate (**2**) (Table 1, entry 1) which must be a result of C–O bond cleavage. Purification of **2** was best achieved by transforming it to its dicyclohexyl ammonium salt, which readily crystallized and, following acidification yields **2**.[18] To unambiguously prove its structure, **2** was derivatized by reaction with diazomethane,[19] obtained from *N*-methyl-*N′*-nitro-*N*-nitrosoguanidine (Scheme 1). This reaction quantitatively produced ethyl methyl (3-phenyl)propyl phosphate (**3**).[20] This result clearly suggests that in contrast to all nucleophiles studied to date the benzyl carbanion attacks on the ring carbon, the softer electrophilic center of **1**, rather than at the P center.

As mentioned earlier, hydrolysis of 2-methoxy-1,3,2-dioxaphospholane 2-oxide and 2-ethoxy-1,3,2-dioxaphospholane 2-oxide (**1**) proceeds *via* P–O bond cleavage (Table 1, entry 10). Methanolysis under alkaline conditions was also reported to take place only with P–O bond fission and ring opening (Table 1, entry 11).[21] Our notion was to explore whether it is possible to obtain an S_N2(C) type product *via* C–O bond cleavage using other alkoxy anions. We figured this goal might be achieved by using bulky alkoxide. Although it is still considered a hard nucleophile it might not be able to approach the phosphorus atom and therefore, attack on the carbon electrophilic center would be preferred (see Table 2 and discussion below). Indeed, reaction of **1** with an equimolar amount of potassium *t*-butoxide resulted in the formation of ethyl (2-*t*-butyloxy)ethyl phosphate (**4**) (Table 1, entry 2).[22] A similar tendency was observed for bulky carbanions.[23]

Compared to oxygen nucleophiles, sulfur anions are softer and therefore, might be expected to attack on the carbon *via* an S_N2(C) type reaction. Indeed, subjecting **1** to sodium thiophenolate and sodium ethanthiolate cleanly produced ethyl (2-thiophenyl)ethyl phosphate (**6**) and ethyl (2-thioethyl)ethyl phosphate (**8**),

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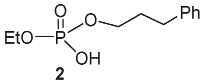
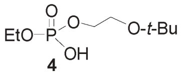
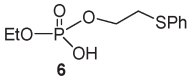
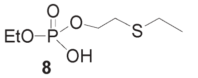
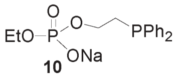
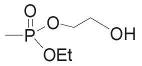
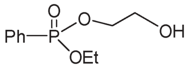
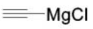
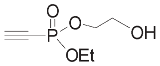
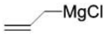
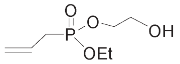
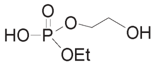
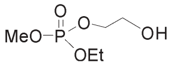
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all new compounds. Details and additional discussion of DFT calculations. See DOI: 10.1039/b512117e

Table 1 Summary of reactions of **1** with various nucleophiles

Entry No.	Nucleophile (MA)	Product	% Isolated yield
1[a]	$PhCH_2MgCl$	 **2**	62
2[a]	*t*-BuOK	 **4**	62
3[a]	PhSNa	 **6**	88
4[a]	EtSNa	 **8**	83
5[a]	PPh_2Na	 **10**	70
6[b]	CH_3MgCl		75
7[b]	PhMgCl		80
8[b]			70
9[b]			30
10[c]	NaOH		
11[d]	$NaOCH_3$		

[a] This work. [b] ref. 15. [c] ref. 12. [d] ref. 21.

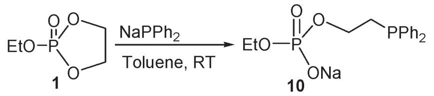
Table 2 Relative energies (kcal mol^{-1}) for the reactions (as shown in Scheme 3) and transition states[a,b]

	Me	OH	OMe	O*t*-Bu	MeS
11	−101.7	−67.1	−61.8	−51.6	−41.7
	(−95.4)	(−40.5)	(−44.4)	(−42.7)	(−38.0)
	[−95.4]	[−42.6]	[−36.5]	[−44.3]	[−20.6]
12	−47.1	−32.4	−23.4	−15.1	9.1
	(−44.2)	(−9.4)	(−9.7)	(−9.3)	(10.1)
	[−43.7]	[−11.1]	[−1.3]	[−10.6]	[27.9]
TS-1		−25.2	−21.3	−13.8	−10.0
(C–O attack)		(9.9)	(7.1)	(9.4)	(3.7)
		[5.9]	[8.7]	[5.7]	[19.4]
TS-2		−12.9	−9.7	−6.1	−1.0
(P–O attack)		(7.7)	(6.6)	(14.3)	(2.2)
		[6.9]	[16.1]	[12.6]	[20.5]

[a] Values in parentheses and [b] square brackets include the reaction energies in solvent medium; water and THF, respectively with the Polarized Continuum Model (PCM), using B3LYP/6-31+G* optimized geometries.

respectively (Table 1, entries 3 and 4) in high yield (88% and 83%, respectively). These products, exclusively obtained from the endocyclic C–O bond scission, were characterized by multinuclear NMR spectroscopy as well as by derivatization with diazomethane.†

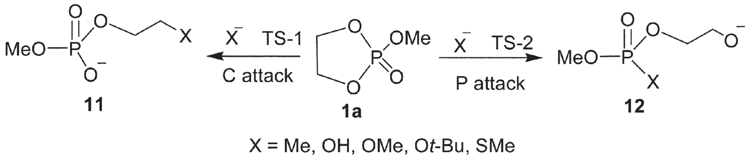
Phosphide anions, which are also considered soft nucleophiles,[24] are commonly employed as nucleophiles in reactions with alkyl halide to form tri-substituted phosphine. Here we investigated the reaction of sodium diphenylphosphide[25] with **1** (Table 1, entry 5 and Scheme 2). The only product obtained was the endocylic C–O bond fission product, sodium ethyl (2-diphenylphosphino)ethyl phosphoric acid (**10**). In the ^{31}P spectrum two singlets, with 1 : 1 integral ratio, at −2.36 (phosphate P) and −27.36 (phosphine P) ppm appeared. In addition, a clear-cut evidence for the structure of **10** is found in the ^{13}C spectrum. Each of the two different carbon atoms on the bridging chain between the P atoms appears as a double doublet (63.20 ppm, $J_{P\text{–}C}$ = 32.6, 4.8 Hz, and 29.70 ppm, $J_{P\text{–}C}$ = 14.0, 6.1 Hz). The relatively small coupling constants of 14.0 and 32.6 Hz are typical for a carbon atom adjacent to $P^{(III)}$ center.[26] None of the two possible P–O bond cleavage products can exhibit such a splitting pattern. Therefore, it is obvious that diphenylphosphide reacts as a soft nucleophile cleaving only the more reactive of the two different C–O bonds.[27] Notably, **10** is a unique bridged $P^{(V)}$–$P^{(III)}$ anionic compound, which may exhibit interesting properties when used as a ligand for transition metals. Attempts to react **1** with soft metal carbanions (*e.g.* $Na_2Fe(CO)_4$) failed so far, probably due to solubility problems of these inorganic salts.



Scheme 2 Reaction of **1** with diphenylphosphide.

In order to shed more light on the selectivity of C–O *vs.* P–O cleavage, we have performed density functional calculations using B3LYP hybrid functional and 6-31+G* basis set (corrected for unscaled ZPVE).[28,29] We have calculated the reaction pathway for the attack of methyl anion, hydroxide, methoxide, *t*-butoxide and thiomethyl anion on **1a** (the ethoxy group in **1** is substituted by methoxy group in **1a**, Scheme 3). Since the solvent effect is expected to be significant in the reactions studied, we have corrected the gas phase values by using single-point B3LYP/6-31+G* calculations for water and THF as a solvent with the Polarized Continuum Model (PCM) using B3LYP/6-31+G* optimized geometries (Table 2).[30] Water was chosen as a model for very polar solvent and THF as experimentally used solvent.

Examination of Table 2 shows that attack on the ring carbon, which leads to the formation of phosphate anions, is always thermodynamically preferred.[31] That is due to the fact that phosphate anion is thermodynamically relatively stable and a good leaving group. For example the product **11** resulted from attack of methyl anion on the ring carbon of **1a** is by 54.6 kcal mol^{-1} more stable than the product **12** which resulted from P–O bond fission. This difference is only slightly decreased to 51.2 kcal mol^{-1} in water and 51.7 kcal mol^{-1} in THF. The corresponding difference for neutral compounds (when the anion is protonated) is 20.0 kcal mol^{-1} in gas phase (20.4 kcal mol^{-1} in water and 20.4 kcal mol^{-1} in THF, C–O cleavage product is always more stable). The preference for the product of C–O attack by methoxy anion is 38.4 kcal mol^{-1} relative to the product of P–O attack. This difference is again only slightly decreased to 34.7 kcal mol^{-1} in water and 35.2 kcal mol^{-1} in THF. Thus, we propose that the P–O bond dissociation product which is observed in most previous experimental studies will be the kinetically controlled product resulted from large activation energy for C–O bond dissociation.



Scheme 3 Model reaction for the theoretical studies of attack of nucleophiles on cyclic phosphate **1**; **1a** is used as a model for **1**.

The above results explain the C–O bond cleavage which we discovered experimentally.

Our calculations predict that the barrier for OH attack on phosphorus (7.7 kcal mol^{-1}) is lower than the barrier for the attack on carbon (9.9 kcal mol^{-1}) in water. Indeed experimentally the reaction with OH was carried out in water and it occurs exclusively at the phosphorus.[32] Similar behavior of methoxy anion in these reactions has been predicted in our calculations. The situation is reverse when *t*-BuO anion is used as a nucleophile. Here, our calculations predict that a lower barrier for C–O bond dissociation (9.4 kcal mol^{-1}, compared to the P–O bond dissociation 14.3 kcal mol^{-1}) is in full agreement with our current experimental study. It is predicted that the soft thiomethyl anion should prefer attack on the carbon instead of the phosphorus. The gas phase calculations indeed predicted preference for C–O attack with a lower barrier of -10.0 kcal mol^{-1} compared to the P–O attack (-1.0 kcal mol^{-1}). The same trend has been followed for the THF reaction (the experimental study has been done in THF), however, on inclusion of water solvent calculations predicted a lower barrier for P–O attack (2.2 kcal mol^{-1} compared to the C–O attack 3.7 kcal mol^{-1}).

In conclusion, the results presented in this paper have demonstrated the dual electrophilic character of **1**. The site of attack depends on the nature of the attacking nucleophile (softness *vs.* hardness, steric bulk, *etc.*). As no exocyclic bond fission could be observed it may be suggested that the 5-membered ring enhances not only the reactivity of the P atom, but also of the ring carbon.

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