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Proton exchange and chemoselectivity in metal cation and hydroxide ion hydrolyses of phosphonoacetate diesters

Robert A. Moss* and Paul K. Gong

Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, New Brunswick, NJ 08903, USA

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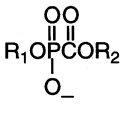
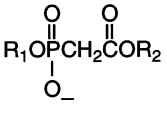
Abstract—Phosphonoacetate diesters exhibit base catalyzed D/H proton exchange and C-OR esterolysis, as well as (acidic) hydrolyses mediated by Th^{4+} and Zr^{4+} ions.

Phosphonoformate diesters, such as dimethylphosphonoformate (**1**, $R_1=R_2=Me$, *DMPF*), are prodrug precursors of the phosphonoformate trianion, 'foscarnet',[1,2] which is active against several human viruses, including herpes simplex and AIDS-related cytomegalovirus.[3] Selective methods for the esterolysis of **1** are therefore desirable.

Aminocyclodextrins regioselectively hydrolyze **1** ($R_1=$ Et, $R_2=$ Ph; $R_1=R_2=$ Et) at the C-OR site.[4] Micellar cetyltrimethylammonium iodosobenzoate also cleaves **1** (DMPF) at C-OMe, but **1** ($R_1=$ Ph, $R_2=$ Et) is mainly cleaved at the *P*-ester site which bears the more reactive phenoxide leaving group.[5] Chemoselective hydrolysis of **1** occurs in metal ion catalyzed reactions: Th^{4+} and Ce^{4+} foster C-OMe hydrolysis of DMPF, whereas Zr^{4+} and Hf^{4+} direct P-OMe hydrolysis of this substrate.[6] Here, dimeric Ce^{4+} or Th^{4+} hydroxo species afford preferential intracomplex M-OH attack at C-OMe via five-membered transition states, while tetrameric or octameric Zr^{4+} or Hf^{4+} hydroxo species direct M-OH attack at P-OMe via six-membered transition states.[6] Finally, the lanthanide cations, Eu^{3+} and La^{3+}, foster C-OMe cleavage of DMPF, presumably via dimeric hydroxo species, although with **1** ($R=$ Ph, $R_2=$ Et), the lanthanide cations engender comparable P-OPh and C-OMe hydrolysis.[7]



1



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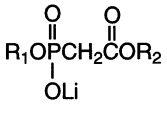
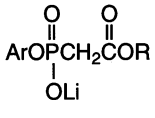


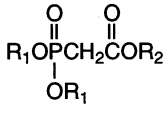
3

a, $R_1=R_2=Me$
b, $R_1=Me$, $R_2=Et$
c, $R_1=Et$, $R_2=Me$
d, $R_1=R_2=Et$



4

a, Ar=Ph, R=Me
b, Ar=Ph, R=Et
c, Ar=PNP, R=Me
d, Ar=PNP, R=Et



5

R_1=Me or Et

The intriguing hydrolytic reactivity of phosphonoformate diesters **1** turned our attention toward the related phosphonoacetate (*PA*) diesters, **2**. Although neutral PA *triesters* are widely used as synthetic reagents in the Horner–Wadsworth–Emmons version of the Wittig reaction,[8] the chemistry of diesters **2** is relatively unexplored. PA monoesters have been prepared and studied as inhibitors of herpes simplex virus DNA polymerase,[9] but the hydrolytic kinetics and chemoselectivity of diesters **2** are unreported. Significant questions attend proton exchange at the interposed methylene group of **2**, the comparative hydrolytic chemistry of **2** and **1**, and C-OR/P-OR chemoselectivity in **2** as a function of R and the hydrolytic reagents. Here, we present the initial studies of these matters.

Eight PA diester substrates were prepared, 4 dialkyl esters (**3a**–**d**) and 4 aryl alkyl esters (**4a**–**d**). PA diesters **3** were generated by the LiBr cleavage[10] of P-OMe or P-OEt (80°C, 30 min) of commercially available PA triesters **5**, where R_1 and R_2 were either Me or Et, as appropriate. The aryl alkyl esters (**4**) were prepared by the sequence shown in Scheme 1. Here, methyl or ethyl

* Corresponding author.

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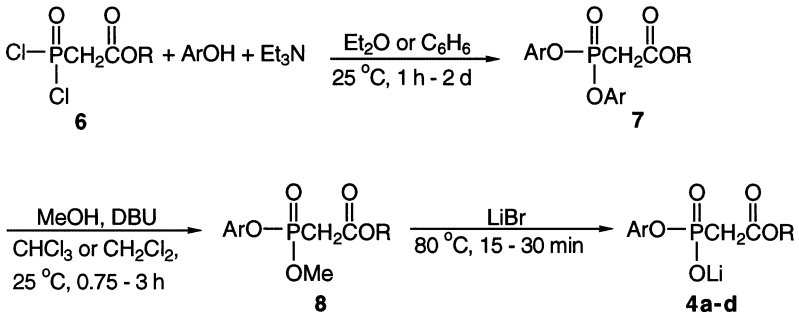

Scheme 1.

dichlorophosphonoacetate (**6**) reacted with phenol or *p*-nitrophenol to yield the diaryl alkylphosphonoacetate triesters **7** (Ar = Ph or *p*-nitrophenyl, *PNP*, and R = Me or Et),[11] which underwent methanolysis in the presence of DBU[12] to afford the aryl methylphosphonoacetate triesters **8** (Ar = Ph or PNP, R = Me or Et). Finally, LiBr cleavage[10] of the P-OMe unit of **8** gave the desired aryl alkylphosphonoacetate diesters **4a**–**4d**.

All of the substrates, as well as the relay compounds (**7** and **8**), were purified by chromatography or crystallization, and were characterized by ^{1}H and ^{31}P NMR spectroscopy, and elemental analysis.[13] Yields of **3a**–**3d** were 55–72%; yields of **7** were ~65%, except for **7** (Ar = PNP, R = Et) where the yield was 18%. For products **8**, the yields ranged from 44 to 80%, while the LiBr cleavages of **8** generated substrates **4a**–**d** in 44–97% yield.[13]

Substrates **3** and **4** each possess three reactive sites: the carbonyl and phosphoryl esters, and the protons of the methylene unit that separates the ester groups. Reactions occur at each site. Consider first the dialkyl PA substrates, **3a**–**d**, which are relatively stable in neutral or moderately acidic aqueous solutions; e.g. **3a** and **3d** are unchanged after 2 days in D_2O at pD 1.8 and 25°C.[14] However, under forcing conditions (12 M DCl, reflux, 24 h) **3d** completely cleaves to phosphonoacetic acid with complete D/H exchange at CH_2.

Reactions in basic solution could be monitored by NMR spectroscopy, with kinetics followed by observing the disappearance of key substrate signals and/or the appearance of products, relative to an internal pyrazine standard. P-OR and C-OR proton signals are readily distinguished by the P-(α)-H coupling in the P-OR moiety.[15] Methylene D/H exchange and C-OR hydrolysis both occur in basic solution, but D/H exchange is more facile: with 25 mM **3a**–**3d** in 10 mM CHES buffer in D_2O containing 0.1 M $NaClO_4$ at pD 10.4 and 37°C, k_{exch} ranges from 1.78×10^{-4} s^{-1} for **3a** to 0.59×10^{-4} s^{-1} for **3d**; see Table 1. Under these conditions, ester hydrolysis does not compete.
However, 10 mM substrate with 25 mM NaOD in D_2O at pD 13.2 undergoes exclusive C-OR cleavage with k_{OD} ranging from 4.53×10^{-4} s^{-1} (**3a**) to 1.58×10^{-4} s^{-1} (**3d**); cf., Table 1.

C-OR hydrolysis and methylene D/H exchange are also mediated by Th^{4+}. NMR reveals downfield substrate proton shifts upon addition of 1–2 equiv. of $Th(NO_3)_4{\cdot}4H_2O$, indicative of substrate–Th^{4+} complexation.[16] With 10 mM **3a**–**3d** and 25 mM Th^{4+} at pD 3.1 in D_2O containing 0.1 M $NaClO_4$ at 37°C, C-OR hydrolysis proceeded with k_{Th} ranging from 3.76×10^{-4} s^{-1} (**3a**) to 1.00×10^{-4} s^{-1} (**3b**). This represents about a 1900-fold enhancement of the acidic C-OR hydrolysis of (e.g.) **3d** by Th^{4+}.[14] Moreover, Th^{4+}-mediated hydrolysis of PA substrates **3** is roughly comparable to the analogous process with phosphonoformates **1**. Thus DMPF (**1**, $R_1 = R_2 = Me$) has $k_{Th} = 1.3\times10^{-4}$ s^{-1} at 25°C,[6] under conditions where **3a** exhibits $k_{Th} = 3.76\times10^{-4}$ s^{-1} at 37°C.

In contrast, Zr^{4+} cleavages of **3a**–**3d** at comparable concentrations are very slow, and occur at C-OR rather than P-OR in contrast to DMPF.[6] For example, at

Table 1. Kinetics of dialkylphosphonoacetate reactions

Substrate	R_1	R_2	10^4 k_{exch} (s^{-1})[a]	10^4 k_{OD} (s^{-1})[b]	10^4 k_{Th} (s^{-1})[c]	10^4 k_{Zr} (s^{-1})[d]
3a	Me	Me	1.78	4.53	3.76	[e]
3b	Me	Et	1.38[f]	1.82	1.00	[g]
3c	Et	Me	0.72	3.41	2.10	0.30
3d	Et	Et	0.59	1.58	1.20	[e]

[a] D exchange of spacer CH_2, pD 10.4, 37°C.
[b] Hydrolysis of C-OR at pD 13.2, 25°C.
[c] k_{obs} for C-OR hydrolysis mediated by Th^{4+} at pD 3.1, 37°C.
[d] k_{obs} for hydrolysis by Zr^{4+} at pD 1.7, 60°C.
[e] Not studied.
[f] 0.66 s^{-1} for CHD exchange.
[g] 30% of C-OMe cleavage was observed after 15 h at 50°C.

Table 2. Kinetics of aryl alkyl phosphonoacetate reactions

Substrate	Ar	R	$10^4\ k_{exch}\ (s^{-1})$[a]	$10^4\ k_{OD}\ (s^{-1})$[b]	$10^4\ k_{Th}\ (s^{-1})$[c]	$10^4\ k_{Zr}\ (s^{-1})$[d]
4a	Ph	Me	4.00	5.79	[e]	[f]
4b	Ph	Et	1.95	2.28	[g]	[h]
4c	PNP	Me	8.73	7.81	[g]	[h]
4d	PNP	Et	4.70	4.79	[i]	[j]

[a] D exchange of spacer CH_2, pD 10.4, 37°C.
[b] Hydrolysis of C-OR with NaOD, pD 13.2, 25°C.
[c] Only C-OR cleavage at pD 3.1, 37°C.
[d] At pD 1.7, 37°C.
[e] Only C-OMe cleavage was observed; see text.
[f] After 2 d at 37°C, 48% of P-O and 52% of C-O cleavage were observed.
[g] Precipitation occurred.
[h] Not studied.
[i] C-OEt was completely cleaved after 5 h at 37°C.
[j] Quantitative P-O cleavage was observed upon mixing 20 mM Zr^{4+} and 6 mM **4d** at 37°C.

pD 1.7, substrate **3c** requires 60°C to afford $k_{Zr}=0.30\times10^{-4}\ s^{-1}$ for C-OEt cleavage. P-OMe cleavage is not competitive in this case, whereas DMPF undergoes Zr^{4+}-mediated P-OMe hydrolysis with $k_{Zr}=4.4\times10^{-4}\ s^{-1}$ at pD 1.7, 25°C.[6] The hydrolytic reactivity and P-OR chemoselectivity of Zr^{4+} toward phosphonoformate diesters are lost with the corresponding PA substrates.[17]

In order to observe P-O esterolysis with PA diesters, we require aryl alkyl substrates **4a**–**d**, where the phosphoryl site features a more reactive aryloxide leaving group, while the carbonyl site remains an alkyl ester. Results for these substrates appear in Table 2.

One first notes that methylene proton exchange is accelerated relative to the dialkyl PA esters of Table 1. Replacement of the Me or Et phosphoryl ester residues of substrates **3** by the inductively withdrawing Ph or PNP residues of substrates **4** enhances base catalyzed D/H exchange by factors up to 10.8 (**4c** versus **3c**), with larger enhancements induced by the more strongly withdrawing PNP residue (**4c**,**4d** versus **4a**,**4b**).

Base-catalyzed hydrolyses of **4** at pD 13.2, 25°C, occur with preferential C-OR scission instead of P-OPh or even P-OPNP cleavage. The recalcitrance of phosphorolysis, relative to C-OR esterolysis, is reminiscent of phosphonoformate chemistry, where basic hydrolysis of **1** ($R_1=Ph$, $R_2=Me$) at pH 8.4 occurs only with C-OMe cleavage ($k=3\times10^{-7}\ s^{-1}$), rather than P-OPh cleavage.[5] Similarly, with **1** ($R_1=R_2=Ph$), C-OPh hydrolysis is observed at pH 11.7–13.4.[5]

Although PA substrates **4** undergo C-OR hydrolysis in preference to P-OAr cleavage, the Ar groups do exert an activating effect. Comparison of Tables 1 and 2 reveals that the PNP and Ph substituents of **4** accelerate C-OR hydrolysis by factors up to ~3 (**4d** versus **3d**); the electron withdrawing inductive properties of PNP or Ph mildly activate the carbonyl esters of **4** toward hydroxide attack.

Studies of Th^{4+} or Zr^{4+} mediated hydrolyses of **4** were hindered by precipitation of substrate–metal ion complexes. These could be redissolved upon gentle heating (and sonication), but rate constants were unobtainable. Nevertheless, some conclusions can be drawn. As with dialkyl PA diesters **3**, and DMPF,[6] Th^{4+} induces C-OR, not P-OR or POAr scission; cf., **4a** and **4d** in Table 2.

On the other hand, Zr^{4+} slowly cleaves C-OMe and P-OPh competitively (substrate **4a**), while P-OPNP cleaves in preference to C-OEt (substrate **4d**). Here we find an echo of the P-OR chemoselectivity that Zr^{4+} exerts in phosphonoformate diester hydrolysis.[6] However, the Th^{4+}/C-OR, Zr^{4+}/P-OR chemoselectivity dichotomy is not as clearly expressed with PA diesters as with DMPF; the PA substrates require a P-OAr leaving group to compete against C-OR, even with Zr^{4+} mediation.

PA diesters are less hydrolytically reactive toward M^{4+} than their phosphonoformate relatives: under otherwise similar conditions, the former require reaction temperatures of 37°C to produce hydrolytic rates comparable to those attained by phosphonoformate analogues at 25°C. Conceivably, electrostatic repulsions between the adjacent P=O and C=O moieties of the phosphonoformate diesters activates them toward esterolytic attack by OH (supplied either as free OH^- or as M-OH in metal ion mediated attacks[6,7]), relative to PA diesters, where P=O and C=O are separated by a methylene spacer.

In summary, phosphonoacetate diesters **3** and **4** exhibit base catalyzed D/H proton exchange and C-OR esterolysis, as well as (acidic) hydrolyses mediated by Th^{4+} and Zr^{4+}. However, esterolytic chemoselectivity on the part of the M^{4+} cations is not as clearly expressed with the phosphonoacetates as with comparable phosphonoformate substrates.

Acknowledgements

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14. After 5.5 months at 37°C, pD 2.3, about 66% of **3d** hydrolyzed at C-OEt. There was a corresponding 66% of H/D exchange at the CH_2 spacer. The estimated rate constant is $\sim 6.4\times10^{-8}$ s^{-1}, comparable to that for hydrolysis of diethylphosphonoformate at pH 7.[4]
15. For example, the NMR spectrum of **3a** features (^1H, D_2O, δ): 3.67 (s, 3H, COMe), 3.54 (d, $J_{P-H} = 10.9$ Hz, 3H, P-OMe), 2.83 (d, $J_{P-H} = 20.4$ Hz, 2H, CH_2). For other substrate spectra, and ^{31}P NMR spectra, see Ref. 13.
16. With **3a** and 1 equiv. of Th^{4+} in D_2O, for example, the $\Delta\delta$ values were C-OMe, 0.05 ppm, P-OMe, 0.12 ppm, and CH_2, 0.22 ppm. Substrate **3d** required 2 equiv. of Th^{4+} to achieve 'full' binding.
17. Complexation of **3a** and Zr^{4+} occurs, however, as demonstrated by downfield ^1H NMR shifts: $\Delta\delta$ for C-OMe = 0.05 ppm, P-OMe, 0.13 ppm, and CH_2, 0.43 ppm.