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Phosphonoformate diester hydrolysis mediated by lanthanide cations

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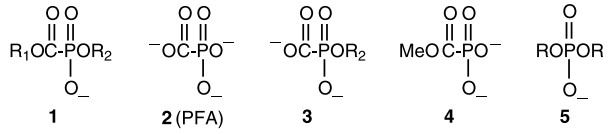
Abstract—Eu(III) and La(III) cations, and their bis–tris propane complexes, mediate the hydrolysis of dimethyl phosphonoformate with C–OMe regiospecificity and substantial rate enhancement.

Monoanionic phosphonoformate diesters (**1**) are of interest as prodrug precursors of the phosphonoformate trianion, 'foscarnet' (**2**, PFA),[1,2] which is active against several human viruses including herpes simplex and AIDS-related human cytomegalovirus.[3] Accordingly, we desire selective methods for the esterolysis of phosphonoformate diesters. Diesters **1** ($R_1 = Ph$, $R_2 = Et$; $R_1 = R_2 = Et$) can be regioselectively hydrolyzed at their *C*-ester sites with aminocyclodextrins yielding dianionic phosphonoformate *P*-monoesters (**3**).[4]



1 **2** (PFA) **3** **4** **5**

a, $R_1 = R_2 = Me$
b, $R_1 = Me$; $R_2 = Ph$

More recently, we reported the catalytic and regioselective hydrolyses of dimethyl phosphonoformate (**1a**, $R_1 = R_2 = Me$, DMPF) at *either* C–OMe by Th^{4+} and Ce^{4+}, or at P–OMe by Zr^{4+} and Hf^{4+}.[5] The latter reactions gave phosphonoformate *C*-monoesters (**4**). The origin of the esterolytic regioselectivity was traced to the structure(s) of the dominant metal ion hydroxo species present in the reaction solution: dimers for Ce^{4+} or Th^{4+} and tetramers or octamers for Zr^{4+} or Hf^{4+}. The dimeric species were suggested to afford preferential intracomplex M–OH attack at the carbonyl group of the bound substrate via a five-membered transition state, whereas the tetrameric or octameric metal cation hydroxo species were believed to foster M–OH attack at the substrate's phosphonyl group via a six-membered transition state.[5]

It is well established that lanthanide cations (Ln^{3+}) greatly accelerate the hydrolytic cleavage of phosphodiesters (**5**), which are relatives of phosphonoformate diesters.[6] How do the catalytic and regioselective properties of Ln^{3+} toward phosphonoformate diesters compare to those expressed[5] by M^{4+}? Here, we report on the esterolysis of substrates **1a** and **1b** mediated by La^{3+} and Eu^{3+}, and by the bis–tris propane (**6**, BTP) complexes[7] of these cations.

$(HOCH_2)_3CHNH(CH_2)_3NHCH(CH_2OH)_3$

6

Hydrolyses of 10 mM DMPF (**1a**) with 25 mM $La(NO_3)_3 \cdot 7H_2O$ or $Eu(NO_3)_3 \cdot 6H_2O$ in D_2O were slow. The kinetics were followed by ^1H NMR at 70°C, monitoring released MeOD at δ 3.65 (La^{3+}) or δ 3.73 (Eu^{3+}). Solution pD's were established by Ln^{3+} hydrolysis (La^{3+}, pD 6.4; Eu^{3+}, pD 6.7). The observed pseudo-first-order rate constants ($3.8–8.4 \times 10^{-5}$ s^{-1}) appear in Table 1. ^{31}P NMR product studies demonstrated that only C–OMe cleavage of DMPF occurred with each lanthanide cation, affording *P*-monoester **3** ($R_2 = Me$) (^{31}P δ –23.2, La^{3+}; –21.8, Eu^{3+}), a conclusion that was confirmed by spiking with authentic material.[5,8] P–OMe hydrolysis of DMPF to *C*-monoester **4** was not competitive.

Yatsimirski and Gomez-Tagle demonstrated that the BTP (**6**) complexes of Ln(III) cations offer substantial rate accelerations in the basic hydrolysis of bis(*p*-nitrophenyl)phosphate (**5**, $R = p\text{-}O_2NC_6H_4$);[7a,b] bis–tris complexes behave similarly.[7c] We find analogous hydrolytic rate enhancements in the Ln^{3+}–BTP hydrolysis of DMPF.

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Hydrolyses of 10 mM DMPF were mediated by 25 mM Ln^{3+} and 125 mM BTP in 0.1 M $NaNO_3$ solution at 25°C. The solution pD was adjusted by additions of μL aliquots of DCl to obtain the optimal pD for the formation of the Ln^{3+}–BTP complexes.[7a,b] Again, the kinetics were monitored by ^1H NMR (MeOD), and the data appear in Table 1. Once more, we find only C–OMe scission of DMPF to *P*-monoester **3** (R_2 = Me), as verified by ^{31}P NMR.

Table 1 reveals that Ln^{3+} provides significant acceleration for the C–OMe regiospecific hydrolysis of DMPF. Enhancements of 390 (La^{3+}) and 860 (Eu^{3+}) are obtained at 70°C, relative to D^+. More substantial increases occur with Ln^{3+}–BTP complexes at 25°C, where we note accelerations of 6630 (La^{3+}) and 1680 (Eu^{3+}) relative to OD^- at pD 8.2.[9] An Arrhenius study of the Eu^{3+}–BTP cleavage of DMPF gave $E_a = 15.9$ kcal/mol, $\Delta S^{\ddagger} = -23.0$ e.u. (five points, 15–55°C, $r = 0.969$).

With methyl esters at both the carbonyl and phosphonyl sites of phosphonoformate **1a**, Ln^{3+} brings about regiospecific C–O cleavage. We also examined the influence of a better leaving group (PhO) at the phosphonyl site using the substrate *C*-methyl, *P*-phenyl phosphonoformate (**1b**, MePhPF).[1,10,11] Ln-mediated hydrolyses were examined with La^{3+} and Eu^{3+} at 70°C, and with their BTP complexes at 25°C, under the same conditions employed with DMPF (see above and Table 1). P–OPh cleavage of MePhPF was followed by UV spectroscopy monitoring released phenol at 282 nm, whereas C–OMe cleavage was followed by ^1H NMR, monitoring released MeOD (δ 3.19–3.75, depending on the presence or absence of BTP). As recorded in Table 2, both P–OPh and C–OMe hydrolyses occur with MePhPF, and in nearly equal amounts. The P–O/C–O ratios range from 1.1 (La^{3+}) to 1.3 (Eu^{3+}), and are identical whether determined from the rate constant ratio or from the product distribution. Products **4** (from P–OPh cleavage) and **3** (R_2 = Ph) were identified by ^{31}P NMR and spiking experiments with authentic materials.

Once again, the Ln^{3+}–BTP complexes are much more reactive than Ln^{3+} alone. For La^{3+}, the BTP complex is ~250 times more reactive than uncomplexed La^{3+} with MePhPF. A substantial portion of the increased reactivity likely reflects the higher pD at which the complex operates, and the attendant greater availability of metal bound OD, the actual nucleophile in the cleavage step (see below). The P–OPh ester of MePhPF is cleaved slightly faster than the C–OMe ester, but both substrate sites are particularly reactive toward La^{3+}–BTP, where k_{P-O} and k_{C-O} exceed 8×10^{-3} s^{-1}.

The Ln^{3+}-mediated, C–OMe regiospecific hydrolysis of DMPF parallels the behavior of Ce^{4+} and Th^{4+}, which likely afford dinuclear hydroxo complexes in aqueous solution.[5,12] The most commonly occurring forms of Ln^{3+} in aqueous solution are considered to be $LnOH^{2+}$,

Table 1. Kinetic data for the C–OMe cleavage of DMPF by Ln^{3+} [a]

Ln(III)	Ligand	pD	10^4 k_{obs} (s^{-1})[b]	$t_{1/2}$ (min)	$k_{Ln(III)}/k_D{}^+$ [c]	$k_{Ln(III)}/k_{OD}{}^-$ [d]
La[e]	None	6.4	0.38	304	390	
Eu[e]	None	6.7	0.84	138	860	
La[f]	BTP	8.5	19.7	6		6630
Eu[f]	BTP	8.2	4.98	23		1680

[a] 25 mM Ln(III), 10 mM substrate, 0.5 M $NaClO_4$ in D_2O.
[b] Monitored by ^1H NMR integration of released MeOD relative to an internal pyrazine standard.
[c] $k_D{}^+ = 9.73\times10^{-8}$ s^{-1} for the acid catalyzed cleavage of **1a** at pD 6.5 and 70°C.
[d] $k_{OD}{}^- = 2.97\times10^{-7}$ s^{-1} for the base catalyzed cleavage of **1a** at pD 8.2.
[e] 70°C.
[f] 25°C; 25 mM Ln(III), 125 mM BTP, 10 mM substrate, 0.1 M $NaNO_3$ (no $NaClO_4$) in D_2O.

Table 2. Kinetic data for esterolyses of MePhPF (**1b**) by Ln^{3+}

Ln^{3+}	Ligand	pD	10^4 k_{obs} (s^{-1})		k_{P-O}/k_{C-O}	Prod. distr. (%)[c]		%**4**/%**3**
			P–O hydrol.[a]	C–O hydrol.[b]		**4**	**3** (R_2 = Ph)	
La[d]	None	6.3	0.34	0.31	1.1	53	47	1.1
Eu[d]	None	6.7	0.73	0.58	1.3	56	44	1.3
La[e]	BTP	8.5	84.9	80.2	1.1	52	48	1.1
Eu[e]	BTP	8.2	24.8[f]	18.5	1.3	57	43	1.3

[a] Monitored by UV spectroscopy at 282 nm (formation of PhOD).
[b] Monitored by ^1H NMR integration of product MeOD, relative to an internal pyrazine standard.
[c] Determined from relative ^1H NMR integrals of products. Products were confirmed by NMR spiking experiments with authentic samples.
[d] Reaction conditions: Table 1, footnote a, 70°C.
[e] Reaction conditions: Table 1, footnote f.
[f] Monitored by ^1H NMR integration of product PhOD relative to an internal pyrazine standard.

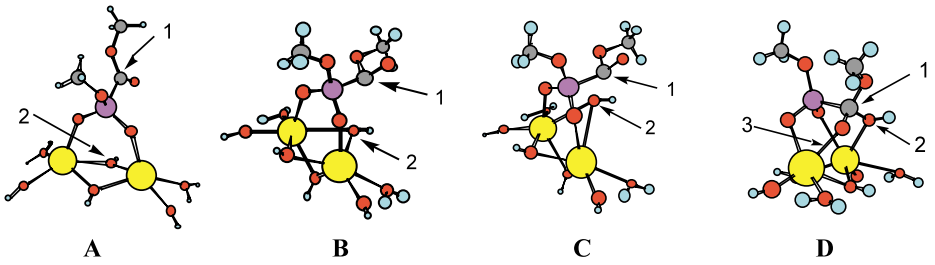

Figure 1. Possible intermediates and metastable constructs for the hydrolytic reaction of DMPF (**1a**) with La^{3+}. (A) 2 La^{3+} ions bridged with 2 hydroxide units and 'capped' by DMPF. (B) 2 La^{3+} ions bridged with 3 hydroxide units. (C) 2 La^{3+} ions bridged with 3 hydroxide units, one of which (2) is displaced toward the DMPF carbonyl carbon (1). (D) Tetrahedral intermediate resulting from attack of bridging OH (2) on carbonyl carbon (1); see text. Colors: La (yellow), C (gray), P (purple), O (red), H (blue).

$Ln_2(OH)_2^{4+}$, and $Ln_3(OH)_5^{4+}$.[12a] Moreover, Ln(III)–bis-tris[7c] and Ln(III)–BTP[7b] complexes afford bimolecular aggregates with OH units bridging the Ln^{3+} cations, analogous to the structure suggested[12c] for aqueous Ce^{4+}. Additionally, Chin et al. postulated dinuclear La^{3+} complexes, bridged by peroxide[13] or hydroxide[14] groups as catalysts for the cleavage of phosphodiesters or RNA, respectively.

As an intial model for a Ln^{3+}–DMPF reaction intermediate, we therefore adopted a structure which featured dinuclear La^{3+}, bridged by 2 OH groups (see Fig. 1, **A**). Each La^{3+} carried an additional hydroxide group and water molecule. The metallic unit was 'capped' by DMPF, with the phosphate oxygens bridging the La centers, as in Chin's constructs,[13,14] and Komiyama's analogous Ce^{4+}–DNA phosphodiester hydrolytic intermediates.[12c] Using typical bond lengths and angles[15] as input, this structure was refined by ab initio calculations.[16] In the final structure for **A**, the bridging hydroxide oxygen atom (2) was 4.43 Å away from the DMPF carbonyl carbon atom (1). Various manipulations of the structure, in which O(2) was displaced upward toward C(1) led (upon further computation) only to relaxation of the OH bridge back to **A**, without bonding to either C(1) or P.

We next examined structure **B**, which includes a third OH bridge between the La^{3+} centers. (Chin has suggested as many as 5 OH bridges for a dinuclear La^{3+} complex capped with a (RNA) phosphodiester.[14]) After computational refinement of **B**, the O(2)–C(1) separation was 2.83 Å, and the O(2)–P distance was 3.10 Å. Next, structure **C** was generated by upward displacement of bridging O(2) until its separations from C(1) and P were 1.50 and 1.64 Å, respectively. Computational evolution of metastable structure **C** now led to the tetrahedral intermediate **D**, in which O(2) has bonded to the carbonyl carbon, C(1) at a distance of 1.47 Å.[17] The former carbonyl oxygen, now anionic, has bonded to one La center (bond '3') at a distance of 2.42 Å, replacing the broken La–O bond to the former bridging oxygen, O(2). Subsequent loss of methanol from C(1) of structure **D** would correspond to the observed C–OMe cleavage of DMPF by La^{3+}.

We have not yet located structures in which O attack on phosphorus is competitive with attack on the carbonyl. Such structures are needed to account for the *P*-cleavage which is observed to compete with *C*-cleavage when the *P*-ester leaving group is made more reactive; e.g. OPh instead of OMe, as in **1b**. Regiospecific Ln^{3+} P–OR cleavage of phosphonoformate diesters, however, would probably require tetrameric or octameric hydroxo-bridged Ln cationic species, in analogy to Zr^{4+}.[5,18–20]

In conclusion, Eu^{3+} and La^{3+}, and their BTP complexes, mediate the hydrolysis of dimethyl phosphonoformate (**1a**) with C–OMe regiospecificity and substantial rate acceleration. Esterolysis at P becomes competitive when a better leaving group is present; *C*-methyl, *P*-phenyl phosphonoformate **1b** affords comparable and very rapid C–OMe and P–OPh scission with La^{3+} or Eu^{3+} BTP complexes.

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8. In the Eu^{3+} hydrolysis of DMPF at 70°C, subsequent decarboxylation of product **3** (with $k=2.8\times10^{-5}$ s^{-1}) gave methyl D-phosphonate [DP(=O)(O^-)OMe]. See: Ref. 5.
9. The Eu^{3+}-bis–tris complex[7c] is slightly inferior to Eu^{3+}–BTP in the cleavage of DMPF; we observe $k=3.1\times10^{-4}$ s^{-1} versus 5.0×10^{-4} s^{-1}, respectively, for the C–OMe hydrolysis of DMPF under the conditions of Table 1.
10. Methoxycarbonyl phosphonodichloridate was prepared from trimethyl phosphonoformate (Aldrich) by activation with trimethylsilylbromide, followed by reaction with PCl_5.[11] Reaction of the dichloridate with 2 equiv. of phenol (DBU, CH_2Cl_2, 0°C) gave methoxycarbonyl diphenyl phosphonoformate, which was hydrolyzed to **1b** (Na salt) with 1 equiv. of $NaHCO_3$ (aq. MeCN, 2 h, 25°C). Substrate **1b** (mp 80–82°C; lit.[1] mp 79–81°C) gave appropriate ^1H and ^{31}P NMR spectra, and a satisfactory C,H elemental analysis.
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16. Gaussian98, Revision A.9. Gaussian, Inc., Pittsburgh, PA, 1998. All structures were optimized at the HF level. C, H, and O atoms utilized the standard 3-21G basis set. Phosphorous basis orbitals used the D95 double zeta set of Dunning/Huzinaga. LANL2DZ pseudo potentials were used for lanthanum. Bond distances for structure **A** are typical of these complexes: La–O(La), 2.4 Å; La/La separation, 3.8 Å; La–OH, 2.2 Å; La–OH_2, 2.5–2.6 Å; La–O(P), 2.3–2.4 Å; P–O(La), 1.6 Å.
17. An alternate O(2) displacement of **B**, featuring O(2)–C(1) and O(2)–P separations of 1.80 and 1.64 Å, respectively, evolved back to **B**.
18. Hydrolysis of DMPF mediated by a trimeric oxo-bridged La^{3+} complex, containing a core hexagonal array of alternating La and O atoms,[14] gave only C–OMe cleavage at pD 7.3, with $k=2.6\times10^{-4}$ s^{-1}.
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20. More complicated structures than **B** are obviously needed to represent the Ln^{3+}–BTP–DMPF reactive aggregates. These can be constructed in analogy to **B**, based on the dinuclear La^{3+}–BTP complex offered by Gomez-Tagle and Yatsimirsky.[7b]