

Loci of Ceric Cation Mediated Hydrolyses of Dimethyl Phosphate and Methyl Methylphosphonate

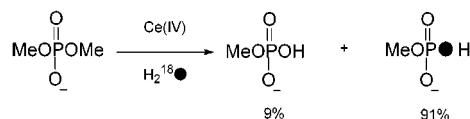
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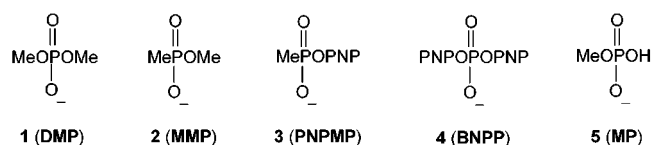
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ABSTRACT



Dimethyl phosphate and methyl methylphosphonate are cleaved by Ce(IV)-mediated hydrolysis with 91% and 88% P–O scission, respectively, and rate accelerations of $\geq 10^{10}$ relative to pH 7 P–O hydrolysis.

Both dimethyl phosphate (**1**, DMP) and methyl methylphosphonate (**2**, MMP) are highly resistant to hydrolysis: $k_{\text{hydrolysis}} = 1.6 \times 10^{-13} \text{ s}^{-1}$ for DMP (pH 7, 25 °C)¹ and, although analogous data are unavailable for MMP, $k_{\text{hydrolysis}}$ must be considerably less than $2 \times 10^{-9} \text{ s}^{-1}$, the rate constant for the hydrolysis of **3**, the *p*-nitrophenyl (PNP) analogue of MMP.² The centrality of the phosphate moiety to nucleic acid backbones and the desire to construct artificial phosphatases have driven many efforts to catalyze the hydrolysis of model esters, for example, bis(*p*-nitrophenyl)phosphate (BNPP, **4**).³ Hydrolyses of MMP and PNPMP are also of interest because of their relation to the primary hydrolytic products of the chemical warfare agents sarin, soman, and VX.⁴



Lanthanide cations are particularly effective mediators of phosphodiester hydrolysis.^{3,5} Among the lanthanide cations,

Ce(IV) is the most reactive species for the mediated hydrolysis of, for example, BNPP.⁶ Moreover, Ce(IV) affords large rate accelerations in the hydrolyses of both DMP and **3**: at 60 °C, $k_{\text{hydrolysis}}(\text{DMP})^7 = 5.3 \times 10^{-4} \text{ s}^{-1}$, compared to $5.2 \times 10^{-8} \text{ s}^{-1}$ without Ce(IV) at pH 1.24,⁸ and $2.6 \times 10^{-12} \text{ s}^{-1}$ at pH 7.¹ (Note that in the absence of Ce(IV) at pH 2.2 and 60 °C, DMP shows no measurable hydrolysis over several weeks.) For **3**, $k_{\text{hydrolysis}}$ (pH 4.0, 37 °C) increases⁹ to

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(7) Moss, R. A.; Raganathan, K. G. *Chem. Commun.* **1998**, 1871. The Ce(IV) concentration was 10 mM, with [DMP] = 1 mM at pH 2.2, 60 °C.

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indicative of a relatively small composite experimental error. Corrected for the ^{18}O content of the water, the results indicate that DMP affords MP with $(0.43/0.47) = 91.5\%$ of P–O cleavage. Table 1 records the extent of P–O scission of DMP, MP, and MMP in Ce(IV) hydrolysis and under other conditions.

Table 1. P–O vs C–O Loci of Phosphate Ester Hydrolysis

substrate	Ce(IV) ^a	conditions		
		acidic	neutral	basic
MMP (2)	88% P–O			
DMP (1)	91% P–O	78% C–O ^b	>99% C–O ^c	>99% C–O ^d
MP (5)	87% P–O	>84% C–O ^e	>99% P–O ^f	>99% P–O ^g

^a This work, pH 2.2, 60 °C. Errors are $\pm 2\%$. ^b pH 1.24, 100 °C, neutral species, ref 8. ^c pH 6.8, 150 °C, monoanion, ref 1. ^d pH 7–13, 150 °C, monoanion, ref 1. ^e pH 1, 100 °C, neutral species (MeH_2PO_4), ref 16. ^f pH 4, 100 °C, monoanion (MeHPO_4^-), ref 16. ^g pH 10–11, 100 °C, dianion (MePO_4^{2-}), ref 1.

From the literature, it is clear that the cleavage site of MP depends on its degree of protonation, with the neutral species hydrolyzing at C–O, while the monoanion undergoes P–O scission.¹⁶ DMP, however, affords mainly C–O cleavage at all common pH's.^{1,8} The sites of the acid, neutral, or basic hydrolyses of MMP are not reported, although Chin's results imply P–O cleavage for the hydrolysis of methyl phenylphosphonate coordinated to a dinuclear Co(III) complex.¹⁷

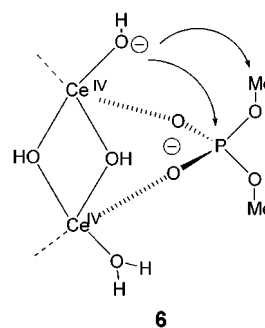
We have shown here that the Ce(IV)-mediated hydrolyses of MMP, DMP, and MP all proceed with dominant P–O cleavage at pH 2.2. For DMP, this represents a *reversal* of the acidic hydrolysis locus from C–O to P–O; coordination⁷ of DMP to Ce(IV) directs a rapid attack of Ce-bound OH at the substrate's P atom in preference to the much slower acid-catalyzed hydrolysis caused by H_2O attack at $\text{Me}-\text{O}$.⁸

Knowing the site of Ce(IV) hydrolysis of DMP, we can refine estimates of the hydrolytic acceleration of its P–O cleavage. In neutral hydrolysis of DMP, P–O cleavage is $\leq 0.5\%$ of the total hydrolysis, setting an upper limit of $(2.6 \times 10^{-12} \text{ s}^{-1} \times 0.005) \sim 1.3 \times 10^{-14} \text{ s}^{-1}$ for $k_{\text{hydrolytic}}$ of DMP by P–O cleavage at pH 7 (extrapolated to 60 °C from the measured activation parameters^{1,7}). With 1 mM DMP and 10 mM Ce(IV) at pD 2.2, 60 °C, $k = 5.3 \times 10^{-4} \text{ s}^{-1}$ with 91% P–O cleavage (Table 1), so that the P–O cleavage of DMP is accelerated by $(0.91 \times 5.3 \times 10^{-4} / 1.3 \times 10^{-14}) \sim 3.7 \times 10^{10}$.

Chin has noted that phosphonate monoesters are about as stable as phosphate diesters.^{17,18} This suggests that the P–O hydrolysis of MMP at pH 7 (60 °C) should, like that of DMP, occur with $k \sim 10^{-14} \text{ s}^{-1}$. The 10-fold excess Ce(IV)–P–O

hydrolysis of MMP occurs with $k \sim 1.2 \times 10^{-3} \text{ s}^{-1}$,¹³ pointing to an acceleration of $\sim 10^{11}$.

The P–O/C–O hydrolysis site data of Table 1 indicate that MMP, DMP, and MP all are cleaved in Ce(IV) hydrolyses with 90% P–O specificity. P–O cleavage is reasonable for a mechanism that involves initial binding of the substrate's P–O⁻ to the Ce(IV), mitigating the former's negative charge and providing a metal-bound hydroxide nucleophile for subsequent attack on the P=O.^{3,5,19} What is surprising, however, is the *persistence* of 10% C–O cleavage for the substrates of Table 1. The C–O hydrolysis cannot come from competitive, non-Ce(IV) hydrolysis, which, even in acidic solutions, is orders of magnitude slower⁸ than the Ce(IV)-mediated process. The residual C–O hydrolysis must therefore also be Ce(IV)-mediated. An attractive rationale makes use of a dimeric Ce(IV)-phosphodiester intermediate (6), analogous to that proposed by Komiyama,^{12b} in which attack of Ce(IV)-bound OH on the complexed DMP can occur either at P–O (90%) or C–O (10%).^{20,21}



The enormous (P–O selective) Ce(IV)-induced rate accelerations of DMP and MMP hydrolyses are rather unique: with $k_{\text{hydrolytic}} \sim 10^{-4} - 10^{-3} \text{ s}^{-1}$, they are several orders of magnitude faster than the Co(III)-cyclen ($2 \times 10^{-7} \text{ s}^{-1}$) or Cp_2MoCl_2 ($8 \times 10^{-7} \text{ s}^{-1}$) mediated hydrolyses.^{10,11} We are continuing to explore Ce(IV) and Zr(IV) hydrolyses of DMP and alkyl methylphosphonate esters; further kinetic and labeling results will appear in due course.

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(19) We determined $\Delta H^\ddagger = 21.6 \pm 1.4 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = -8.3 \pm 0.7 \text{ eu}$ for the Ce(IV) hydrolysis of DMP (30–70 °C; with $[\text{Ce(IV)}] = 25 \text{ mM}$, $[\text{DMP}] = 2.5 \text{ mM}$, pD 1.9 in D_2O). For comparison, the uncatalyzed hydrolysis of DMP at pH 6.8 displays $\Delta H^\ddagger = 25.9 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = -34 \text{ eu}$.¹ Remarkably, the major portion of the Ce(IV) hydrolytic rate acceleration results from the 25.7 eu (7.7 kcal mol⁻¹ at 25 °C) favorable $\Delta\Delta S^\ddagger$ for the metal-mediated hydrolysis. This is in accord with the entropic advantage anticipated for prior association of the Ce(IV) and DMP, followed by rate-limiting attack of a Ce-bound hydroxyl ligand on the substrate's P atom.

(20) Attack at P by the bridging oxide of 6 is also possible; cf. Williams, N. H.; Takasaki, B.; Wall, M.; Chin, J. *Acc. Chem. Res.* **1999**, 32, 485 and references therein.

(21) The binding constant of Ce(IV) and DMP is reported as $\sim 95 \text{ M}^{-1}$.⁷

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(18) Second-order rate constants for the OH⁻-catalyzed hydrolyses of BNPP (4) and *p*-nitrophenyl methylphosphonate² (PNPMP, 3) are comparable. The parity is not expected to change much with poorer leaving groups such as OMe.¹⁷