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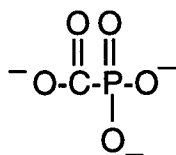
**METAL CATION MEDIATED HYDROLYSIS OF PHOSPHONO-
FORMATE DIESTERS: CHEMOSELECTIVITY AND CATALYSIS**

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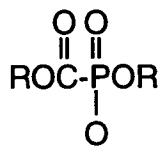
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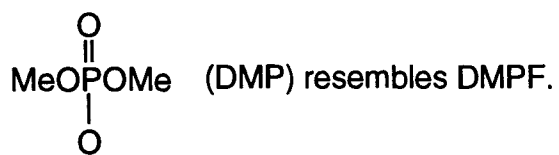
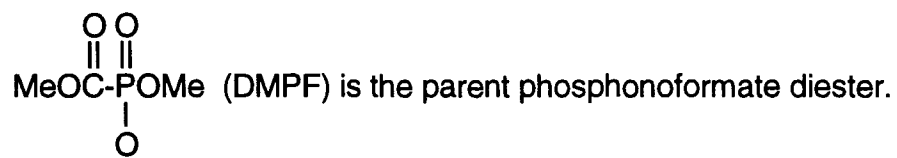
Phosphonoformate trianion ("Foscarnet") is an antiviral agent active against herpes simplex and AIDS-related cytomegalovirus.

Poor membrane permeability. Phosphonoformate diesters and triesters of interest as "prodrugs."

Monoanionic phosphonoformate *diesters* exhibit antiviral activity in prodrug studies.



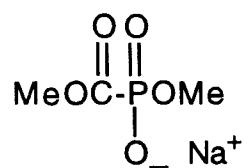
DIMETHYLPHOSPHONOFORMATE



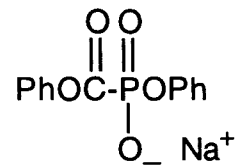
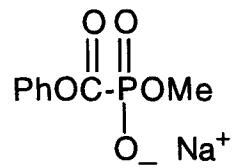
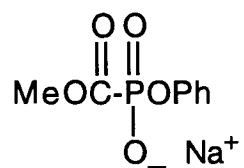
How will metal cation cleavage of DMPF compare to that of DMP?

DMPF has 3 sites for cleavage: O-C, P-O, and C-P. What sort of *chemoselectivity* can be observed?

SUBSTRATES AND METAL CATIONS



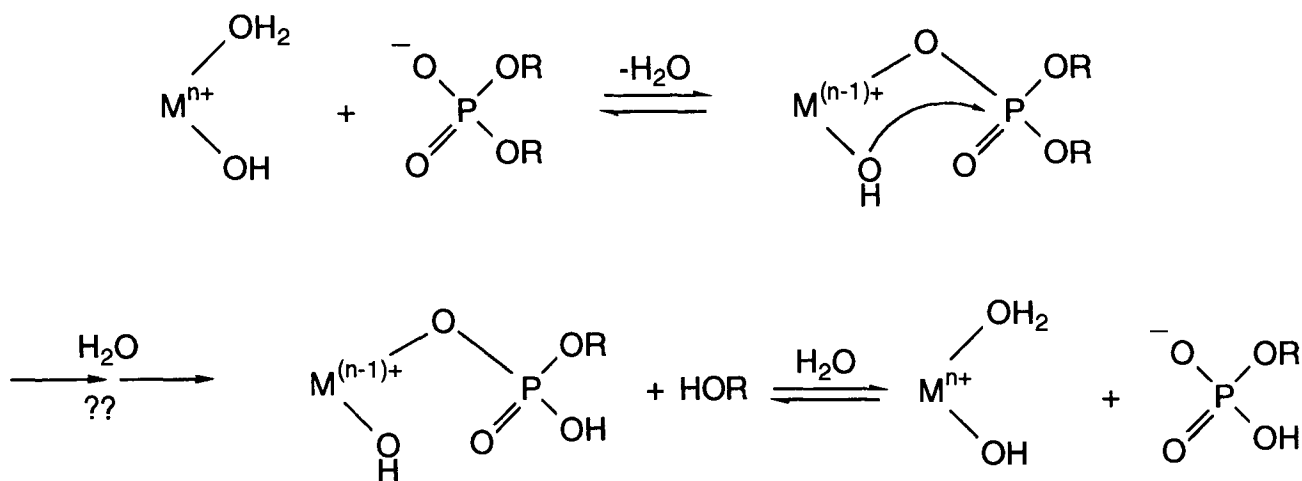
(DMPF)



Ce^{4+} Th^{4+} Zr^{4+} Hf^{4+}

Why these cations?

POLYVALENT METAL CATIONS CAN MEDIATE PHOSPHODIESTER HYDROLYSIS



M^{n+} provides electrophilic/nucleophilic catalysis. Require good Lewis acidity to bind $\text{P}-\text{O}^-$ and to acidify H_2O of hydration to afford metal bound OH nucleophile. Turnover catalysis is possible in some cases.

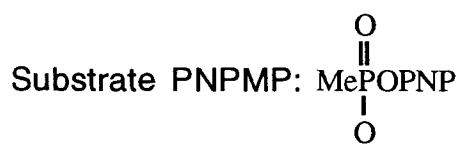
Desire highly charged, small M^{n+} ("hard" cation"), but also with high-lying vacant d or f orbitals to bind $\text{P}-\text{O}^-$, *transition metals, lanthanides, or actinides*.

Most Commonly Employed Metal
Cations for Hydrolysis of Phosphodiester

Most Commonly Employed Metal										13	
Cations for Hydrolysis of Phosphodiesters										3B IIIA 4B	
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6 57 57La Lanthanum	6 58 58Ce Cerium	6 59 59Pr Praseodymium	6 60 60Nd Neodymium	6 61 61Pm Promethium	6 62 62Sm Samarium	6 63 63Eu Europium	6 64 64Gd Gadolinium	6 65 65Tb Terbium	6 66 66Dy Dysprosium	6 67 67Ho Holmium	6 68 68Er Erbium
7 89 89Ac Actinium	7 90 90Th Thorium	7 91 91Pa Protactinium	7 92 92U Uranium	7 93 93Np Neptunium	7 94 94Pu Plutonium	7 95 95Am Americium	7 96 96Cm Curium	7 97 97Bk Berkelium	7 98 98Cf Californium	7 99 99Es Einsteinium	7 100 100Fm Fermium

METAL ION CATALYZED CLEAVAGES OF PHOSPHONATE MONOESTERS



H_2O , pH 7.6, 30 °C, $k_{\text{hydrol}} = 2.0 \times 10^{-9} \text{ s}^{-1}$; $k_2 = 3.6 \times 10^{-11} \text{ M}^{-1}\text{s}^{-1}$

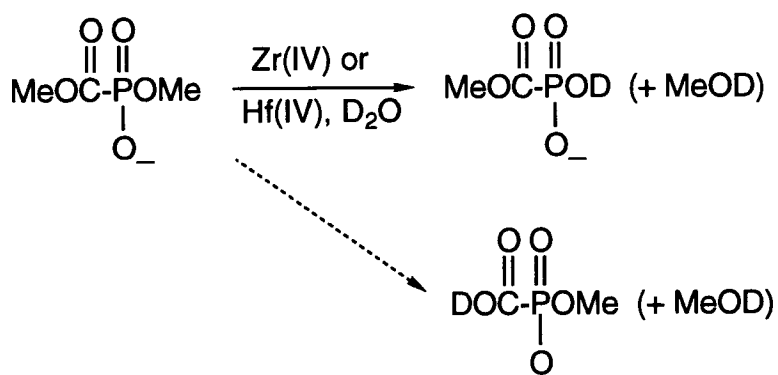
M^{4+}	pH	Brij, mM	$k_{\text{obs}}, \text{s}^{-1}$	k_{obs}/k_0
Zr^{4+}	3.5	0.0	0.11	5.5×10^7
Ce^{4+}	4.0	2.0	0.036	1.8×10^7
Th^{4+}	6.0	2.0	0.015	7.5×10^6

With 0.05 mM PNPMP, 1.0 mM M^{4+} , 37 °C.

Note enormous accelerations with Zr^{4+} , Ce^{4+} , and Th^{4+} . *Polymer or resin-bound M^{4+} might be excellent materials for the degradation of phosphonate monoesters.*

In the Zr^{4+} case, the half-life of PNPMP is reduced from 11 years to 6.3 seconds!

Zr(IV) or Hf(IV) CLEAVAGE OF DMPF

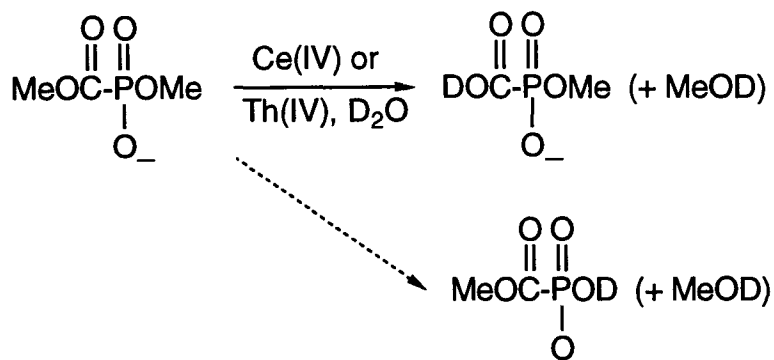


Kinetics are followed by monitoring released MeOD (^1H NMR); products are monitored by ^{31}P NMR.

M(IV)	$10^4 k_{\text{obs}} (\text{s}^{-1})$	% P-OMe	% C-OMe	$k_{\text{M(IV)}}/k_{\text{D}^+}$
Zr	4.4	79	21	3300
Hf	4.0	90	10	3100

Zr and Hf exhibit *P-O chemoselectivity*, with significant hydrolytic acceleration.

Ce(IV) or Th(IV) CLEAVAGE OF DMPF



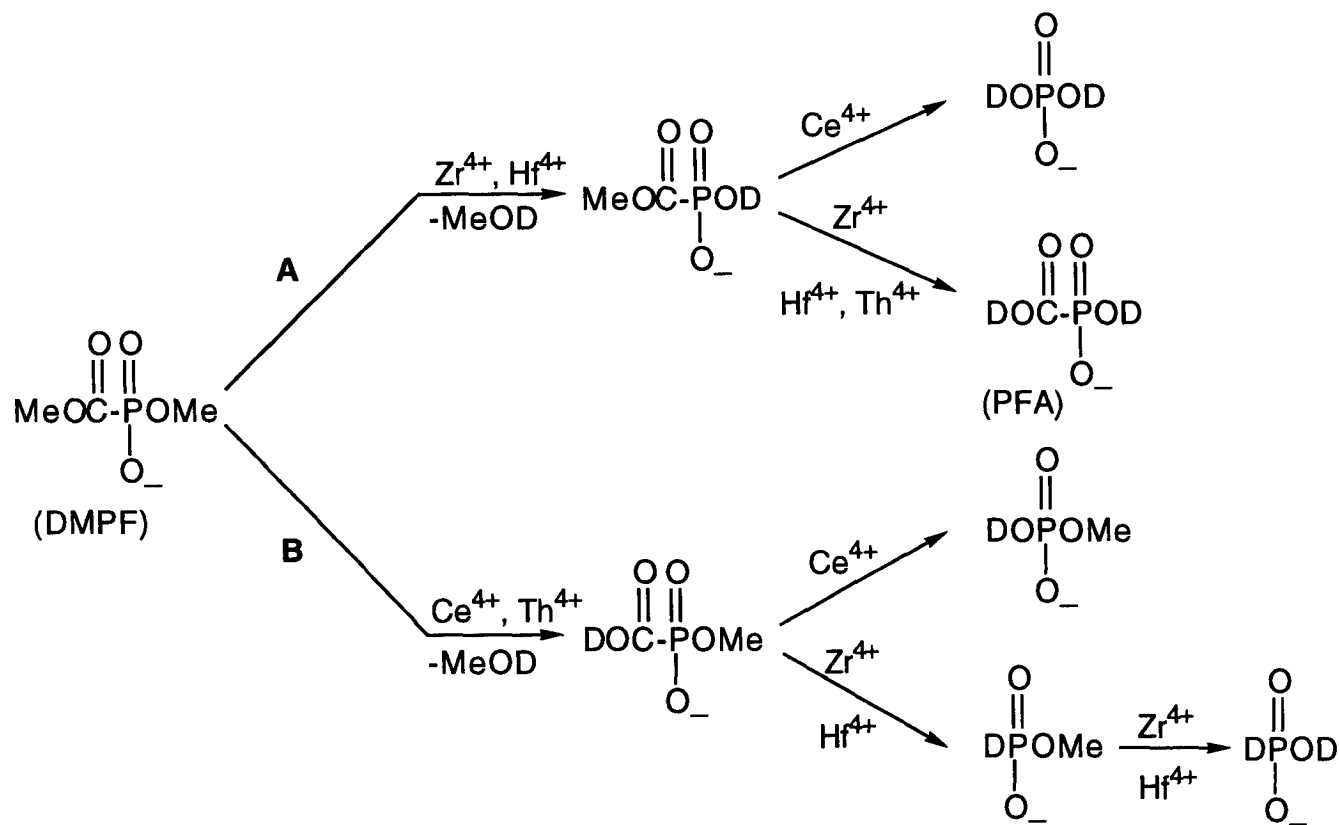
Kinetics are followed by monitoring released MeOD (^1H NMR); products are monitored by ^{31}P NMR.

M(IV)	$10^4 k_{\text{obs}} (\text{s}^{-1})$	% P-OMe	% C-OMe	$k_{\text{M(IV)}}/k_{\text{D}^+}$
Th	1.3	--	95	980
Ce	5.2	10	90	3900

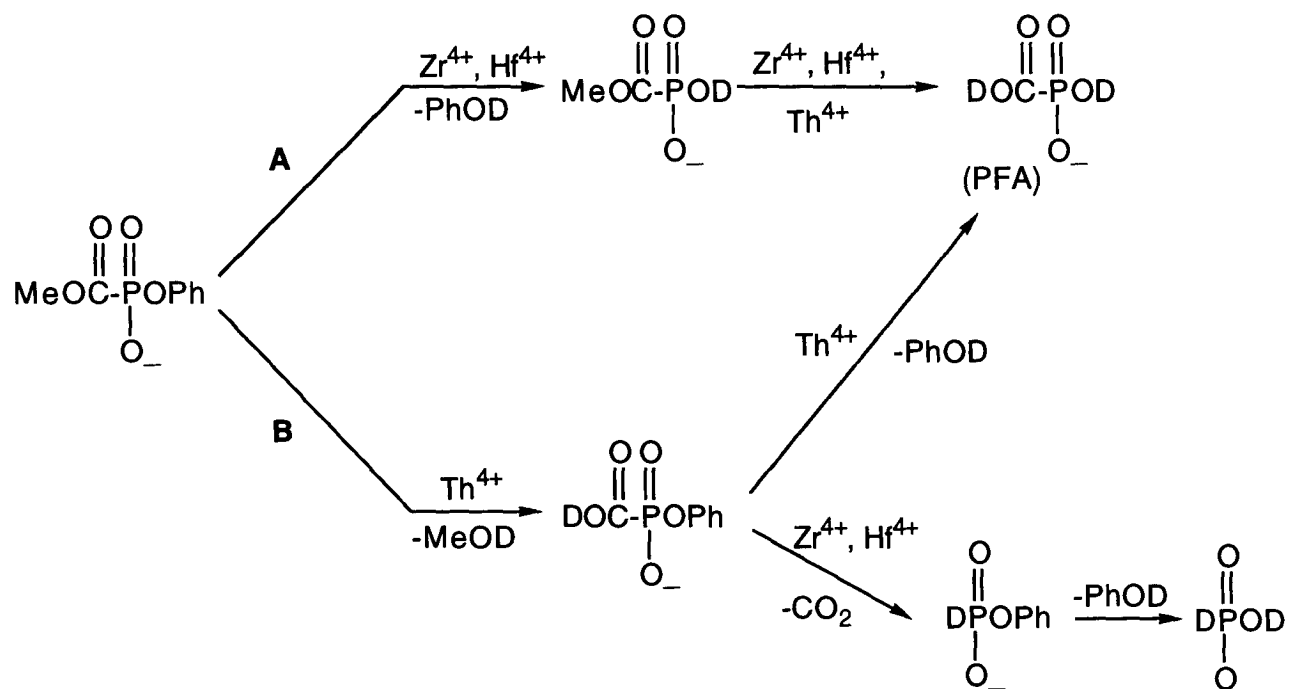
Th and Ce exhibit *C-O chemoselectivity*, with significant hydrolytic acceleration.

OVERVIEW OF DMPF REACTIONS

Cleavages of the monoesters are 10-100 times slower than cleavages of DMPF



CLEAVAGE OF C-OMe/P-OPh PHOSPHONOFORMATE



1. For Pathway A at pD 1.7 or 2.2:

$k_{\text{Zr}} = 2.3 \times 10^{-2} \text{ s}^{-1}$; $k_{\text{Hf}} = 0.65 \times 10^{-2} \text{ s}^{-1}$. Faster than DMPF cleavage.

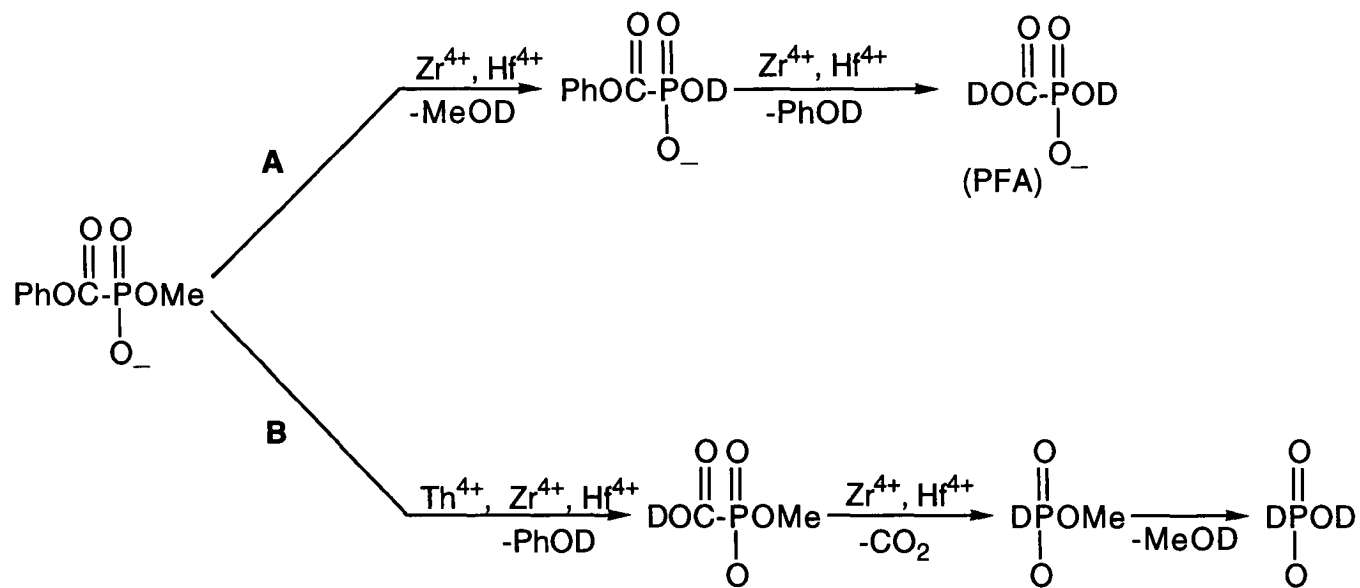
Selectivity for Zr^{4+} and Hf^{4+} is >95% P-OPh cleavage.

2. For Pathway B, Th^{4+} is >95% selective for C-OMe cleavage;

$k_{\text{Th}} = 1.6 \times 10^{-4} \text{ s}^{-1}$.

3. Chemoselectivity seen with DMPF is preserved.

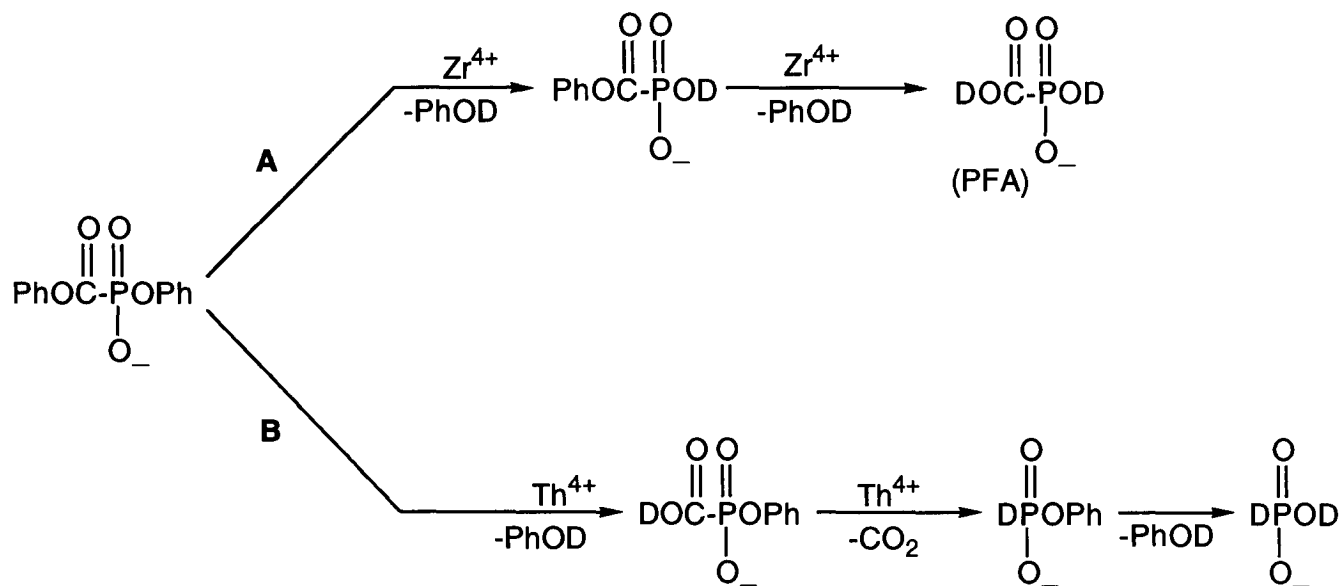
CLEAVAGE OF C-OPh/P-OMe PHOSPHONOFORMATE



With the better PhO leaving group now at C, the P-chemoselectivity of Zr^{4+} or Th^{4+} is lost. Here, C-OPh cleavage > P-OMe cleavage by 90:10 (Zr) or 79:21 (Hf): $k_{\text{Zr}} = 1.79 \times 10^{-2} \text{ s}^{-1}$, $k_{\text{Hf}} = 0.61 \times 10^{-2} \text{ s}^{-1}$.

Th^{4+} gives >95% C-OPh cleavage, as expected: $k_{\text{Th}} = 0.18 \times 10^{-2} \text{ s}^{-1}$.

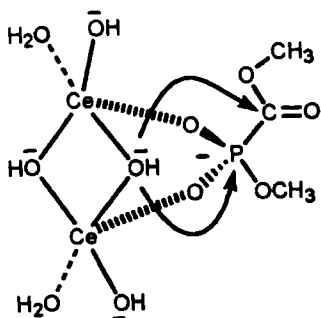
CLEAVAGE OF C-OPh/P-OPh PHOSPHONOFORMATE



1. Cleavage by Zr^{4+} was >95% P-selective; $k_{\text{Zr}} = 1.3 \times 10^{-2} \text{ s}^{-1}$ in 1:1 $\text{D}_2\text{O}/\text{CD}_3\text{CN}$ at pD 1.7.
2. Cleavage by Th^{4+} was 90:10 C-selective: $k_{\text{Th}} = 4.7 \times 10^{-3} \text{ s}^{-1}$ at pD 3.1 in $\text{D}_2\text{O}/\text{CD}_3\text{CN}$.
3. Chemoselectivity here is analogous to DMPF.

SOURCE OF CHEMOSELECTIVITY

At pH 2-3, Ce(IV) and Th(IV) will be mainly dimeric or monomeric.



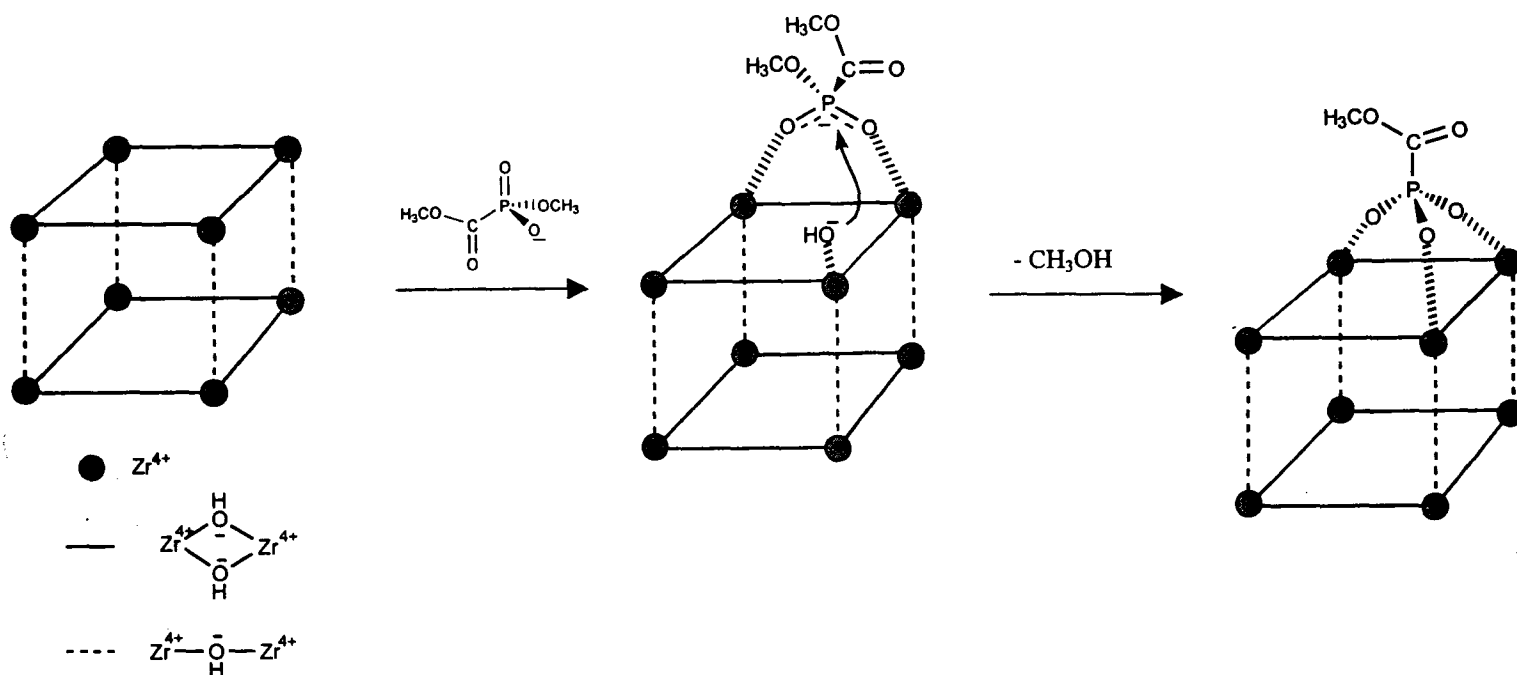
OH^- attack at $\text{C}=\text{O}$ involves a 5-membered cyclic TS; OH^- attack at $\text{P}-\text{OMe}$ involves a 4-membered cyclic TS.

Attack at *trigonal* C in 5-membered cyclic TS (addition-elimination) is kinetically preferred to attack at *tetrahedral* P ($\text{S}_{\text{N}}2$) in 4-membered cyclic TS.

Ce(IV) and Th(IV) afford C-O chemoselectivity.

P-O CHEMOSELECTIVITY

At pH ~ 2, Zr(IV), and presumably Hf(IV), exist as octamers or tetramers:



Cleavage at P can now occur via a 6-membered cyclic TS and lead directly to a tripodal phosphonate product with the same structure as the lamellar Zr phosphonates. Zr(IV) and Hf(IV) give P-O chemoselectivity.

P-O CHEMOSELECTIVITY LINKED TO M(IV) OCTAMERS

	P-O		C-O	
	Zr	Hf	Zr	Hf
M(IV)	79	90	21	10
M(IV) + Tris (1:1) ^a	40	66	60	34
M(IV) + Tris(1:2) ^a	15	19	85	81
M(IV) + NaOD (1:1) ^b	50	58	50	42

^aTris forms 1:1 complexes with Zr(IV). ^b OH⁻ promotes formation of Zr oligomers.

Destruction of M(IV) octamers/tetramers shifts P-O to C-O chemoselectivity.

SUMMARY

1. Ce^{4+} , Th^{4+} , Zr^{4+} , and Hf^{4+} ions accelerate the hydrolysis of phosphonoformate diesters.
2. With identical C-OR and P-OR leaving groups, Zr^{4+} and Hf^{4+} direct scission to the P-O ester site, whereas Ce^{4+} and Th^{4+} mediate attack at the C-O site.
3. Leaving group efficiency ($\text{PhO} > \text{MeO}$) can modulate the chemoselectivity.
4. P-O selectivity is associated with tetrameric or octameric forms of Zr^{4+} or Hf^{4+} aqueous complexes.
5. C-O selectivity is associated with dinuclear or mononuclear forms of Ce^{4+} or Th^{4+} .