Supporting Information

Intramolecular general base catalysis in the hydrolysis of a phosphate diester. Experimental and calculational guidance to a choice of mechanism.

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S.1 Kinetic data

Table S.1.1 First order rate constants for the hydrolysis of DPP as a function of pH, at ionic strength 1.0 M (KCl).

	Hydrolysis at 25°C			Hydrolysis at 75°C	
pH	k_{obs} **(s^{-1})**	**log k_{obs} (s^{-1})**	**pH**	k_{obs} **(s^{-1})**	**log k_{obs} (s^{-1})**
0	2.81×10^{-3}	-2.5514			
0.5	1.93×10^{-3}	-2.7150			
1	1.34×10^{-3}	-2.8746			
1.5	9.56×10^{-4}	-3.0195	5.0	1.10×10^{-4}	-3.96
2	5.49×10^{-4}	-3.2607	7.0	1.21×10^{-6}	-5.9605
2.5	2.52×10^{-4}	-3.5981	7.8	3.16×10^{-7}	-6.5001
3.3	3.58×10^{-5}	-4.4456	8.2	1.91×10^{-7}	-6.7185
9.4	3.31×10^{-10}	-9.4802	8.6	1.35×10^{-7}	-6.8701
12	1.33×10^{-8}	-7.8760	8.6	1.43×10^{-7}	-6.8446
13	1.52×10^{-7}	-6.8180	11.7	9.74×10^{-6}	-5.0115
14	1.60×10^{-6}	-5.7960	12.7	9.74×10^{-5}	-4.0115

Table S.1.2. Isotope effect measurements for spontaneous hydrolysis

Conditions	pH	k_{obs} (s^{-1})	Mean value	k_{H2O}/k_{D2O}
CHES, H_2O, 25°C	9.4	3.31 x 10^{-10} s^{-1}		
CHES, H_2O, 25°C	9.4	3.12 x 10^{-10} s^{-1}	3.37±0.28	
CHES, H_2O, 25°C	9.4	3.67 x 10^{-10} s^{-1}		
CHES, D_2O, 25°C	9.4	3.22 x 10^{-10} s^{-1}		
CHES, D_2O, 25°C	9.4	2.17 x 10^{-10} s^{-1}	2.64±0.53	1.28±0.22
CHES, D_2O, 25°C	9.4	2.54 x 10^{-10} s^{-1}		
CHES, H_2O, 45°C	9.4	1.51 x 10^{-8}		
CHES, D_2O, 45°C	9.4	1.26 x 10^{-8}		1.20

S.1.3 Data for the calculation of activation parameters.

Data for spontaneous hydrolysis.

Rate constants were evaluated by the initial rate method, in CHES buffer (50 mM, 70% free base, I = 1.0 M (KCl)) at 25°C (298.15 K), 45°C (318.15 K), 60°C (333.15 K), 75°C (348.15 K), 90°C (363.15 K) and (following reaction to completion by HPLC) at 100°C (373.15 K). These data appear in Table 2b and the Experimental Section of the full paper. The Eyring plot of ln ($k.h$/T.K_B) vs. 1/T (r^2 = 0.998) had gradient -12609 ± 265 and intercept -9.03 ± 0.79; giving the quoted values of

$\Delta H^{\ddagger}$ = 25.1 ±0.5 kcal/mol, $\Delta S^{\ddagger}$ = -17.8 ±1.6 cal/K/mol, $\Delta G^{\ddagger}$ = 30.4 kcal/mol.

Data for alkaline hydrolysis.

The second order rate constant k_{OH} for the alkaline hydrolysis of **DPP** was derived from rate constants measured in 1 M and 0.1 M potassium hydroxide at five different temperatures; 25°C (298.15 K), 45°C (318.15 K), 60°C (333.15 K), 75°C (348.15 K), 90°C (363.15 K).

T (K)	1/T (K^{-1})	k_{OH} (s^{-1})
298.15	0.003356	1.56×10^{-6}
318.15	0.003145	1.10×10^{-5}
333.15	0.003003	2.72×10^{-5}
348.15	0.002874	9.31×10^{-5}
363.15	0.002755	2.61×10^{-4}

The Eyring plot using these data ($r^2 = 0.997$) had gradient -8080.6 ± 252 and intercept -15.73 ± 0.76. Giving values for the hydroxide-catalyzed hydrolysis of

$\Delta H^{\ddagger}$ = 67.2 kJ mol^{-1} (16.07 kcal mol^{-1}), **$\Delta S^{\ddagger}$ = -130.8 J mol^{-1} K^{-1} (–31.3 cal/mol^{-1} K^{-1}),**

$\Delta G^{\ddagger}$ = 25.4 kcal/mol at 25C.

Table S.1.4 Calculation of rate constants for DPP hydrolysis when the rate is close to that of the disappearance of the first product MPP.

We use the equation $[P] = Ai + [A_0]\left[1 + \frac{1}{k_1 - k_2}\left(k_2 e^{-k_1 t} - k_1 e^{-k_2 t}\right)\right] + [A_0]\left(1 - e^{-k_1 t}\right)$

Where **A** is absorbance. Note that the corrections are generally small.

pH	k_2, MPP, s^{-1}	A_0	k_{obs}, DPP, s^{-1}	k_1, DPP, s^{-1} (*corrected*)
-2,12	2.22E-2	0.060	5.07E-3	8.00E-3
-1,69	1.89E-2	0.062	6.34E-3	7.83E-3
-1,25	1.51E-2	0.062	3.95E-3	6.85E-3
-1,05	1.12E-2	0.060	4.62E-3	6.99E-3
-0,69	7.70E-3	0.061	4.18E-3	6.84E-3
0	4.53E-3	0.080	3.33E-3	5.20E-3
0.5	2.04E-3	0.104	1.99E-3	3.95E-3
1	1.48E-3	0.176	1.30E-3	1.40E-3
1.5	2.01E-3	0.174	9.21E-4	1.22E-3
2	2.25E-3	0.214	3.64E-4	3.82E-4
3	1.26E-2	0.229	6.06E-5	6.05E-5
4	1.63E-2	0.233	1.05E-5	1.05E-5

Dependence of reactivity on the non-leaving group.

We examine data for the hydrolysis of four diesters $RO(PO_2^-)$–O-2,4-DNP: with R = methyl, phenyl, 4-nitrophenyl and 2,4-dinitrophenyl, with 2,4-dinitrophenol as the common leaving group. k_0 values for the pH-independent reaction at 100ºC are collected in **Table S.1.5**, and the Brønsted (non-leaving) group plot is shown as **Figure S.1**

Table S.1.5 Data for the hydrolysis of diesters $RO(PO_2^-)$–O-2,4-DNP at 100ºC and ionic strength 1.0 M.

Non-leaving group RO	*pK_a of ROH*	k_0, s^{-1}
2,4-dinitrophenyl [1]	4.07	5.72×10^{-5}
4-nitrophenyl	7.14	4.72×10^{-5}
Phenyl	9.95	3.87×10^{-5}
Methyl *	15.54	4.20×10^{-5}

* Note. k_0 calculated from the rate at 39°C,[2] assuming the reaction to have the same entropy of activation as the hydrolysis of the bis-2,4-dinitrophenyl ester.

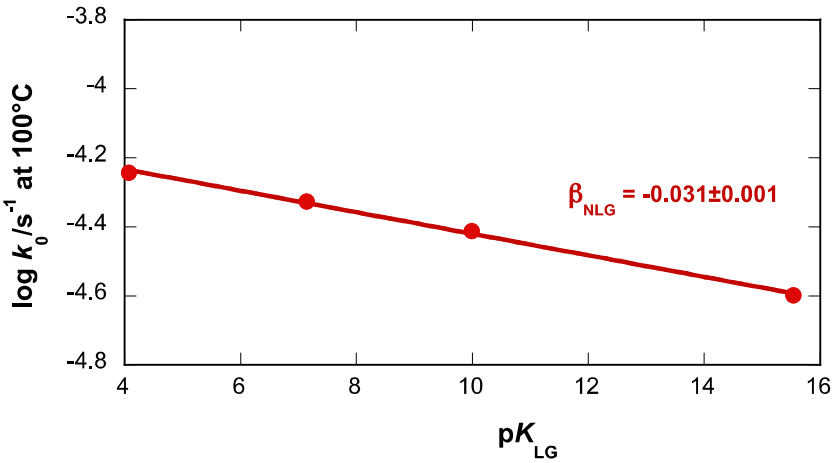

Figure S.1 The minimal dependence of the rates of hydrolysis of diesters $RO(PO_2^-)$–O-2,4-DNP at 100°C on the pK_a of the conjugate acid of the non-leaving group ROH.

S.1.6 Predicted rates from Linear Free Energy Relationships.

The most extensive dataset is (still) that of Kirby and Younas,[1] for the hydrolysis of diaryl phosphate esters at 100°C. Replotting their data (in sec^{-1}) gives a linear Brønsted (leaving group) plot described by the equation $\log k_0 = 0.30\pm0.21 - 1.04\pm0.03*pK_{LG}$ which predicts a rate constant of 7.02×10^{-10} s^{-1} at 100°C for the hydrolysis of **DPP**, with $pK_{LG} = 9.09$: the observed k_0 at 100°C is 2.06×10^{-6} s^{-1}, 2934 times faster than predicted.

To predict the rate at 25°C we use the reciprocal dependence of β_{LG} on temperature to give $\beta_{LG} = 1.30$; and the estimated rate constant for the hydrolysis of bis-4-nitrophenyl phosphate ($pK_{LG} = 7.14$) of 1.1×10^{-11} s^{-1} at pH 7 * and 25°C[3] to make the short extrapolation to $pK_{LG} = 9.09$. This predicts a rate constant of 3.2×10^{-14} s^{-1} and thus an acceleration of the order of 10,000.

* We note that k_0 for the hydrolysis of bis-4-nitrophenyl phosphate will be significantly slower (5-6x) than the value at pH 7 because the actual pH-rate minimum is close to 4.0.

Note*: *by way of confirmation of the methodology*. The rate calculated by this procedure for the hydrolysis of **DPP$^{\pm}$ at 25°C, based on the rates measured for the hydrolysis of 24DNPP at a range of temperatures extrapolated to 25°C, and a longer extrapolation from pK_{LG} 4.07 to 0.75 (making no allowance for non-leaving group effects), is 2.06×10^{-3} s^{-1}, 5.8 times faster than observed (Table 2 of the main paper).

S.1.7 Estimation of Effective Molarities (EM) for suggested Mechanism (ii).

Need best estimates of second order rate constants k_N for pyridine nucleophiles of pK_a 0.33 and 2.73 with diesters $DPP^{\pm}$ and DPP^{-}, with leaving groups of pKa 0.75 and 9.09.

Second order rate constants are available for the primarily nucleophilic reactions of substituted pyridines with methyl aryl phosphates in min^{-1} at 39°C (**Table S.1.7**).[2] They show relatively low sensitivities to the pK_a of the nucleophile (from β_{nuc} = 0.38 for the methyl 2-nitrophenyl to 0.31 for the methyl 2,4-DNP ester).

Table S.1.7 Second order rate constants $\boldsymbol{k_N}$ (M^{-1} min^{-1}, 39°C) for pyridines + diesters.[2]

Methyl aryl diester: Ar =	**pK_a ArOH**	**Py (pK_a = 5.17) β_{LG} = -1.06**	**4-Me-Py (6.02) β_{LG} = -1.03**	**4-NH_2-Py (8.96) β_{LG} = -0.98**	**β_{nuc}**
2-nitro	7.23	2.63×10^{-6}	7.86×10^{-6}	8.86×10^{-5}	0.38
4-Cl-2-nitro-	6.36	2.0×10^{-5}	5.0×10^{-5}	5.0×10^{-4}	0.35
4-Ac-2-nitro-	5.09	4.3×10^{-4}	1.04×10^{-3}	8.65×10^{-3}	0.33
2,4-Dinitro	4.07	6.15×10^{-3}	1.47×10^{-2}	0.11	0.31

Plotting β_{nuc} against pK_{LG} gives the LFER $\beta_{nuc} = 0.22 + 0.022pK_{LG}$: and thus for p$K_{LG}$ of 0.75 and 9.09 $\rightarrow$ extrapolated values for $\boldsymbol{\beta_{nuc}}$ of **0.24**, and **0.42,** respectively. Taking the literature data points[2] closest in pK_{nuc} (1.56×10^{-4} and 8.60×10^{-4} $M^{-1}min^{-1}$ for 3-cyanopyridine and nicotinamide, with pK_as of 1.45 and 3.40 respectively, reacting with Me24DNPP) the appropriate values of β_{nuc} give the following estimated values of k_N:

For $DPP^{\pm}$

A pyridine of pK_a = 0.33 reacting with Me24DNPP would have

k_N = 1.56e-4 x 10^(- 0.24 x 1.12) min^{-1} $\rightarrow$ 1.40 e-6 $M^{-1}s^{-1}$.

Expect $\beta_{LG} \approx$ -1.12 so for pK_{LG} = 0.75 $\rightarrow$ $\boldsymbol{k_N}$ **= 7.32 e-3 M^{-1} s.$^{-1}$**

For DPP^-

A pyridine of pK_a = 2.73 reacting with Me24DNPP would have

k_N = 8.60e-4 x 10^(-0.42 x 0.67) min^{-1} $\rightarrow$ 7.50e-6 $M^{-1}s^{-1}$.

Expect $\beta_{LG} \approx$ -1.10 so for pK_{LG} = 9.09 $\rightarrow$ $\boldsymbol{k_N}$ **= 2.25 e-11 M^{-1} s.$^{-1}$**

S.2 Theoretical study

S.2.1 Cartesian coordinates for hydrolysis reaction of DPP.

2.1.1 Reactant

Atom	X	Y	Z
P	0.01107700	-1.26107700	-0.43030500
O	0.40911800	-0.86923600	-1.82798000
O	-1.54936700	-0.81528800	-0.08501500
O	0.75647400	-0.26803400	0.68051000
O	0.09241200	-2.69262600	0.04045000
C	-2.12007200	0.42892700	-0.25653700
C	-1.51066100	1.48267200	-0.94611600
C	-3.99832300	1.67761200	0.18643900
C	-2.21693700	2.67845700	-1.05060600
H	-0.53187700	1.36932600	-1.39220700
C	-3.48690600	2.78733300	-0.47682800
H	-4.97979500	1.70526800	0.65089000
H	-1.77524300	3.51689800	-1.58032000
H	-4.06389200	3.70308700	-0.54016700
C	1.98010800	0.34583600	0.51523700
C	2.06400300	1.69971700	0.85220700
C	3.30854000	2.31414800	0.75814200
H	1.17745800	2.23495600	1.17286600
C	4.21196900	0.22537300	0.01519300
C	4.40932900	1.56558200	0.32692900
H	3.41737700	3.36388500	1.01206400
H	5.03647300	-0.39692700	-0.32116100
H	5.39548700	2.00738800	0.23660400
N	3.01402200	-0.38808400	0.11164300
N	-3.32939400	0.51452400	0.29763500
O	2.91019200	-3.29822200	-0.16483800
H	1.93565900	-3.35108300	-0.12001900
H	3.05969200	-2.32904000	-0.09592100
O	-4.40860100	-1.67658600	1.73742200
H	-4.01285400	-0.92544400	1.22822500
H	-3.72747400	-2.36415100	1.72557700

2.1.2. Transition state (**TS**)

Atom	X	Y	Z
P	0.18465400	-1.69343700	-0.38389700
O	0.17844100	-1.33735100	-1.86153200
O	-1.45513100	-0.94279500	0.02862400
O	0.82182200	-0.47944200	0.69152600
O	-0.20585100	-2.97007100	0.34567500
C	-1.92143600	0.27967000	-0.24831000
C	-1.21281400	1.28486200	-0.94338800
C	-3.74691900	1.69848000	0.00092900
C	-1.82451400	2.51585900	-1.14673800
H	-0.21571000	1.09690200	-1.31639500
C	-3.12158700	2.74256300	-0.66875000
H	-4.75409400	1.81273100	0.39473100
H	-1.28941200	3.29789300	-1.67833700
H	-3.62673300	3.69170200	-0.80987300
C	1.92152400	0.28360700	0.57906300
C	1.97193100	1.52369000	1.22822100
C	3.13725300	2.27048100	1.12524400
H	1.11040300	1.86689200	1.78793800
C	4.11145800	0.55535100	-0.23039400
C	4.22860800	1.78693200	0.38265500
H	3.20139000	3.23402800	1.62066600
H	4.90603500	0.10494100	-0.81399700
H	5.14569400	2.35595400	0.28954200
N	2.97429300	-0.16665500	-0.12264900
N	-3.17284800	0.49944700	0.20869200
O	2.03605200	-2.36200200	-0.58804400
H	2.23222800	-2.93217700	0.17272700
H	2.75346100	-1.26685600	-0.47080800
O	-4.42078600	-1.50772900	1.70567300
H	-3.95727300	-0.81073900	1.16541600
H	-3.78330400	-2.23311100	1.76795000

2.1.3 Product

Atom	X	Y	Z
P	0.70881300	-2.02125700	-0.45149300
O	0.30268100	-1.49117400	-1.79668800
O	-1.89932700	-0.71644300	0.18042200
O	1.03589300	-0.67704200	0.58369100
O	-0.08666900	-2.96483900	0.40162100
C	-2.29363800	0.46767500	-0.11446400
C	-1.46526300	1.39860700	-0.83282800
C	-3.98307900	2.09524400	-0.03285700
C	-1.93755100	2.66145000	-1.13226400
H	-0.47295300	1.08376400	-1.13610000
C	-3.23420400	3.03652000	-0.72727500
H	-4.98997900	2.34059400	0.30267500
H	-1.30991800	3.36233400	-1.67848400
H	-3.64142300	4.01859800	-0.94249200
C	2.02733500	0.20674800	0.52197800
C	1.94534500	1.41253500	1.23019200
C	3.01902900	2.28851500	1.19215500
H	1.04362500	1.62404800	1.79122500
C	4.21191700	0.79139500	-0.23736500
C	4.17427300	1.98004700	0.45004100
H	2.96357200	3.22198100	1.74255500
H	5.04984300	0.45536800	-0.83462000
H	5.02107300	2.65368700	0.41141100
N	3.15137400	-0.05634300	-0.18458800
N	-3.55395900	0.85628200	0.27325200
O	2.23323000	-2.60340300	-0.65131000
H	2.51991800	-3.15435400	0.09767900
H	3.21381000	-0.96795300	-0.65107600
O	-4.54329200	-1.34738400	1.71832700
H	-4.23333000	-0.54792300	1.20641600
H	-3.81291100	-1.97591900	1.62993800

S.2.2. Cartesian coordinates for hydrolysis reaction of 4-ClPP

2.2.1 Reactant

Atom	X	Y	Z
P	0.08418700	1.30510300	-1.07021900
O	-0.90771700	2.33636400	-0.56438800
O	0.99736900	0.92658500	0.25381000
O	0.96182700	1.55810500	-2.26551600
C	2.13196100	0.11753300	0.15821000
C	4.53137200	-0.07647000	-0.00888100
C	3.15031900	-2.06740600	0.23818000
C	4.39846100	-1.46087800	0.09785000
C	2.00568000	-1.26750800	0.27081900
H	5.50902300	0.38084000	-0.11488600
H	3.06482200	-3.14511500	0.32402800
H	1.02522900	-1.71694000	0.38572500
O	-0.71200700	-0.10213500	-1.41357000
C	-1.82583000	-0.58797200	-0.73418300
C	-1.94397500	-0.54460600	0.65704600
C	-3.95200500	-1.72408700	-0.90926900
C	-3.07729200	-1.08734600	1.26856200
C	-4.06805400	-1.66935300	0.47983900
C	-2.82078200	-1.17802300	-1.51734900
H	-1.16847500	-0.09774300	1.26756900
H	-4.72786400	-2.18112200	-1.51358900
H	-3.17647000	-1.05491500	2.34804300
O	1.85754200	3.21905700	2.60655400
H	2.07336300	2.42907000	2.09020400
H	1.03977800	3.56965300	2.18386400
O	-0.43870700	4.22038200	1.38085300
H	-0.61889700	3.53973400	0.68986800
H	-1.17617100	4.15467900	2.00455200
H	-2.70852600	-1.20469300	-2.59614200
C	3.38369800	0.71856100	0.02248800
H	3.45955900	1.79796200	-0.05643800
Cl	5.84786200	-2.47154500	0.05864100
Cl	-5.50118700	-2.35459600	1.25572100
O	-3.59220800	2.46852500	-1.36730300
H	-3.91255500	1.55498200	-1.38313000
H	-2.64920900	2.39171200	-1.10394600

2.2.2. Transition state (**TS**)

Atom	X	Y	Z
P	0.43444100	1.84616800	-0.52098000
O	-0.86114900	2.39976100	-0.00012700
O	1.09147300	0.83878200	0.57631300
O	0.98936600	1.84785800	-1.91162900
C	2.16705900	-0.02181300	0.35200100
C	3.35038100	0.40273500	-0.25405600
C	4.41228700	-0.49573000	-0.38562000
C	3.09474100	-2.21988700	0.71454200
C	4.27249300	-1.79518200	0.09973600
C	2.03247600	-1.32288300	0.83740600
H	3.45712100	1.41768200	-0.61643900
H	5.33556100	-0.17511500	-0.85564000
H	2.99837800	-3.23251500	1.09040600
H	1.10435200	-1.62854200	1.30785600
O	-0.74525200	-0.11827900	-1.28351200
C	-1.86835100	-0.58833200	-0.77885300
C	-2.06018700	-0.79376100	0.61802400
C	-4.16588800	-1.42638100	-1.11398600
C	-3.25612200	-1.29799200	1.13046600
C	-4.30347500	-1.61151000	0.26259000
C	-2.96876600	-0.92040500	-1.62239100
H	-1.25124600	-0.55397800	1.30142100
H	-4.98241100	-1.67157500	-1.78663800
H	-3.36789700	-1.44552200	2.20065300
H	-2.86101400	-0.77717700	-2.69477000
O	1.57584200	3.26733900	0.12133800
H	1.67497600	3.95616300	-0.55988900
H	1.24331400	3.72281800	0.97473100
O	0.74799300	4.43398900	2.27460600
H	-0.17944500	4.18452400	2.41418800
H	1.22072400	4.10111700	3.05356900
Cl	-5.82585800	-2.25743500	0.91551600
Cl	5.61886500	-2.92823500	-0.06289000
O	-3.47239700	2.47240500	-0.99809300
H	-3.69367300	1.55323500	-1.21437900
H	-2.54334000	2.42476300	-0.68533600

2.2.3. Product

Atom	X	Y	Z
P	-1.42069400	-0.83104300	0.26495400
O	-1.11917700	0.29972700	1.21657300
O	3.17905400	1.91446300	-0.28631600
O	-1.77149600	-0.08936100	-1.16540400
O	-0.51160200	-2.01042800	0.05452600
C	3.25714300	1.93211500	1.02432400
C	2.67129200	2.97604700	1.80421200
C	4.01295400	0.92492900	3.15071000
C	2.74942800	2.99633500	3.19648800
H	2.14577500	3.77578700	1.28754400
C	3.41983400	1.96880500	3.86564600
H	4.53441400	0.12892100	3.67450600
H	2.29032100	3.80631600	3.75585400
C	-1.77541800	-0.69779100	-2.41885500
C	-2.41765400	-1.91321600	-2.66455100
C	-2.43112600	-2.43416100	-3.96127300
H	-2.91078700	-2.45658700	-1.86663300
C	-1.17510500	-0.50705800	-4.75138600
C	-1.81183100	-1.72506400	-4.98933400
H	-2.92670700	-3.37833500	-4.15925100
H	-0.69644100	0.03667900	-5.55845400
O	-2.92779300	-1.39152600	0.73987000
H	-3.10338600	-2.31667800	0.49370000
H	-3.56153400	-0.96995200	1.95757700
O	-4.06127300	-0.67713500	2.84046500
H	-3.45596900	-0.15594400	3.40254700
H	-4.82335100	-0.11029900	2.61475200
O	0.28722600	0.17718100	3.61343900
H	1.11829300	0.65286100	3.46349500
H	-0.17542000	0.19131300	2.74652500
C	3.93166800	0.90862800	1.75852800
H	4.39190500	0.09245700	1.20651700
C	-1.15650900	0.00574900	-3.45364900
H	-0.66582700	0.94989000	-3.24198300
Cl	3.53690300	2.00055100	5.64056200
Cl	-1.83651900	-2.38138700	-6.63040900

Table S.2.3. NBO and Hirshfeld charges for reactant (**R**), transition state (**TS**) and product (**P**) at the B3LYP/6-31+G(d,p) level of theory. In parenthesis are the Hirshfeld charges.

				DPP			
	P_1	**O_2**	**H_3**	**N_4**	**C_5**	**O_8**	**O_6**
R	2.583	-1.103	0.520	-0.548	0.532	-0.844	-1.193
	(0.494)	(-0.422)	(0.084)	(-0.136)	(0.138)	(-0.215)	(-0.491)
TS1	2.536	-1.096	0.507	-0.555	0.588	-0.796	-1.226
	(0.440)	(-0.320)	(0.098)	(-0.039)	(0.173)	(-0.200)	(-0.578)
P	2.568	-1.086	0.506	-0.532	0.608	-0.781	-1.191
	(0.478)	(-0.251)	(0.153)	(-0.010)	(0.196)	(-0.184)	(-0.541)
	O_7	**O_9**	**N_{10}**	**H_{11}**			
R	-0.825	-1.196	-0.543	0.521			
	(-0.210)	(-0.526)	(-0.130)	(0.078)			
TS1	-0.812	-1.218	-0.578	0.519			
	(-0.281)	(-0.558)	(-0.149)	(0.068)			
P	-0.857	-1.192	-0.637	0.516			
	(-0.480)	(-0.531)	(-0.189)	(0.058)			
				4-ClPP			
	P_1	**O_2**	**H_3**	**O_4**	**H_5**	**O_6**	**O_7**
R	2.607	-1.092	0.528	-1.076	0.543	-1.203	-0.841
	(0.515)	(-0.402)	(0.093)	(-0.301)	(0.108)	(-0.379)	(-0.210)
TS2	2.566	-1.001	0.570	-1.029	0.558	-1.177	-0.878
	(0.526)	(-0.139)	(0.143)	(-0.214)	(0.201)	(-0.421)	(-0.441)
P	2.589	-1.076	0.586	-0.904	0.605	-1.199	-0.930
	(0.517)	(-0.176)	(0.175)	(-0.021)	(0.275)	(-0.454)	(-0.613)
	O_8	**O_9**	**H_{10}**	**H_{13}**			
R	-0.848	-1.197	0.523	0.534			
	(-0.195)	(-0.547)	(0.137)	(0.093)			
TS2	-0.829	-1.165	0.584	0.533			
	(-0.192)	(-0.505)	(0.225)	(0.088)			
P	-0.838	-1.197	0.592	0.533			
	(-0.215)	(-0.535)	(0.224)	(0.090)			

Table S.2.4. Wiberg bond indices for Reactant (**R**), transition state (**TS**) and product (**P**) at the B3LYP/6-31+G(d,p) level of theory.

				DPP			
	P_1-O_2	**O_2-H_3**	**H_3-N_4**	**N_4-C_5**	**C_5-O_8**	**O_8-P_1**	**P_1-O_7**
R	0.0032	0.6726	0.0553	1.3974	0.9537	0.5930	0.5988
TS1	0.3613	0.2684	0.4498	1.2893	1.0603	0.5140	0.4256
P	0.6651	0.0379	0.6766	1.2392	1.1003	0.5030	0.0169
$\%E_v$	54.1	63.7	63.5	68.3	72.7	87.8	29.8
	P_1-O_6 , P_1-O_9		**N_{10}-H_{11}**				S_y
R	1.1110, 1.1348		0.0780				
TS1	1.0791, 1.0878		0.0955				0.889
P	1.1560, 1.0956		0.1251				
				4ClPP			
	P_1-O_2	**O_2-H_3**	**H_3-O_4**	**O_4-H_5**	**H_5-O_6**	**O_6-P_1**	**P_1-O_7**
R	0.0004	0.6590	0.0646	0.6466	0.0579	1.0384	0.6177
TS2	0.3433	0.5341	0.1367	0.6885	0.0009	1.1227	0.1420
P	0.5906	0.1710	0.4825	0.6327	0.0008	1.0918	0.0002
$\%E_v$	58.1	25.6	17.3	---	---	---	77.0
	P_1-O_8	**P_1-O_9**	**O_9-H_{10}**	**O_6-H_{13}**			S_y
R	0.6202	1.1363	0.0001	0.0473			
TS2	0.6569	1.1730	0.0007	0.0455			0.654
P	0.6228	1.1462	0.0005	0.0519			

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