Supporting Materials: Description of phosphate hydrolysis reactions with the Self-Consistent-Charge Density-Functional-Tight-Binding (SCC-DFTB) theory. 1. Parameterization

[1]Yang Yang, [1]Haibo Yu, [2]Darrin York, [3]Marcus Elstner and [1]Qiang Cui

[1]Department of Chemistry and Theoretical Chemistry Institute
University of Wisconsin, Madison
1101 University Avenue, Madison, WI 53706

[2]Department of Chemistry
University of Minnesota
207 Pleasant St. SE, Minneapolis, MN 55455

[3]Department of Physical and Theoretical Chemistry
TU Braunschweig, Hans-Sommer-Strass 10
D-38106 Braunschweig, Germany

The following materials are included in the **Supporting Materials**.

The detailed energetics and dipole moment information regarding the performance of the second-order SCC-DFTB and optimized SCC-DFTBPR on model molecules in the QCRNA database are summarized in Table S1 and S2, respectively. The reference B3LYP results are from the QCRNA database website (http://theory.chem.umn.edu/QCRNA/).

The average binding energies between MMP in different chemical states along the dissociative pathway and nearby water molecules at different QM and QM/MM levels are summarized in Table S3. Encouragingly, the B3LYP and full SCC-DFTBPR results are very similar despite the large magnitude of total interaction energies. The SCC-DFTBPR/MM results, on the other hand, are substantially different from the full QM results if the standard Coulombic expression is used for the QM/MM interaction, regardless of the QM van der Waals parameters. Using the Klopman-Ohno formulation for the QM/MM interaction, by contrast, gives substantially closer agreement with the full QM calculations even without any attempt to optimize the relevant parameters (e.g., including the charge dependence of the Hubbard parameters). These data suggest that the Klopman-Ohno formulation can be further optimized to produce much improved QM/MM interactions, especially when the solute is highly charged (Hou and Cui, work in progress).

In Fig.S1-S9, structures optimized at the SCC-DFTBPR level for the model compounds are presented. In Fig. S10, the radial distribution functions of water surrounding the oxygen in the solute from SCC-DFTBPR/TIP3P simulations are summarized; red (blue) corresponds to the solute in the reactant (zwitterionic) state of MMP. The dotted lines give the corresponding integrated numbers of water molecules.

Table S1 Energetics Benchmark Calculations for SCC-DFTB with different parameterizations[a] Based on 19 Phosphate Reactions from the QCRNA Database[b]

Reactions[c]	States[c]	DFT Reference[d]	SCC-DFTBPR SP [e]	SCC-DFTB, SP [e]	SCC-DFTBPR Opt Stable States [e]	SCC-DFTB, Opt Stable States [e]
C6H5OH...P(O)(O)(-O-sugar-O-)	P(O)(O)(-O-sugar-O-)					
	C6H5-OH					
	C6H5OH...P(O)(O)(-O-sugar-O-)_min1	-21.4	1.5	1.5	1.1	0.9
	C6H5OH...P(O)(O)(-O-sugar-O-)_ts12	9.9	-5.6	-12.9		
	C6H5OH...P(O)(O)(-O-sugar-O-)_min2	9.6	-5.3	-13.4	-7.6	-14.6
	C6H5OH...P(O)(O)(-O-sugar-O-)_ts23	18.1	-10.3	-17.7		
	C6H5OH...P(O)(O)(-O-sugar-O-)_min3	9.6	-7.5	-12.5	-8.9	-14.0
	C6H5OH...P(O)(O)(-O-sugar-O-)_ts34	12.9	-8.7	-7.3		
	C6H5OH...P(O)(O)(-O-sugar-O-)_min4	-11.7	-3.0	-1.0	-4.1	-1.6
(CH3)2CHOH...P(O)(O)(-O-sugar-O-)	(CH3)2CHOH					
	P(O)(O)(-O-sugar-O-)					
	(CH3)2CHOH...P(O)(O)(-O-sugar-O-)_min1	-12.8	0.0	1.3	-1.0	-0.1
	(CH3)2CHOH...P(O)(O)(-O-sugar-O-)_ts12	22.7	-3.6	-2.5		
	(CH3)2CHOH...P(O)(O)(-O-sugar-O-)_min2	14.1	-2.9	-7.0	-3.9	-8.5
	(CH3)2CHOH...P(O)(O)(-O-sugar-O-)_ts23	23.1	-6.7	-10.8		
	(CH3)2CHOH...P(O)(O)(-O-sugar-O-)_min3	13.8	-4.6	-7.4	-7.6	-8.8
	(CH3)2CHOH...P(O)(O)(-O-sugar-O-)_ts34	14.5	-5.8	-5.1		
	(CH3)2CHOH...P(O)(O)(-O-sugar-O-)_min4	-13.0	-0.8	3.5	-0.7	3.4
CH3COO...P(O)(OCH3)(OCH3)(OCH3)	CH3COO					
	P(O)(OCH3)(OCH3)(OCH3)					
	CH3COO...P(O)(OCH3)(OCH3)(OCH3)_min1	-13.0	-2.6	-1.4	-4.5	-3.9
	CH3COO...P(O)(OCH3)(OCH3)(OCH3)_ts12a	9.2	-5.8	-14.4		
	CH3COO...P(O)(OCH3)(OCH3)(OCH3)_min2a	9.4	-5.2	-14.4	Become min1	-19.7
	CH3COO...P(O)(OCH3)(OCH3)(OCH3)_ts2a3a	28.7	-10.0	-13.0		
	CH3O					
	CH3COO...P(O)(OCH3)(OCH3)(OCH3)_min3a	46.2	-6.9	-8.8	-7.3	-10.7
CH3COO...P(O)(OH)(-O-CH2CH2-O-)	CH3COO					
	P(O)(OH)(-O-CH2CH2-O-)					
	CH3COO...P(O)(OH)(-O-CH2CH2-O-)_min1	-38.0	7.4	7.2	4.3	5.1
	CH3COO...P(O)(OH)(-O-CH2CH2-O-)_ts12a	-0.5	-6.6	-12.6		

	CH3COO...P(O)(OH)(-O-CH2CH2-O-)_min2a	-7.0	-5.3	-8.9	-8.0	-10.5
	CH3COO...P(O)(OH)(-O-CH2CH2-O-)_ts2a3a	-3.7	-5.5	-3.6		
	CH3COO...P(O)(OH)(-O-CH2CH2-O-)_min3a_1	-35.3	0.5	3.0	-1.0	3.2
CH3COO...P(O)(OH)(OH)(OCH3)	CH3COO					
	P(O)(OH)(OH)(OCH3)					
	CH3COO...P(O)(OH)(OH)(OCH3)_min1	-45.8	7.2	8.6	7.4	9.4
	CH3COO...P(O)(OH)(OH)(OCH3)_ts12a	3.1	-7.2	-11.0		
	CH3COO...P(O)(OH)(OH)(OCH3)_min2a	-3.2	-5.5	-6.5	-7.0	-8.2
	CH3COO...P(O)(OH)(OH)(OCH3)_ts2a3a'	N/A				
	CH3COO...P(O)(OH)(OH)(OCH3)_min3a	-33.4	-0.9	2.7	-2.1	3.6
CH3COO...P(O)(OH)(-O-sugar-O-)	CH3COO					
	P(O)(OH)(-O-sugar-O-)					
	CH3COO...P(O)(OH)(-O-sugar-O-)_ts12a	-14.0	-1.2	-6.0		
	CH3COO...P(O)(OH)(-O-sugar-O-)_min2a	-14.2	-1.0	-6.2	-3.1	-7.7
	CH3COO...P(O)(OH)(-O-sugar-O-)_ts2a3a_1	-4.1	-6.2	-12.0		
	CH3COO...P(O)(OH)(-O-sugar-O-)_min3a	-11.5	-5.3	-8.5	-7.9	-9.6
	CH3COO...P(O)(OH)(-O-sugar-O-)_ts3a4a	-7.1	-5.5	-3.6		
	CH3COO...P(O)(OH)(-O-sugar-O-)_min4a	-33.7	-0.6	2.6	-3.3	1.5
CH3OH...P(O)(O)(-O-CH2CH2-O-)	P(O)(O)(-O-CH2CH2-O-)					
	CH3OH					
	CH3OH...P(O)(O)(-O-CH2CH2-O-)_min1	-14.7	0.2	2.0	-0.6	1.5
	CH3OH...P(O)(O)(-O-CH2CH2-O-)_ts12	22.4	-3.8	-2.5		
	CH3OH...P(O)(O)(-O-CH2CH2-O-)_min2	13.7	-1.6	-5.8	-2.4	-7.2
	CH3OH...P(O)(O)(-O-CH2CH2-O-)_ts23a	22.7	-5.8	-10.0		
	CH3OH...P(O)(O)(-O-CH2CH2-O-)_min3	13.8	-3.5	-5.3	-6.3	-7.9
	CH3OH...P(O)(O)(-O-CH2CH2-O-)_ts34	13.8	-4.0	-3.9		
	CH3OH...P(O)(O)(-O-CH2CH2-O-)_min4	-18.4	1.3	5.7	1.0	5.7
CH3OH...P(O)(O)(-O-sugar-O-)	CH3OH					
	P(O)(O)(-O-sugar-O-)					
	CH3OH...P(O)(O)(-O-sugar-O-)_min1	-14.0	-0.6	1.5	-0.8	1.2
	CH3OH...P(O)(O)(-O-sugar-O-)_ts12	23.4	-5.4	-3.9		
	CH3OH...P(O)(O)(-O-sugar-O-)_min2	13.5	-2.0	-6.0	-2.8	-7.3
	CH3OH...P(O)(O)(-O-sugar-O-)_ts23	22.4	-6.3	-10.0		
	CH3OH...P(O)(O)(-O-sugar-O-)_min3	13.1	-4.2	-6.5	-7.2	-7.9
	CH3OH...P(O)(O)(-O-sugar-O-)_ts34	13.8	-5.4	-4.5		

	CH3OH...P(O)(O)(-O-sugar-O-)_min4	-14.4	0.6	5.5	-0.7	4.3
CH3O...P(O)(OCH3)(-O-CH2CH2-O-)	CH3O					
	P(O)(OCH3)(-O-CH2CH2-O-)					
	CH3O...P(O)(OCH3)(-O-CH2CH2-O-)_ts12	-9.7	0.5	-1.0		
	CH3O...P(O)(OCH3)(-O-CH2CH2-O-)_min2	-29.2	4.4	-4.9	2.4	-4.5
	CH3O...P(O)(OCH3)(-O-CH2CH2-O-)_ts23	-28.5	4.3	-4.8		
	CH3O...P(O)(OCH3)(-O-CH2CH2-O-)_min3	-30.3	4.2	-4.4	2.2	-3.7
	CH3O...P(O)(OCH3)(-O-CH2CH2-O-)_ts34	-26.1	1.3	1.9		
	CH3O...P(O)(OCH3)(-O-CH2CH2-O-)_min4	-22.6	2.3	7.5	-6.7	5.9
CH3O...P(O)(OH)(OH)(OCH3)	CH3O					
	P(O)(OH)(OH)(OCH3)					
	CH3O...P(O)(OH)(OH)(OCH3)_ts12	-24.2	6.0	5.9		
	CH3O...P(O)(OH)(OH)(OCH3)_min2	-30.5	6.0	2.3	6.5	3.2
	CH3O...P(O)(OH)(OH)(OCH3)_ts23	-25.3	5.9	5.8		
	CH3OH					
	P(O)(O)(OH)(OCH3)	-51.5	8.5	10.8	8.6	13.3
HOH...P(O)(O)(-O-2'methyl-sugar-O-)	HOH					
	P(O)(O)(-O-2'methyl-sugar-O-)					
	HOH...P(O)(O)(-O-2'methyl-sugar-O-)_min1	-14.4	-2.3	2.1	-2.7	1.6
	HOH...P(O)(O)(-O-2'methyl-sugar-O-)_ts12a	24.6	-2.3	3.4		
	HOH...P(O)(O)(-O-2'methyl-sugar-O-)_min2a	14.4	-3.4	-4.2	-4.3	-6.4
	HOH...P(O)(O)(-O-2'methyl-sugar-O-)_ts23a	23.7	-7.1	-9.6		
	HOH...P(O)(O)(-O-2'methyl-sugar-O-)_min3a	13.7	-3.9	-5.1	-7.1	-7.4
	HOH...P(O)(O)(-O-2'methyl-sugar-O-)_ts34a	14.1	-3.9	-3.2		
	HOH...P(O)(O)(-O-2'methyl-sugar-O-)_min4a	-13.6	1.7	4.4	-0.2	3.0
HOH...P(O)(O)(-O-CH2CH2-O-)	HOH					
	P(O)(O)(-O-CH2CH2-O-)					
	HOH...P(O)(O)(-O-CH2CH2-O-)_min1	-15.3	-2.1	2.4	-2.7	1.9
	HOH...P(O)(O)(-O-CH2CH2-O-)_ts12	23.4	-1.3	4.6		
	HOH...P(O)(O)(-O-CH2CH2-O-)_min2	13.7	-2.3	-2.8	-2.9	-5.2
	HOH...P(O)(O)(-O-CH2CH2-O-)_ts23	23.3	-6.6	-8.6		
	HOH...P(O)(O)(-O-CH2CH2-O-)_min3	13.1	-3.0	-3.8	-5.1	-5.9
	HOH...P(O)(O)(-O-CH2CH2-O-)_ts34	14.4	-4.6	-2.6		
	HOH...P(O)(O)(-O-CH2CH2-O-)_min4	-19.4	3.3	6.5	2.6	6.1

HO...P(O)(OCH3)(-O-CH2CH2-O-)	HO					
	P(O)(OCH3)(-O-CH2CH2-O-)					
	HO...P(O)(OCH3)(-O-CH2CH2-O-)_ts12	-13.8	1.3	-6.0		
	HO...P(O)(OCH3)(-O-CH2CH2-O-)_min2	-39.3	9.8	-19.1	3.5	-27.2
	HO...P(O)(OCH3)(-O-CH2CH2-O-)_ts23	-39.5	8.1	-18.6		
	HO...P(O)(OCH3)(-O-CH2CH2-O-)_min3	-39.6	9.7	-19.7	3.2	-20.8
	HO...P(O)(OCH3)(-O-CH2CH2-O-)_ts34	-34.5	6.6	-15.1		
	HO...P(O)(OCH3)(-O-CH2CH2-O-)_min4_1	-37.3	8.4	-12.0	3.8	-16.1
HO...P(O)(OCH3)(OCH3)(OCH3)	HO					
	P(O)(OCH3)(OCH3)(OCH3)					
	HO...P(O)(OCH3)(OCH3)(OCH3)_ts12	-16.8	-1.7	-13.5		
	HO...P(O)(OCH3)(OCH3)(OCH3)_min2	-29.9	4.7	-22.1	3.3	-23.5
	HO...P(O)(OCH3)(OCH3)(OCH3)_ts23	-27.2	4.8	-23.2		
	HO...P(O)(OCH3)(OCH3)(OCH3)_min3	-30.5	6.0	-21.5	4.1	-22.9
	HO...P(O)(OCH3)(OCH3)(OCH3)_ts34	-25.7	3.7	-24.0		
	HO...P(O)(OCH3)(OCH3)(OCH3)_min4	-27.4	4.0	-23.9	0.7	-26.0
	HO...P(O)(OCH3)(OCH3)(OCH3)_ts45	-18.8	-0.8	-24.6		
	CH3O					
	P(O)(OH)(OCH3)(OCH3)_min1	-7.9	5.5	-19.9	4.7	-22.0
HO...P(O)(OCH3)(-O-sugar-O-)	HO					
	P(O)(OCH3)(-O-sugar-O-)					
	HO...P(O)(OCH3)(-O-sugar-O-)_ts12	-16.8	1.3	-5.4		
	HO...P(O)(OCH3)(-O-sugar-O-)_min2	-46.7	9.3	-16.9	4.8	-24.7
	HO...P(O)(OCH3)(-O-sugar-O-)_ts23	-44.1	8.4	-18.0		
	HO...P(O)(OCH3)(-O-sugar-O-)_min3	-45.5	6.6	-18.8	3.0	-26.0
	HO...P(O)(OCH3)(-O-sugar-O-)_ts34	-39.9	7.7	-13.4		
	HO...P(O)(OCH3)(-O-sugar-O-)_min4	-41.3	8.7	-11.7	4.2	-15.3
HO...P(O)(OH)(OH)(OCH3)	HO					
	P(O)(OH)(OH)(OCH3)					
	HO...P(O)(OH)(OH)(OCH3)_ts12	-32.1	12.8	-4.1		
	HO...P(O)(OH)(OH)(OCH3)_min2	-39.4	9.9	-11.8	9.7	-13.3
	HO...P(O)(OH)(OH)(OCH3)_ts23	-34.8	10.5	-9.6		
	CH3OH					
	P(O)(O)(OH)(OH)	-60.7	14.4	-5.2	14.8	-4.5
P(O)(O)(OH)(OC6H5)	P(O)(O)(OH)(OC6H5)					

	P(O)(O)(OH)(OC6H5)_ts12	30.1	5.2	1.8		
	P(O)(O)(O)					
	C6H5-OH	26.4	2.7	3.5	4.4	4.4
P(O)(OH)(OH)(OH)(OH)_PR	P(O)(OH)(OH)(OH)(OH)_min1_PR					
	P(O)(OH)(OH)(OH)(OH)_ts1_PR	7.0	-5.9	-6.2		
	P(O)(OH)(OH)(OH)(OH)_min1_PR					
P(O)(OH)(-O-CH2CH2-O-)(OCH3)_Mig	P(O)(OH)(-O-CH2CH2-O-)(OCH3)_min2_PR					
	P(O)(OH)(-O-CH2CH2-O-)(OCH3)_ts2_PR	7.4	-3.9	-2.3		
	P(O)(OCH3)(-O-CH2CH2-O-)(OH)_min2_PR	7.2	-2.7	-1.8	-7.6	-1.4
	HO...P(O)(OCH3)(-O-CH2CH2-O-)_ts34	12.3	-5.8	2.8		
	HO...P(O)(OCH3)(-O-CH2CH2-O-)_min4_1	9.5	-4.0	5.9	-7.0	3.3
Error Analysis						
Overall Performance	MAXE[†]		14.4	-24.6		
	RMSE[†]		5.6	10.3		
	MUE[†]		4.8	8.2		
	MSE[†]		-0.2	-6.0		
Stable States Performance	MAXE		14.4	-23.9	14.8	-27.2
	RMSE		5.3	9.9	5.3	11.8
	MUE		4.3	7.9	4.5	9.1
	MSE		1.0	-4.6	-0.8	-6.1
Transition State Performance	MAXE		12.8	-24.6		
	RMSE		6.0	10.6		
	MUE		5.4	8.7		
	MSE		-1.6	-7.5		

a) See Table 1 in the main text for notation of different SCC-DFTB parameterizations .
b) http://theory.chem.umn.edu/QCRNA/ generated by Darrin York's group of the Department of Chemistry of the University of Minnesota.
c) Reaction and state naming scheme follows QCRNA convention, please refer to http://theory.chem.umn.edu/QCRNA/Nomenclature.html
d) Reaction energetics (relative energy with respect to the reactant state; exothermicity and energy barrier) in kcal/mol; energies are from single point energy calculations at the B3LYP/6-311++G(3df, 2p) level based on the optimized geometry at the

B3LYP/6-31++G(d, p) level from QCRNA; gas phase 0K electronic energy without zero-point vibrational energy correction is used.

e) Energy difference from the DFT reference, i.e., $\Delta E_{SCCDFTB}$-ΔE_{DFT}. "SP" refers single point energy calculations with a SCC-DFTB parameterization at the QCRNA structures; "Stable Opt" refers to calculations in which the structure is also optimized at the SCC-DFTB level, which is only done for the stable state.

f) MAXE: largest error; RMSE: root-mean-square error, defined as $\langle(err)^2\rangle^{1/2}$; MUE: mean unsigned error; MSE: mean signed error.

Table S2 Dipole moment Benchmark Calculations for SCC-DFTB with different parameterizations Based on Representative Phosphate Species from QCRNA Database[a]

Related Reactions	States	DFT Reference	Standard SCC-DFTB, SP	SCC-DFTBPR, SP	Standard SCC-DFTB, Opt Stable States	SCC-DFTBPR, Opt Stable States
CH3OH...P(O)(OCH3)(-O-CH2CH2-O-)	P(O)(OCH3)(-O-CH2CH2-O-)	3.88	-0.81	0.10	-0.78	0.22
	CH3OH...P(O)(OCH3)(-O-CH2CH2-O-)_ts12	3.47	-0.50	0.41	N/A	N/A
	CH3OH...P(O)(OCH3)(-O-CH2CH2-O-)_min2	2.29	-0.55	0.09	-0.70	0.04
	CH3OH...P(O)(OCH3)(-O-CH2CH2-O-)_ts23	3.04	-0.54	-0.02	N/A	N/A
	CH3OH...P(O)(OCH3)(-O-CH2CH2-O-)_min3	3.76	-0.94	-0.35	-0.91	-0.74
	CH3OH...P(O)(OCH3)(-O-CH2CH2-O-)_ts34	3.45	-0.26	0.59	N/A	N/A
	CH3OH...P(O)(OCH3)(-O-CH2CH2-O-)_min4	4.71	-0.72	0.46	-0.61	0.76
P(OCH3)(OCH3)(OCH3)(OCH3)(OCH3)_PR	P(OCH3)(OCH3)(OCH3)(OCH3)(OCH3)_min1_PR	1.17	-0.19	-0.07	-0.10	-0.17
	P(OCH3)(OCH3)(OCH3)(OCH3)(OCH3)_ts1_PR	1.47	-0.13	0.07	N/A	N/A
P(O..H..O)(-O-CH2CH2-O-)	P(O)(OH)(-O-CH2CH2-O-)	4.10	-0.93	-0.09	-0.91	0.21
	P(O..H..O)(-O-CH2CH2-O-)_ts12	5.26	-1.24	-0.27	N/A	N/A
CH3OH...P(O)(OH)(OCH3)(OCH3)	P(O)(OH)(OCH3)(OCH3)_min1	1.24	-0.28	0.29	-0.49	0.19
	CH3OH...P(O)(OH)(OCH3)(OCH3)_ts12	1.64	0.05	0.51	N/A	N/A
	CH3OH...P(O)(OH)(OCH3)(OCH3)_min2	1.69	-0.34	0.10	-0.51	-0.26
	CH3OH...P(O)(OH)(OCH3)(OCH3)_ts23	2.99	0.20	0.84	N/A	N/A
Individual molecule	P(OCH3)(OCH3)(-O-CH2CH2-O-)(OCH3)	1.51	-0.34	-0.01	-0.17	0.12
	P(O)(OCH3)(-O-sugar-O-)	2.91	-0.81	0.02	-1.17	-0.29
	P(O)(OH)(OH)(OCH3)	0.98	-0.22	0.19	-0.26	0.33
	P(O)(OH)(OH)(OH):HOH	1.68	-0.12	0.20	0.53	-0.05
	P(O)(OH)(OH)(OH)	0.51	-0.03	0.26	0.19	0.60
	P(O)(O)(OH)	3.21	-0.50	-0.38	-0.25	-0.06
	P(O)(OH)(-O-CH2CH2-O-):CH3OH	2.61	-0.62	0.07	0.13	1.14
	P(OCH3)(OCH3)(OCH3)(OH)(OH)	1.05	-0.16	-0.07	-0.10	-0.10
Error Analysis						
MAXE			-1.24	0.84	-1.17	1.14
RMSE			0.56	0.32	0.59	0.45
MUE			0.46	0.24	0.49	0.33
MSE			-0.43	0.13	-0.38	0.12

a. The format of the table is the same as Table S1, except that the reference values are dipole moments calculated at the B3LYP/6-311++G(3df,2p)//B3LYP/6-31++G(d,p) level and given in Debye

Table S3. Binding energy between MMP in different chemical states in the dissociative pathway and nearby water molecules

Chemical State[a]	Binding Energy[b] (kcal/mol)		
	B3LYP/6-31++G**	SCC-DFTBPR[c]	SCC-DFTBPR/MM[d]
Reactant	-89.7	-94.3	-129.1 (-128.1) [-97.8]
Zwitterionic	-109.1	-116.7	-165.1 (-163.4) [-126.4]
Intermediate	-63.4	-67.4	-90.6 (-89.8) [-75.2]

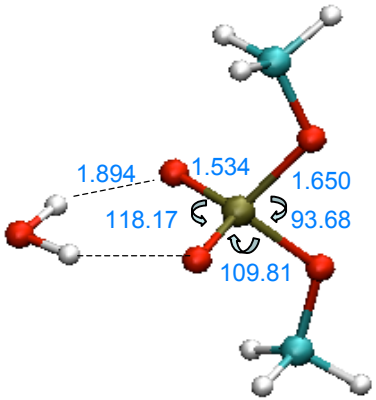
a) Ten snapshots are collected from the last 20 ps trajectory from 2D PMF simulations for the relevant region. For each chemical state, 10 snapshots are studied and the average values are presented in the table.

b) Water molecules within 3 Å from atoms O7, O8 or O9 (see Fig. S10) are selected as the first solvation shell. The binding energies studied are vertical values, i.e., using the structure collected from the trajectory without any further geometry optimization.

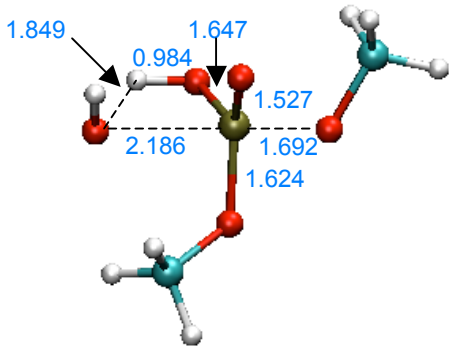
c) All atoms are treated with SCC-DFTBPR.

d) The MMP is described by SCC-DFTBPR, and water molecules are treated as the TIP3P model. Numbers without parentheses are results using the standard (CHARMM lipid) van der Waals parameters for the QM atoms and Coulombic QM/MM interaction; numbers with parentheses are obtained with the optimized QM van der Waals parameters (following the standard procedure as described in Ref. 82 of the main text, for example, based on the molecular complex between MMP in the reactant state and a water molecule) and Coulombic QM/MM interaction; numbers with brackets are obtained with the standard (CHARMM lipid) QM van der Waals parameters and Klopman-Ohno QM/MM interaction (see, for example, Ref. 60).

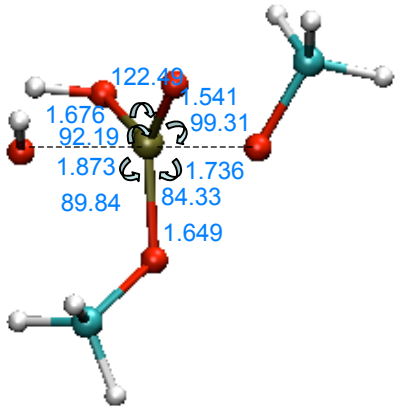
DMP (Di-methyl Phosphate) Associative Mechanism



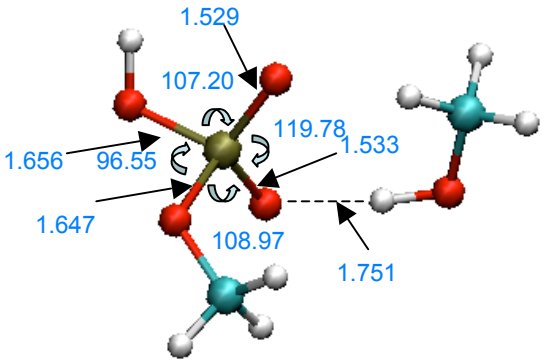
com1



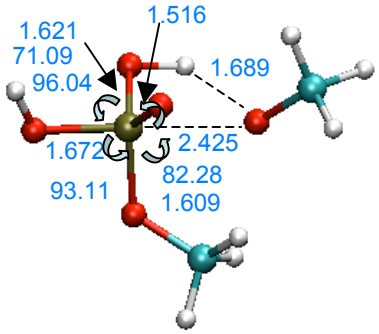
ts1



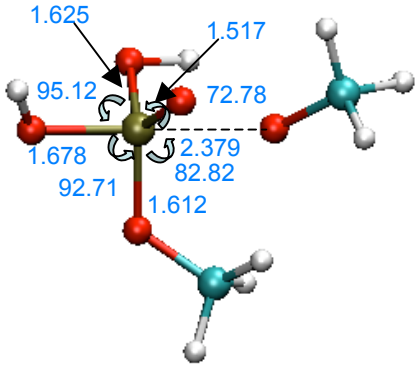
int1



com2



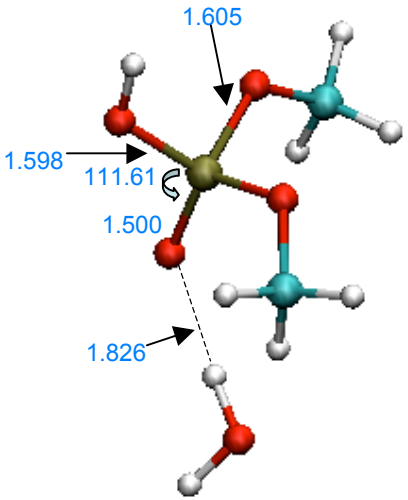
ts2



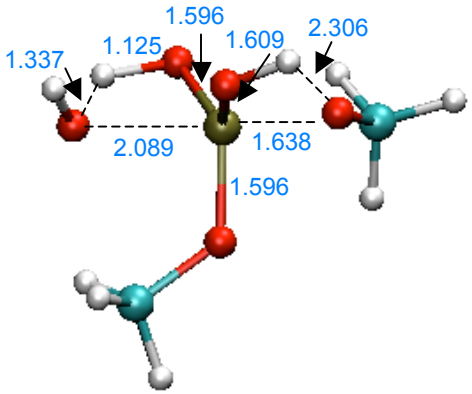
Int1_2

Fig. S1

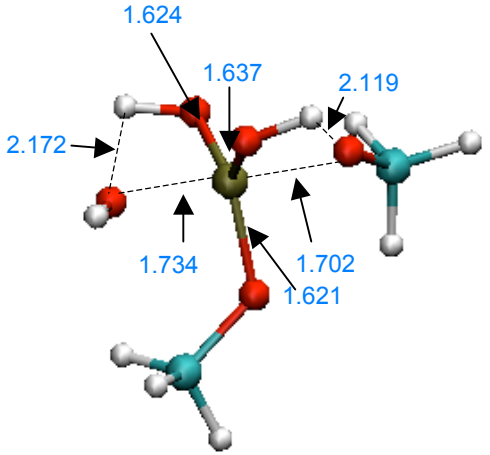
Protonated DMP (DMP_P) Associative Mechanism



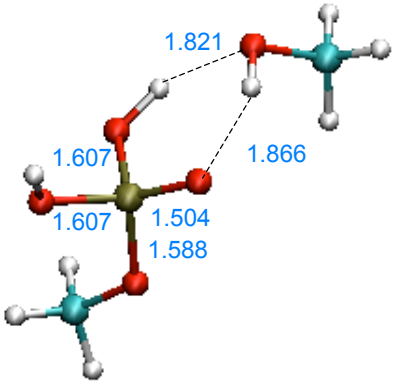
n_com1



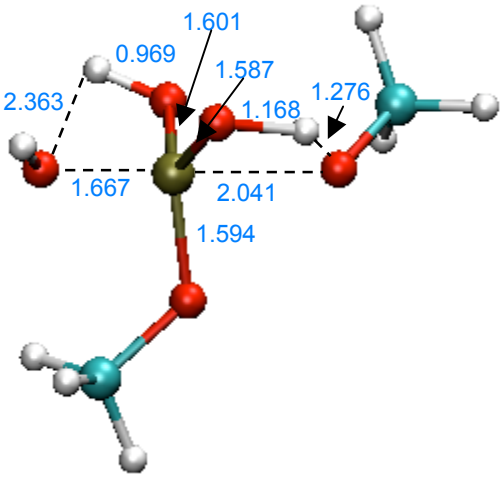
n_ts3



n_int1



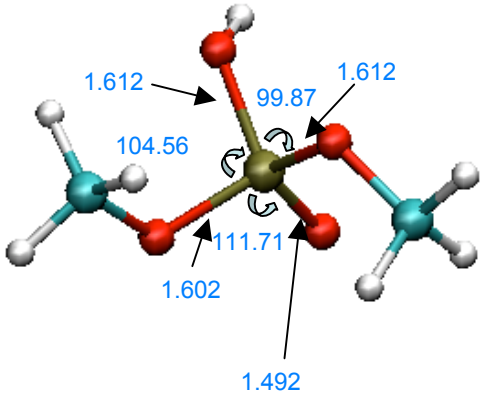
n_com2



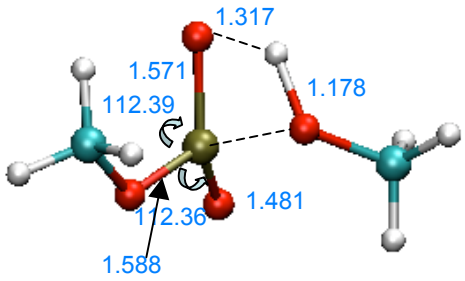
n_ts4

Fig. S2

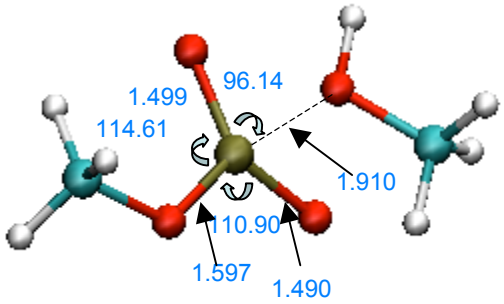
Protonated DMP (DMP_P) Dissociative Mechanism



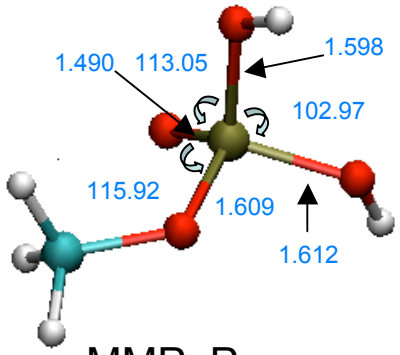
DMP_P



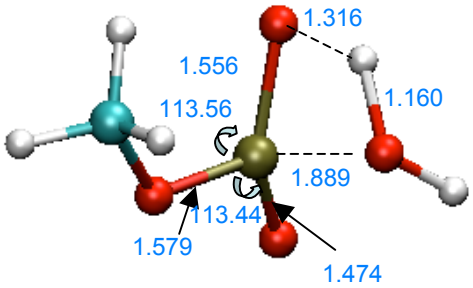
diss_TS



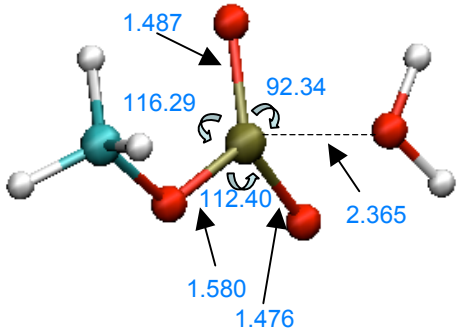
diss_prod



MMP_P



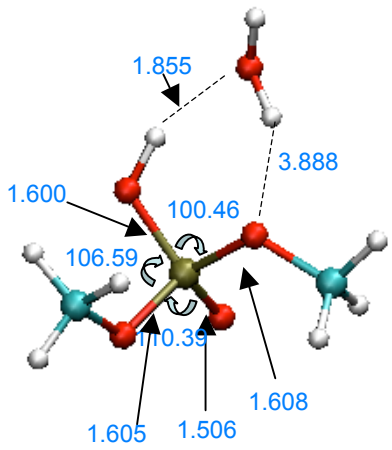
diss_TS2



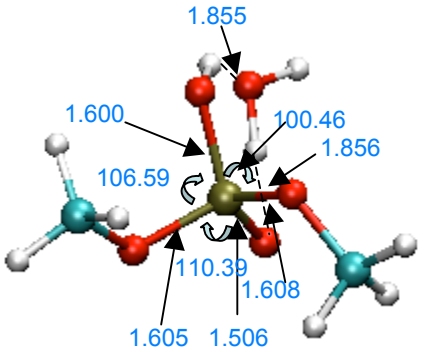
diss_prod2

Fig. S3

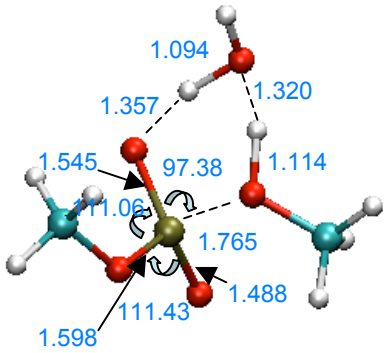
DMP_P + extra water Dissociative Mechanism



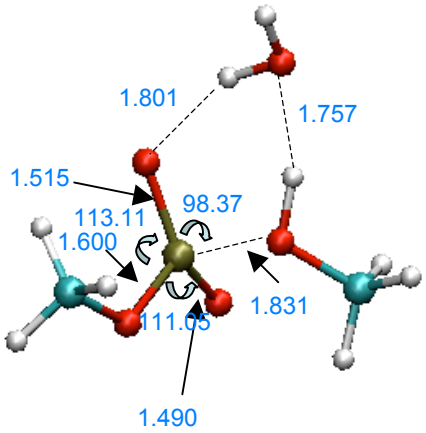
diss_w_reac



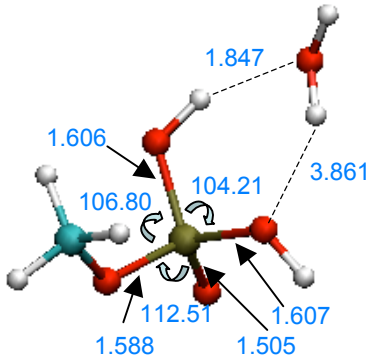
diss_w_reac



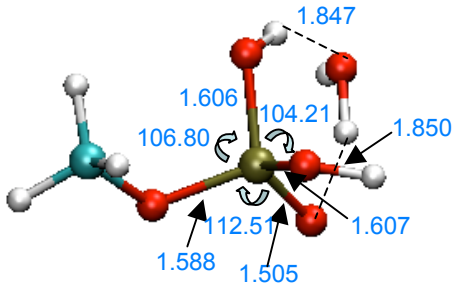
diss_w_ts



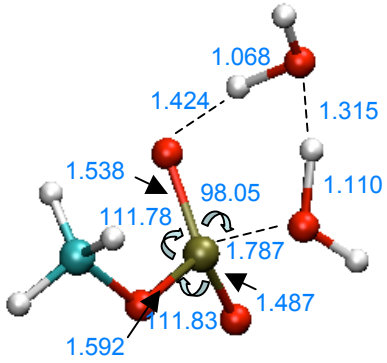
diss_w_prod



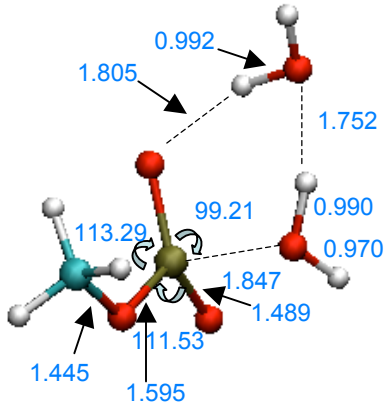
diss_w_reac2



diss_w_reac2



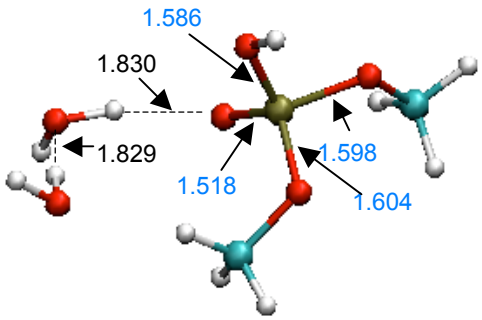
diss_w_ts2



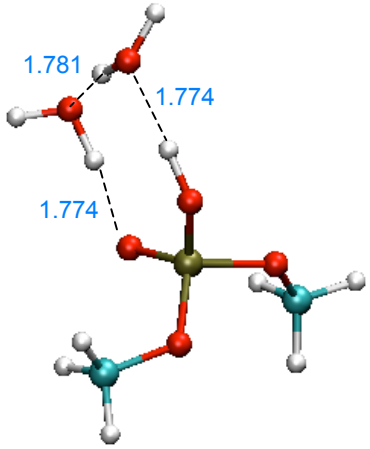
diss_w_prod2

Fig. S4

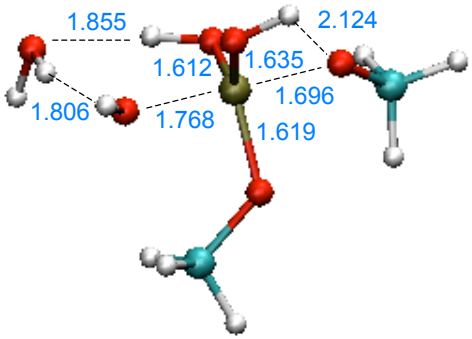
DMP_P + extra H_2O Associative Mechanism



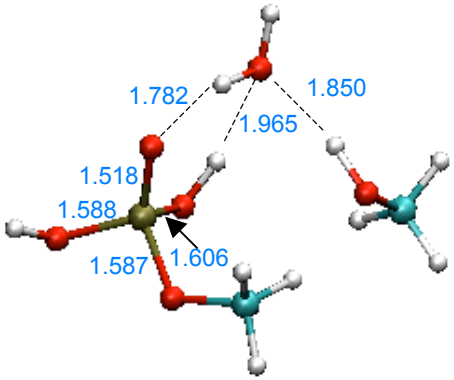
n_w_com1



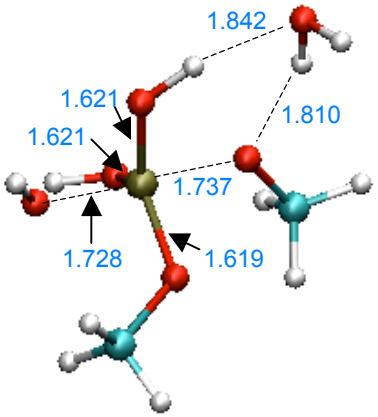
n_w_com1



n_w_int1



n_w_com2



n_w_int2

Fig. S5

MMP Associative Mechanism

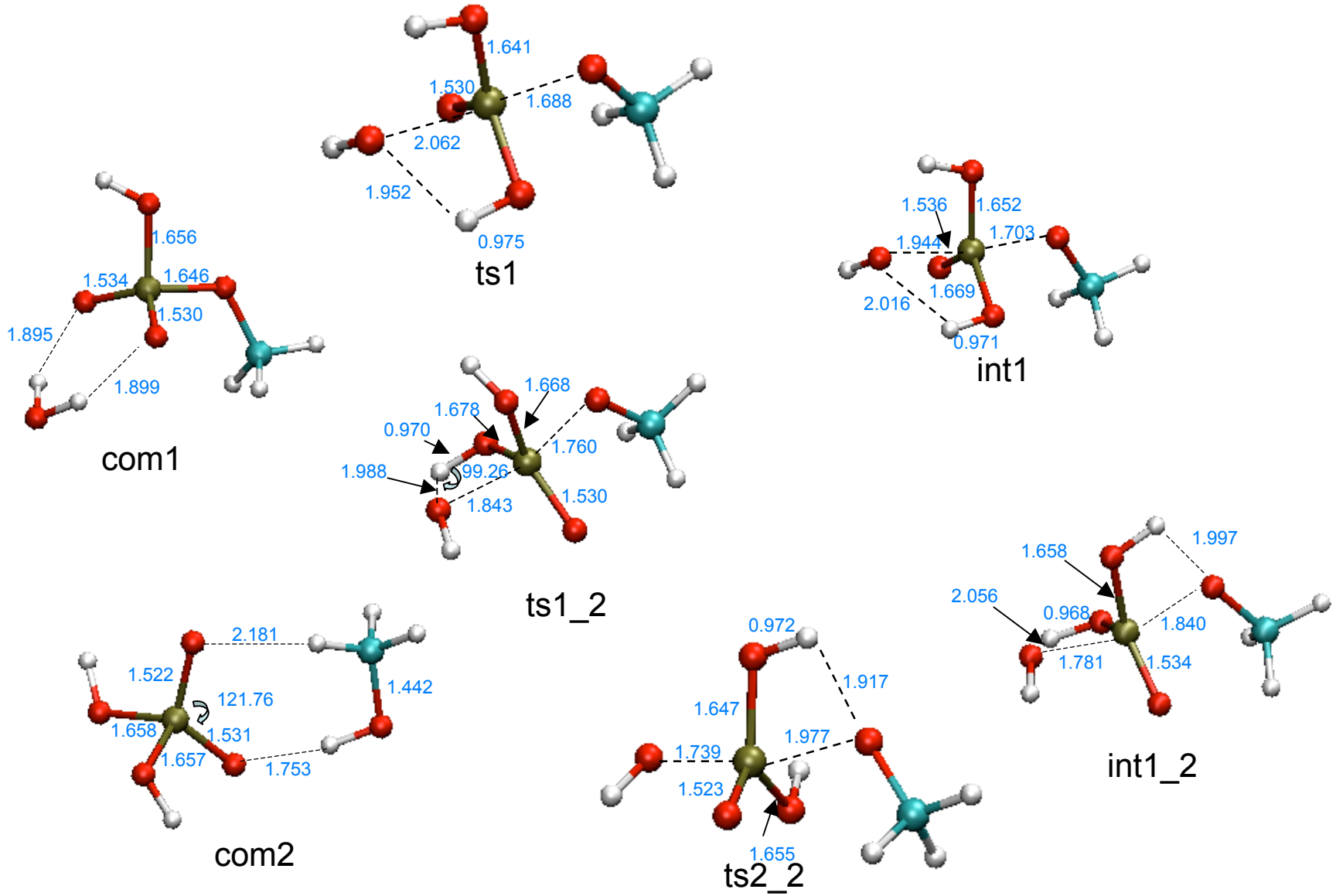
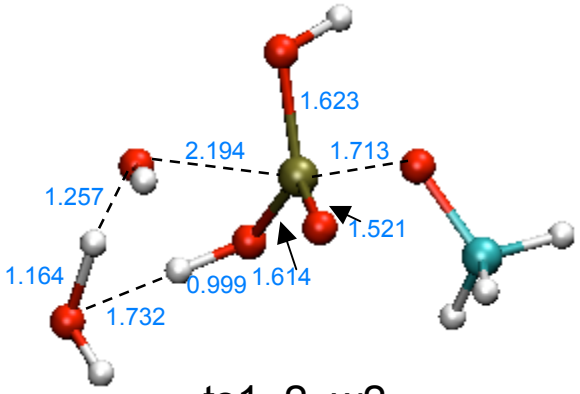
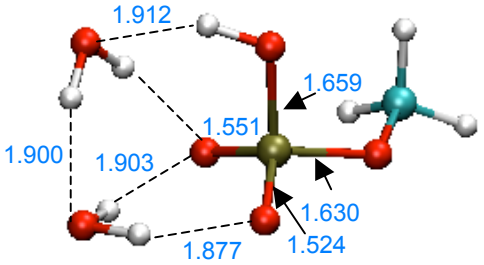


Fig. S6

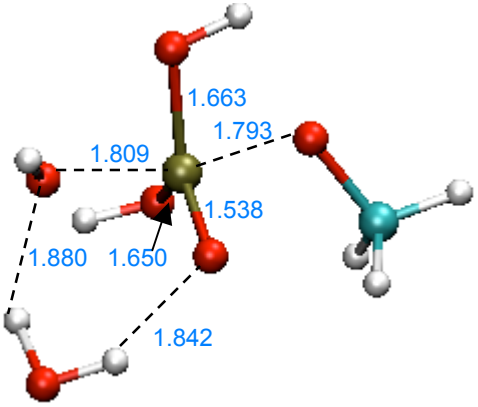
MMP + extra H_2O Associative Mechanism



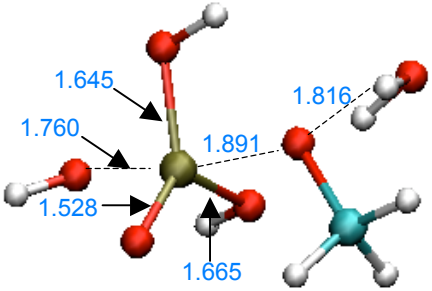
ts1_2_w2



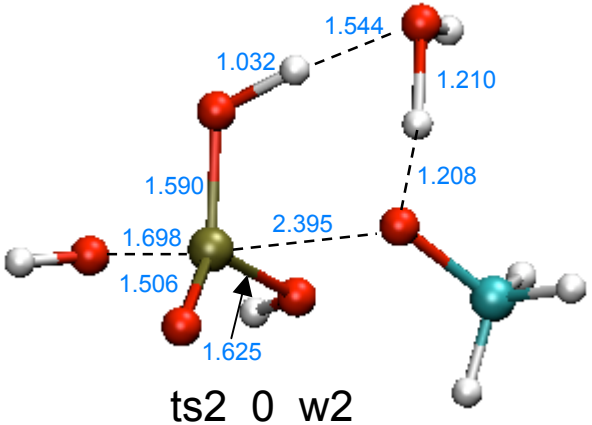
com1_w2



int1_2a_w2



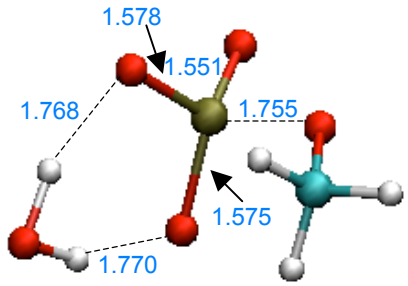
int1_2_w2



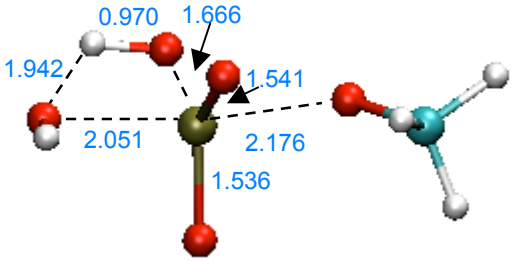
ts2_0_w2

Fig. S7

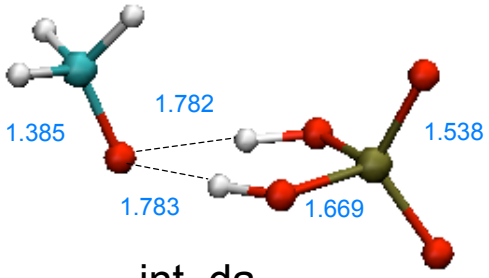
Dianionic MMP Associative & Dissociative Mechanisms



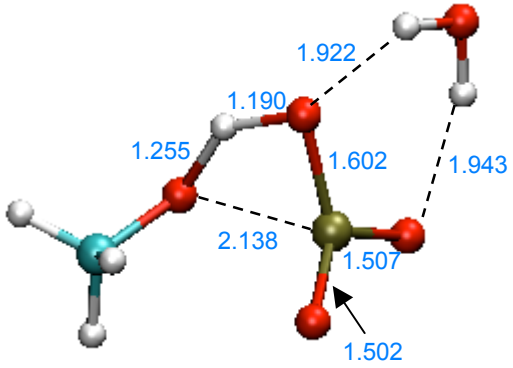
com1_da



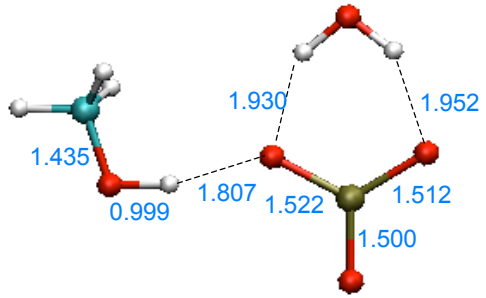
ts1_da



int_da



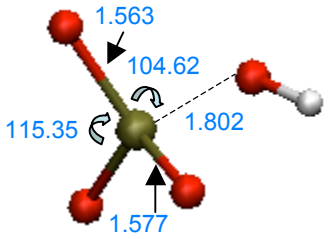
diss_tsa



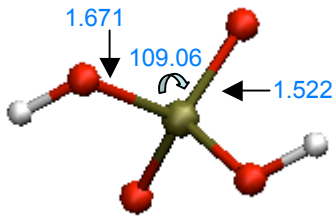
diss_int

Fig. S8

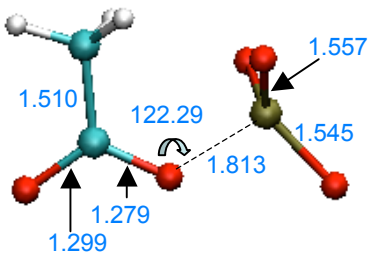
Phosphate



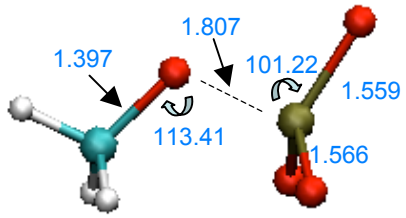
HPO_4^{2-}



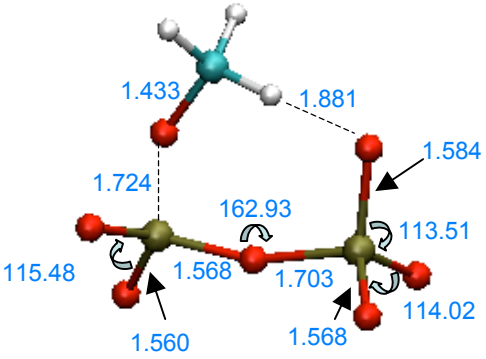
$H_2PO_4^-$



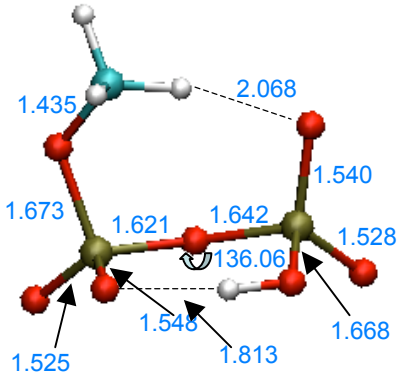
Asp_P



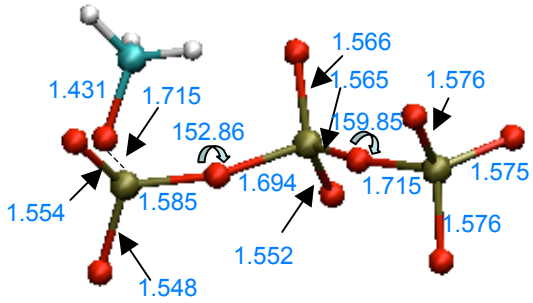
Ser_P



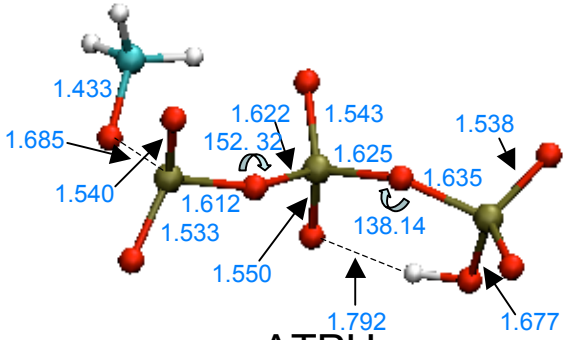
ADP



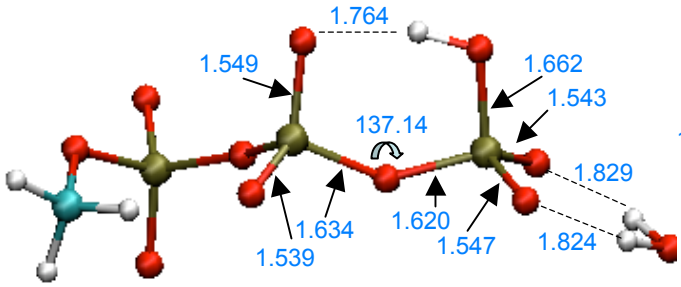
ADPH



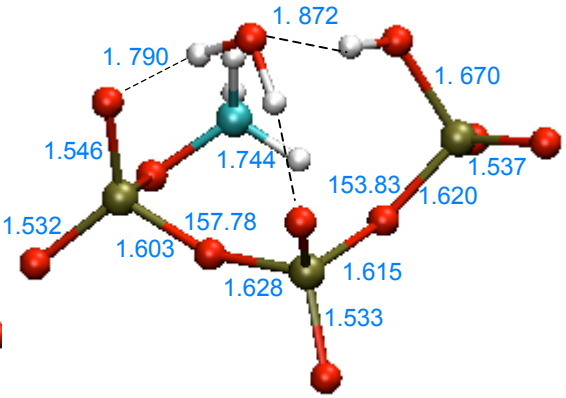
ATP



ATPH



ATPH_w_com1



ATPH_w_com1b

Fig. S9

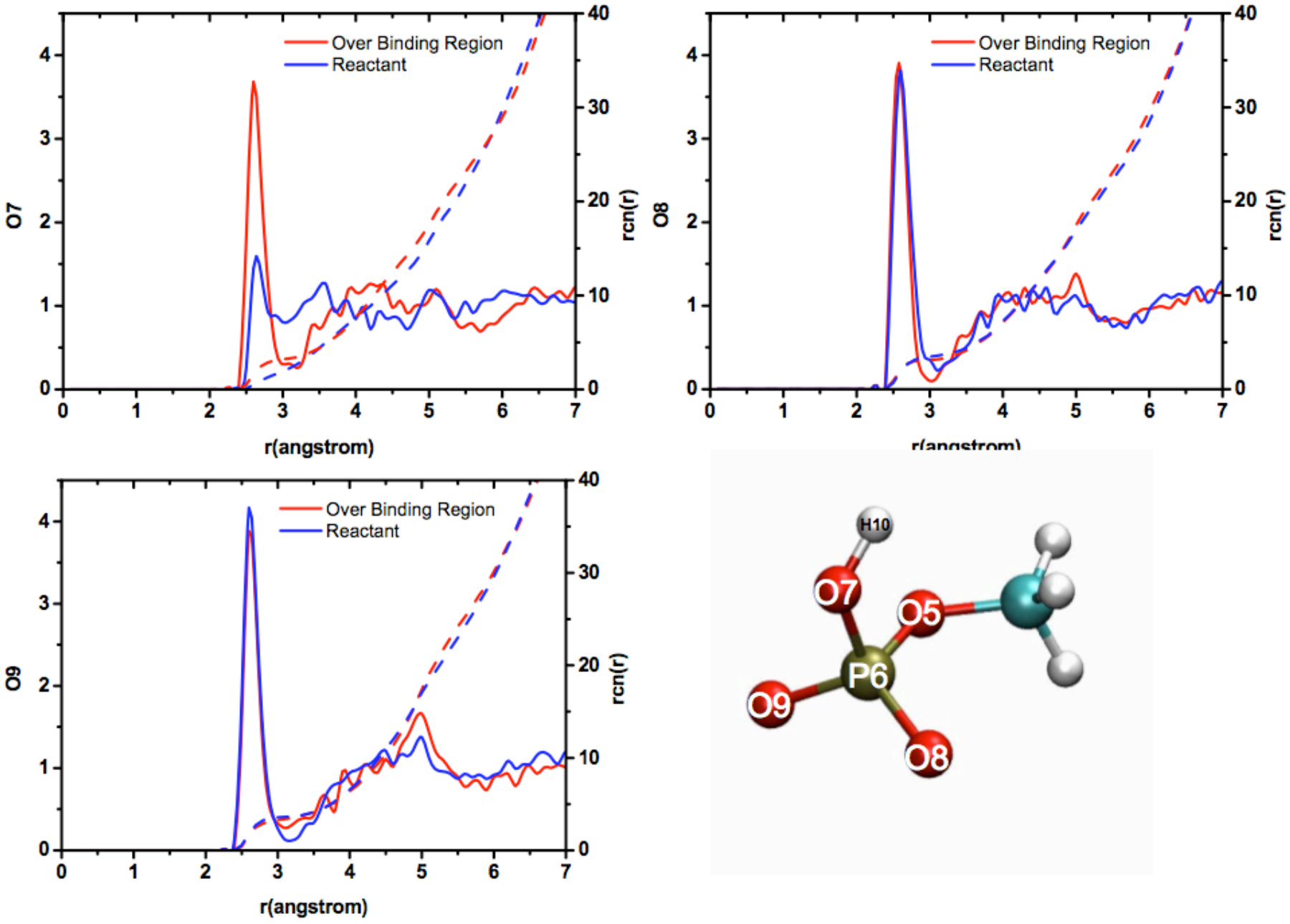

Over Binding Region
Reactant
O7
rcn(r)
r(angstrom)
Over Binding Region
Reactant
O8
rcn(r)
Over Binding Region
Reactant
O9
rcn(r)
r(angstrom)
H10
O7
O5
P6
O9
O8

Fig. S10