Supporting Information for

How is Acetylcholinesterase Phosphonylated by Soman? An *ab initio* QM/MM Molecular Dynamics Study

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Figure S1-S7 and Table S1-S2.

Figure S1. Illustration of the chemical structures of some organophosphate compounds.

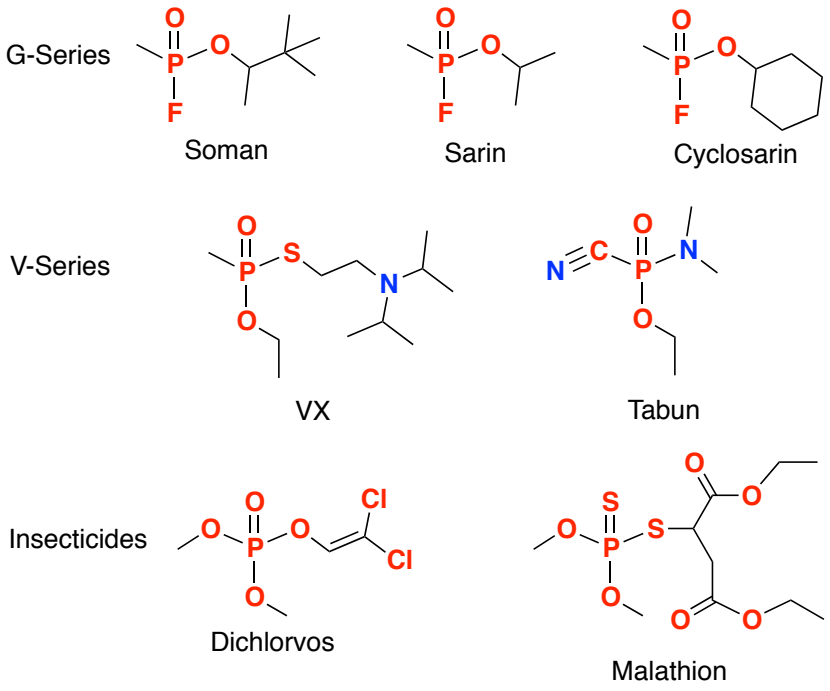

Figure S2. Illustration of the QM/MM partition for non-covalent AChE – soman reactant complex. The QM atoms (blue) are assigned 6-31G* basis set, the boundary atoms (red) are treated with pseudo-bond parameters. The rest of the system is treated classically.

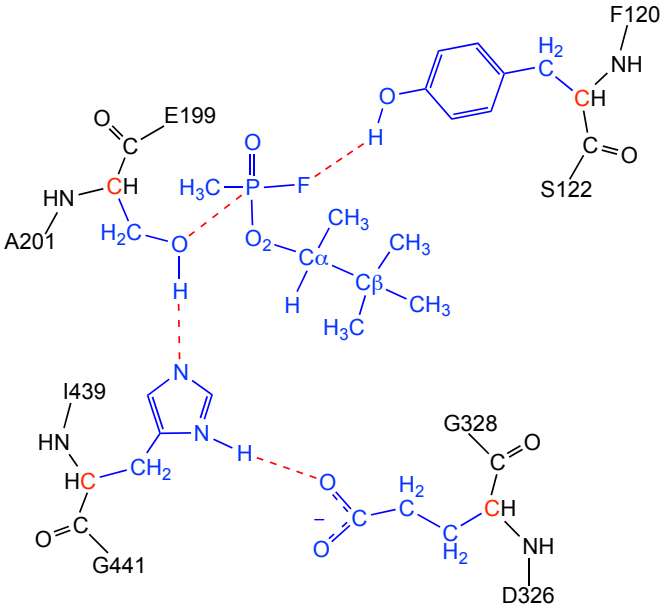

Figure S3. Two-dimensional minimal energy surface of the AChE – soman phosphonylation reaction defined along its addition and elimination steps. The addition step is defined as the linear combination 2 bond lengths: $RC_{addition}$ = – d($Ser201_{OG}$…$soman_{P}$) – d($Ser201_{HG}$…$His440_{NE2}$). And the elimination step is defined as the dissociation of the fluorine atom defined as: $RC_{elimination}$ = d($soman_{P}$…$soman_{F}$). Snapshots along the black dashed line were taken as starting structures to characterize the phosphonylation reaction.

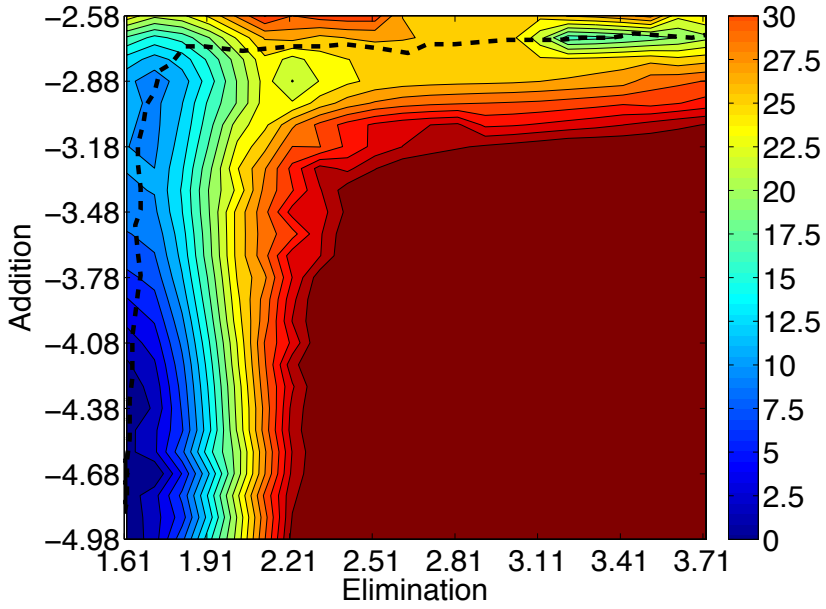

Figure S4. Calculated key distances during the characterized addition-elimination phosphonylation reaction mechanism determined along the last 20 ps of 25 ps QM/MM MD simulations.

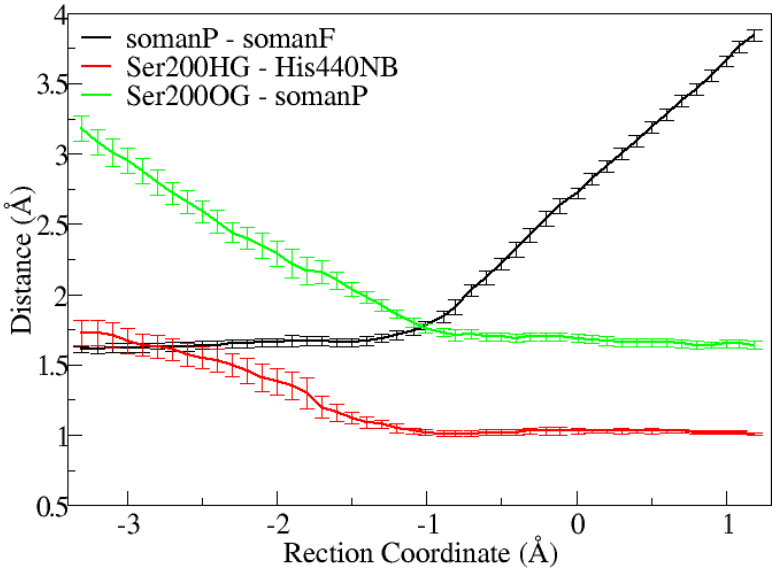

Figure S5. (a) Illustration of the non-covalent reactant complex. Frame corresponds to the snapshot collected at 11.25 ps in QM/MM MD simulations. (b) Calculated distances in QM/MM MD simulations at the reactant state.

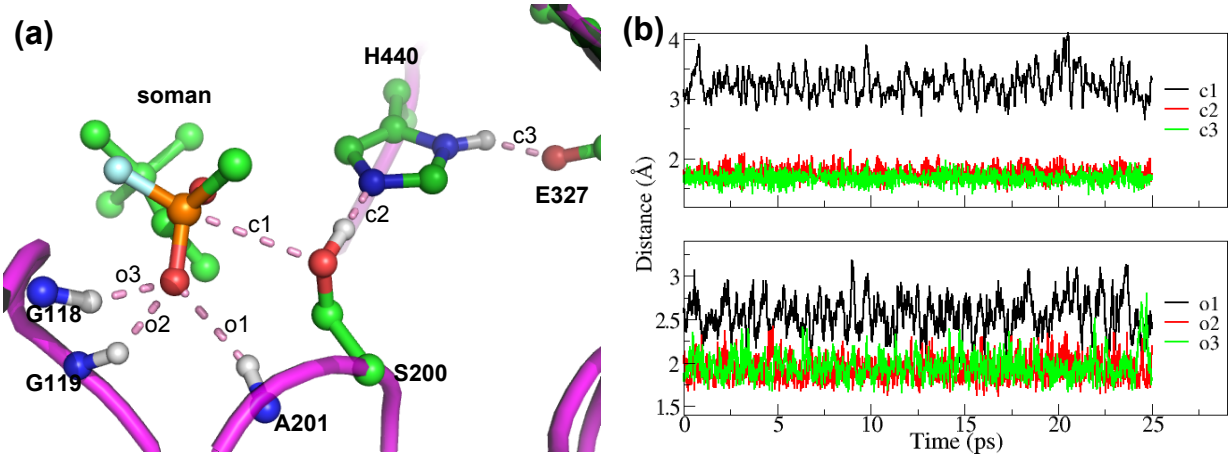

Figure S6. (a) Illustration of the trigonal bipyrimidal pentacovalent phosphorus intermediate. Frame corresponds to the snapshot collected at 10.24 ps in QM/MM MD simulations. (b) Calculated distances in QM/MM MD simulations at the intermediate state.

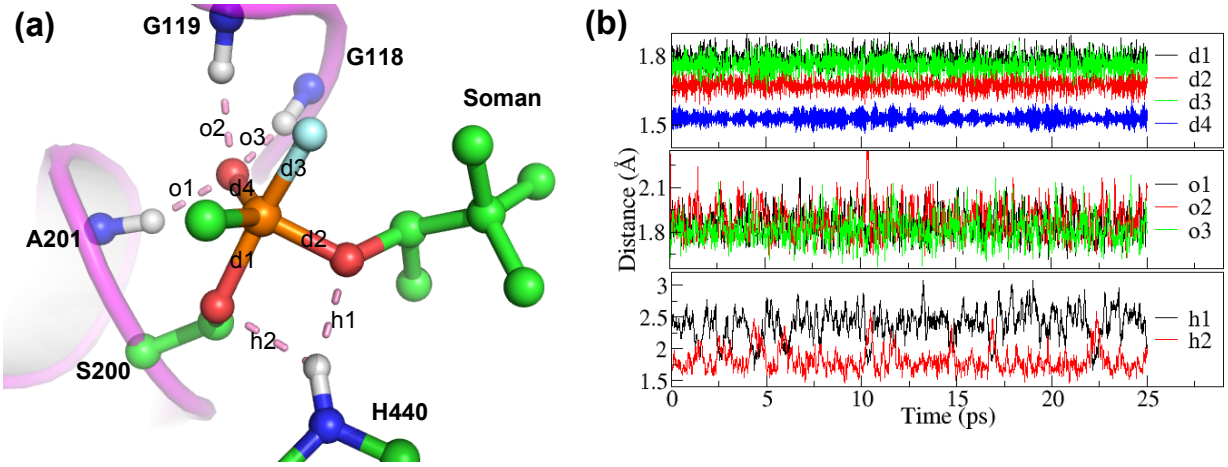

Figure S7. (a) Illustration of the covalent AChE – soman conjugate product, (b) enlarged view of the hydrogen bond network around the eliminated fluorine ion, (c) enlarged view of the oxyanion hole hydrogen bond network, and (d) calculated distances from QM/MM MD simulations at the product state. Frame corresponds to the snapshot collected at 5.91 ps in QM/MM MD simulations at the product state.

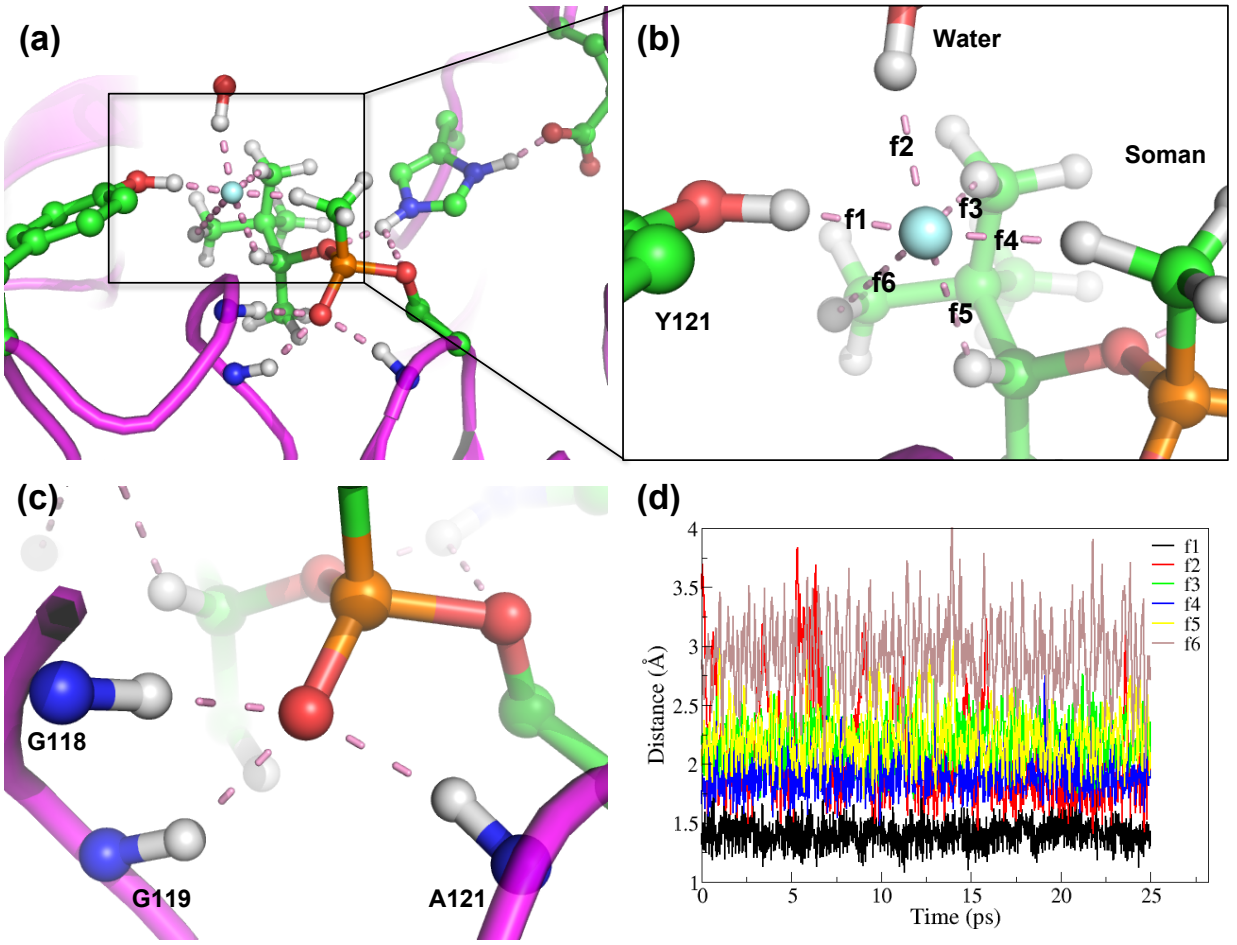

Table S1. Partial charges, atom types and connectivity assignments for nerve agent soman.

	Atom Name	Atom Type	Connectivity Type	Partial Charge
1	C1	CT	M	-0.5942
2	H13	HC	E	0.1755
3	H12	HC	E	0.1755
4	H11	HC	E	0.1755
5	F	F	E	-0.2852
6	O1	O2	E	-0.7104
7	P	P	M	1.2402
8	O2	OS	M	-0.524
9	C3	CT	3	-0.5591
10	H33	HC	E	0.1537
11	H32	HC	E	0.1537
12	H31	HC	E	0.1537
13	C2(α)	CT	M	0.2998
14	H2	H1	E	0.0457
15	C5	CT	3	-0.3991
16	H53	HC	E	0.0876
17	H52	HC	E	0.0876
18	H51	HC	E	0.0876
19	C6	CT	3	-0.3991
20	H63	HC	E	0.0876
21	H62	HC	E	0.0876
22	H61	HC	E	0.0876
23	C4(β)	CT	M	0.5082
24	C7	CT	M	-0.3991
25	H73	HC	E	0.0876
26	H72	HC	E	0.0876
27	H71	HC	E	0.0876

Tables S2. Lists of some of the key geometric parameters for the phosphonylation/inhibition reaction of AChE – soman calculated along the last 20 ps of 25 ps from B3LYP/6-31G* QM/MM MD simulations.

Distance (Å)	***Reactant***	***TS1***	***Int.***	***TS2***	***Product***
F(soman) – P(soman)	1.61 ± 0.03	1.66 ± 0.03	1.71 ± 0.03	2.44 ± 0.05	3.81 ± 0.05
OG(Ser200) – P(soman)	3.21 ± 0.10	2.10 ± 0.06	1.85 ± 0.03	1.70 ± 0.03	1.63 ± 0.03
NE2(His440) – HG(Ser200)	1.75 ± 0.10	1.16 ± 0.06	1.05 ± 0.03	1.03 ± 0.02	1.02 ± 0.02
OG(Ser201) – HG(Ser200)	1.00 ± 0.02	1.40 ± 0.11	1.68± 0.13	2.20 ± 0.31	2.44 ± 0.24
O2(soman) – HG(Ser200)	3.53 ± 0.18	2.63 ± 0.15	2.44 ± 0.21	2.18 ± 0.31	2.18 ± 0.28
ND1(His440) – OE2(Glu327)	2.68 ± 0.08	2.62 ± 0.08	2.59 ± 0.07	2.58 ± 0.08	2.59± 0.07
HD1(His440) – OE1(Glu327)	1.67 ± 0.09	1.59 ± 0.09	1.56 ± 0.09	1.55 ± 0.10	1.52 ± 0.12
HD1(His440) – ND1(His440)	1.04 ± 0.03	1.06 ± 0.04	1.07 ± 0.03	1.08 ± 0.04	1.10 ± 0.08
F(soman) – HH(Tyr121)	4.91 ± 0.35	5.21 ± 0.62	5.59 ± 0.47	1.54 ± 0.12	1.39 ± 0.09
F(soman) – OH(Tyr121)	4.24 ± 0.33	4.82 ± 0.39	5.05 ± 0.32	2.55 ± 0.10	2.44 ± 0.07
O2(soman) – P(soman)	1.59 ± 0.03	1.64 ± 0.03	1.67 ± 0.03	1.63 ± 0.03	1.61 ± 0.02
O1(soman) – P(soman)	1.50 ± 0.02	1.52 ± 0.02	1.53 ± 0.02	1.51 ± 0.02	1.50 ± 0.03
O1(soman) – HN(A201)	2.52 ± 0.19	1.93 ± 0.10	1.87 ± 0.09	1.95 ± 0.11	1.97 ± 0.11
O1(soman) – HN(G119)	1.92 ± 0.13	1.90 ± 0.12	1.88 ± 0.11	1.83 ± 0.09	1.85 ± 0.09
O1(soman) – HN(G118)	1.95 ± 0.14	1.87 ± 0.11	1.85 ± 0.10	1.87 ± 0.11	1.89 ± 0.10
NE2(His440) – HG(Ser200) – OG(Ser201) *angle* (°)	164.30 ± 6.82	167.96 ± 5.98	160.46 ± 10.37	138.58 ± 16.66	133.91 ± 11.53
NE2(His440) – HG(Ser200) – O2(soman) *angle* (°)	93.13 ± 5.70	116.51 ± 5.75	126.51 ± 8.84	150.04 ± 16.59	156.40 ± 11.41
OG(Ser200) – P(soman) – F(soman) *angle* (°)	166.07 ± 4.88	168.66 ± 3.24	167.65 ± 3.24	164.42 ± 3.76	151.81 ± 4.27