Supporting Information for

Aging Mechanism of Soman Inhibited Acetylcholinesterase

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Figure S1-S6 and Table S1.

Figure S1. Illustration of the QM/MM sub-system partition for the (a) initial dealkylation and the (b) hydration of tertiary carbenium ion reaction steps of aging: Black, MM subsystem; Red, boundary carbon atoms in the QM subsystem described by improved pseudobond parameters; Blue (magenta), all other atoms in the QM sub-system.

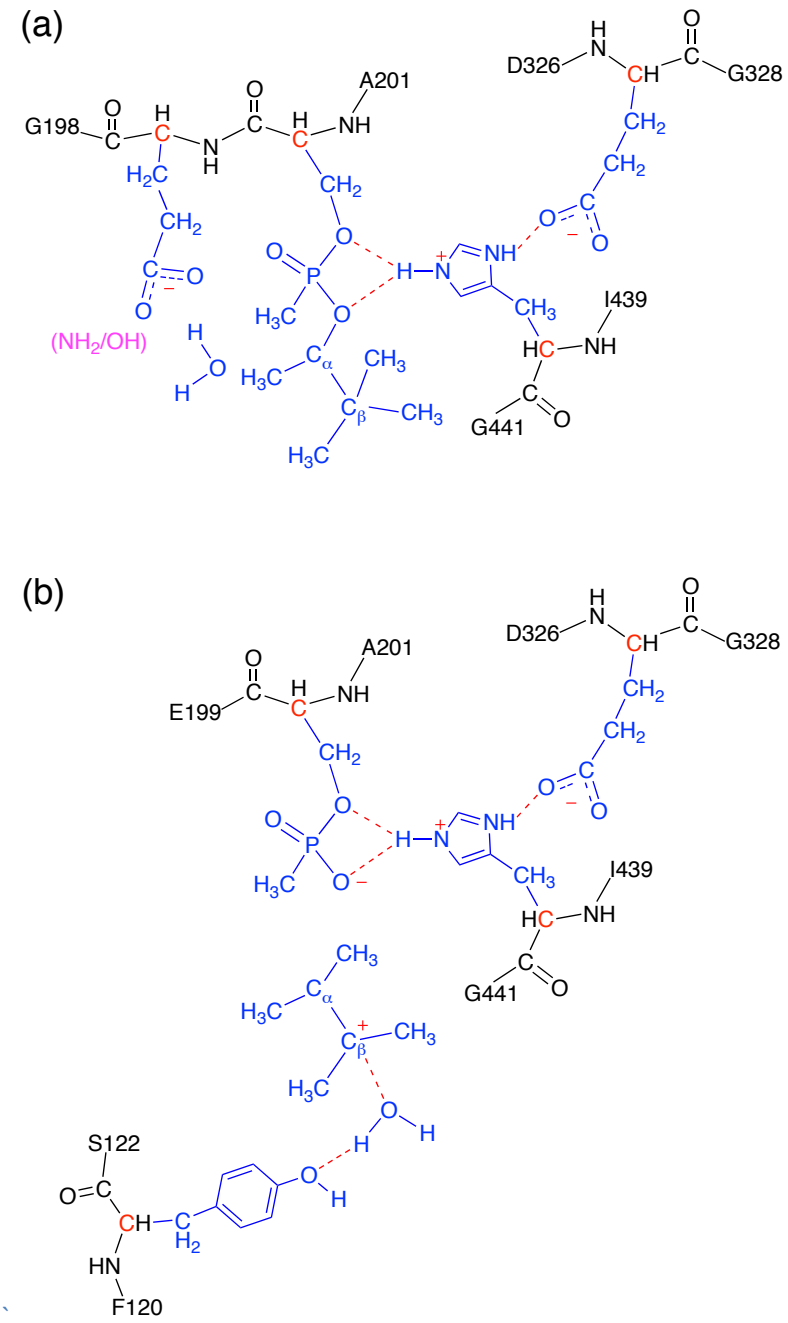

Figure S2. *Unprotonated Glu199 model (the attempt to examine the proposed protonation-deprotonation mechanism):* (a) The chosen reaction coordinate; (b) potential energy profile; and (c) illustration of structures along the reaction coordinate for proton transfer from the doubly protonated His440^{+} NE2 nitrogen to soman O2 oxygen. Protonated soman is energetically unfavorable and collapses back to the reactant conformation during unrestrained geometry optimization.

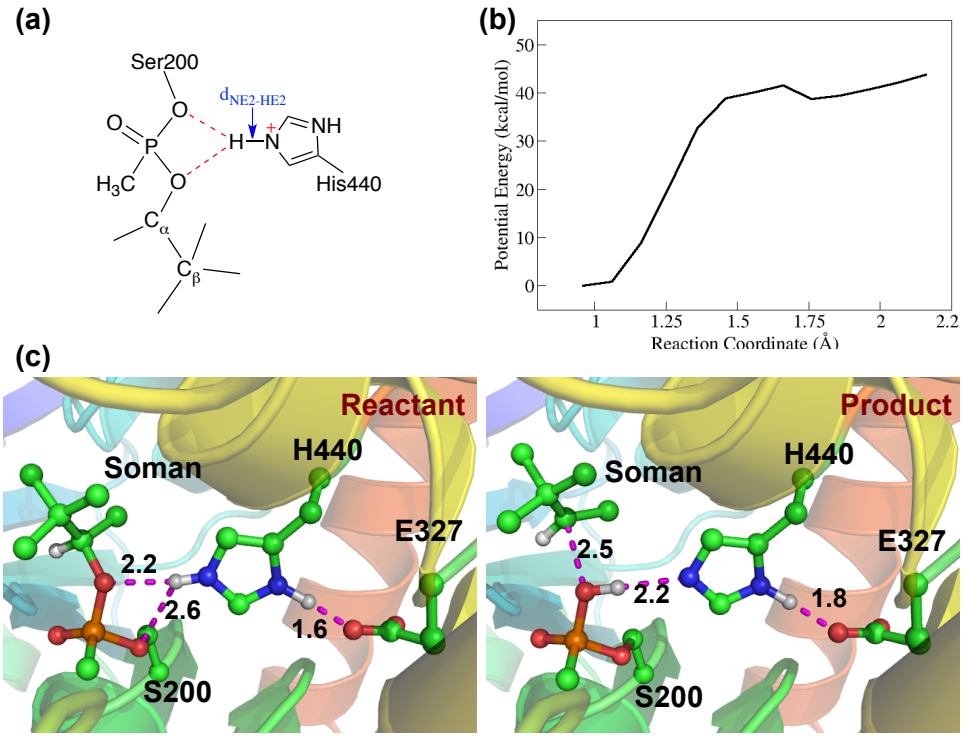

Figure S3. *Unprotonated Glu199 model (another attempt to examine the proposed protonation-deprotonation mechanism):* (a) The chosen reaction coordinate; (b) calculated free energy profile; and (c) illustration of key structures along proton transfer and concerted cleavage of the alkyl chain reaction. The total length of ab initio QM/MM MD simulations for this reaction path is 460 ps (23 windows * 20 ps each).

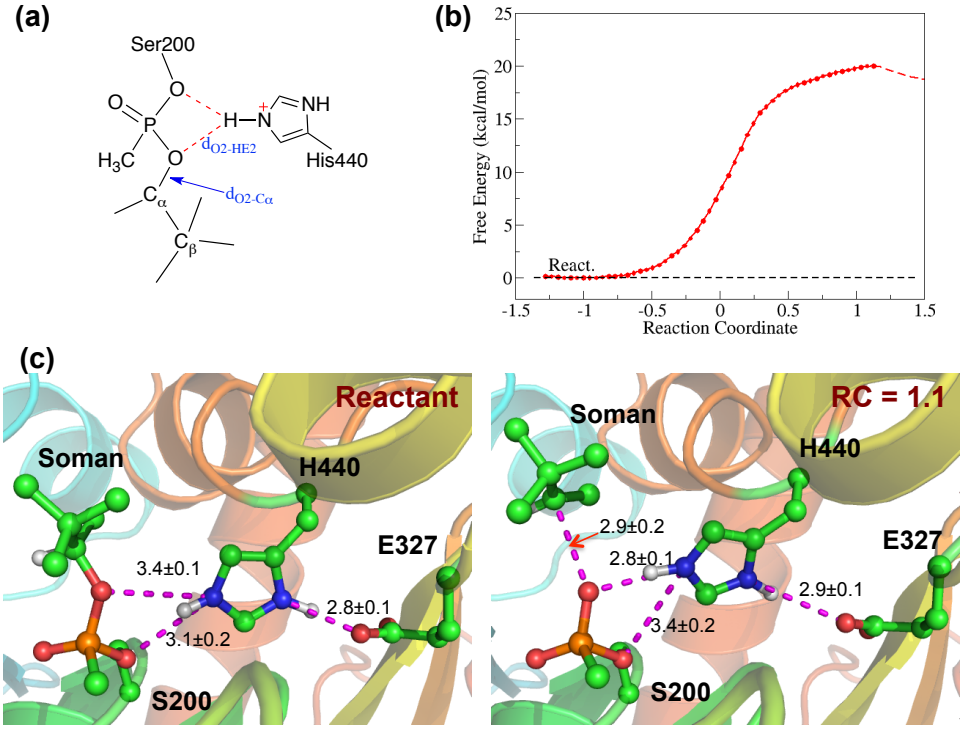

Figure S4. *Unprotonated Glu199 model (the attempt to examine the O-dealkylation mechanism):* (a) The chosen reaction coordinate; (b) calculated free energy profile; and (c) illustration of key structures along the O-dealkylation mechanism of aging. The total length of ab initio QM/MM MD simulations for this reaction path is 540 ps (27 windows * 20 ps each).

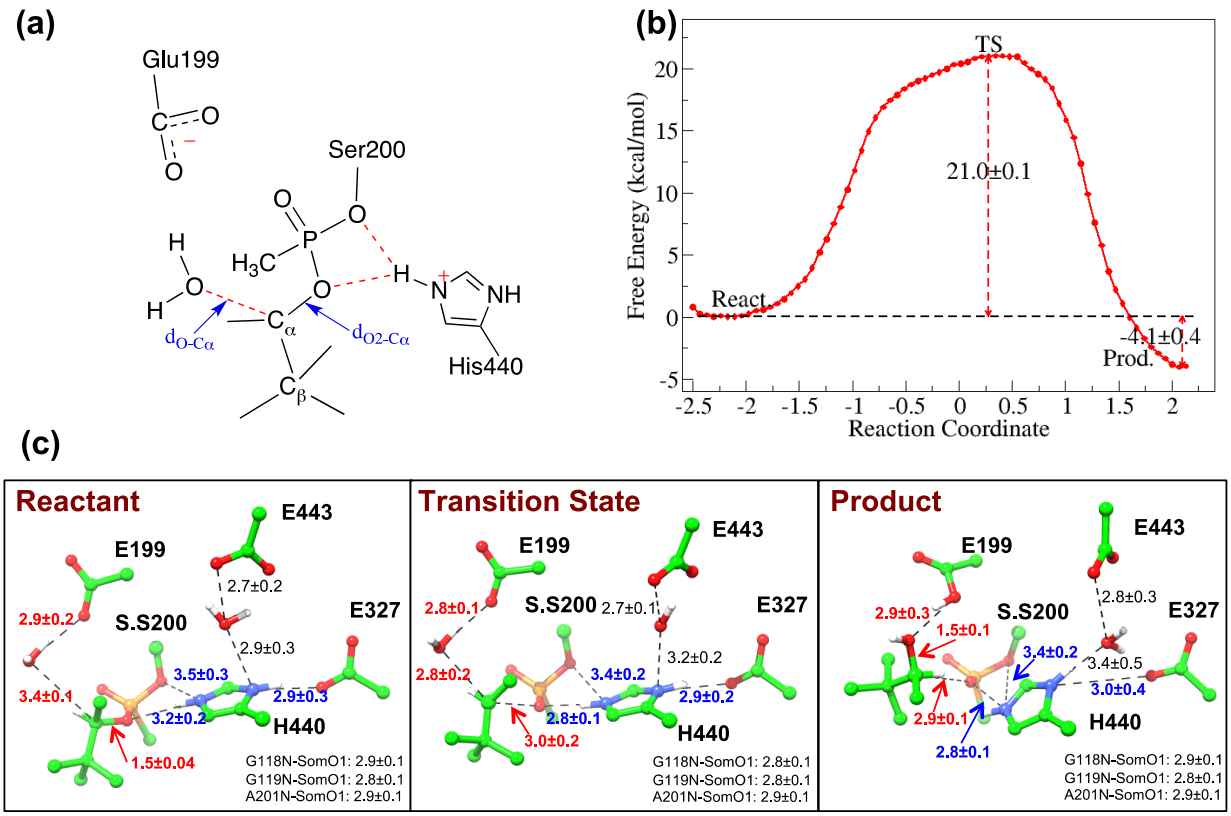

Figure S5. Illustration of the chosen reaction coordinates used to characterize (a) the initial methyl-migration and (b) the secondary hydration steps of the aging/dealkylation mechanism.

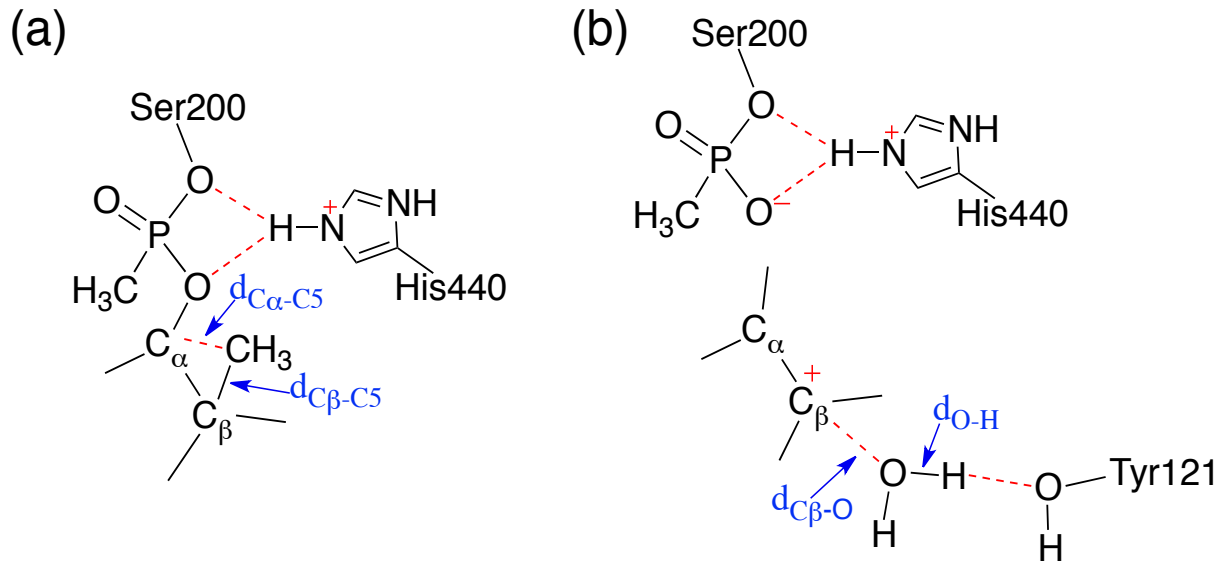

Figure S6. (a) Scatter plot of His440$^+$ χ_1 and χ_2 torsion angles measured for the reactant (red) and the rate determining transition state (blue) for the methyl migration step of aging. (b) Histograms of His440$^+$ χ1 and χ2 torsion angles for the reactant (R) and transition state (TS): red, Glu199; blue, Glu199Gln; green; Glh199. Torsion angles χ1 and χ2 are measured along the last 15ps of QM/MM MD simulations and negative values were transposed by adding 360° in an effort to provide better visualization.

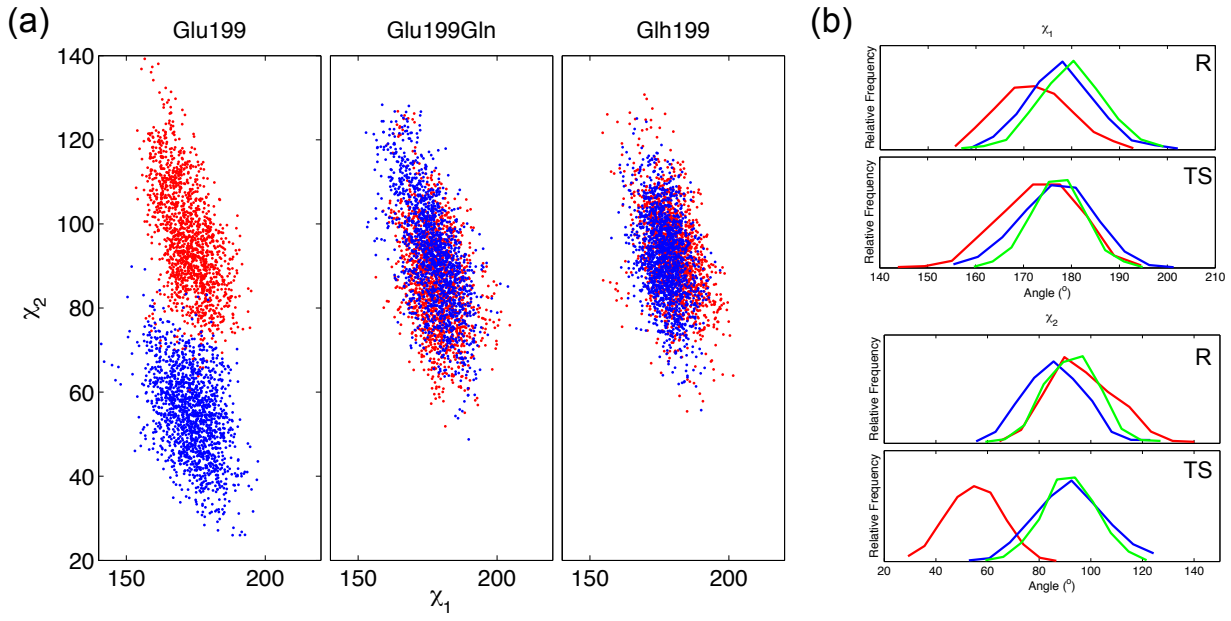

Table S1. RESP partial charges, atom types and connectivity for soman modified serine residue.

	Atom Name	Atom Type	Connectivity	Partial Charge
1	N	N	M	-0.4147
2	H	H	E	0.2719
3	CA	CT	M	-0.0420
4	HA	H1	E	0.0962
5	CB	CT	3	0.1929
6	HB1	H1	E	0.0622
7	HB2	H1	E	0.0622
8	OG	OS	S	-0.4692
9	P	P	3	1.1479
10	C1	CT	3	-0.6429
11	HC11	HC	E	0.1871
12	HC12	HC	E	0.1871
13	HC13	HC	E	0.1871
14	O1	O2	E	-0.6749
15	O2	OS	S	-0.4630
16	C2(α)	CT	3	0.1855
17	HC21	H1	E	0.0621
18	C3	CT	3	-0.5486
19	HC31	HC	E	0.1551
20	HC32	HC	E	0.1567
21	HC33	HC	E	0.1415
22	C4(β)	CT	3	0.5255
23	C5	CT	3	-0.2916
24	HC51	HC	E	0.0617
25	HC52	HC	E	0.0617
26	HC53	HC	E	0.0617
27	C6	CT	3	-0.4144
28	HC61	HC	E	0.0888
29	HC62	HC	E	0.0888
30	HC63	HC	E	0.0888
31	C7	CT	3	-0.3773
32	HC71	HC	E	0.0790
33	HC72	HC	E	0.0790
34	HC73	HC	E	0.0790
35	C	C	M	0.5973
36	O	O	E	-0.5679