Supplementary Information (SI) for Physical Chemistry Chemical Physics.

Unraveling the Stereoisomeric Toxicity of V-series Nerve Agent VX on Human Acetylcholinesterase: A Well-Tempered Metadynamics Study

Dipankar Das,[a,b] Shibaji Ghosh,[a,b] Kalyanashis Jana,[c] Bishwajit Ganguly*[a,b]

[a] Computational and Simulation Unit (Marine Elements and Marine Environment Division and Centralized Instrument Facility), CSIR- Central Salt & Marine Chemicals Research Institute, Bhavnagar-364002, Gujarat, India.

[b] Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, Uttar Pradesh, India.

[c]School of Science, Constructor University, Campus Ring 1, 28759 Bremen, Germany.

*Corresponding Author. Fax: (+91)-278-2567562, E-mail: ganguly@csmcri.res.in

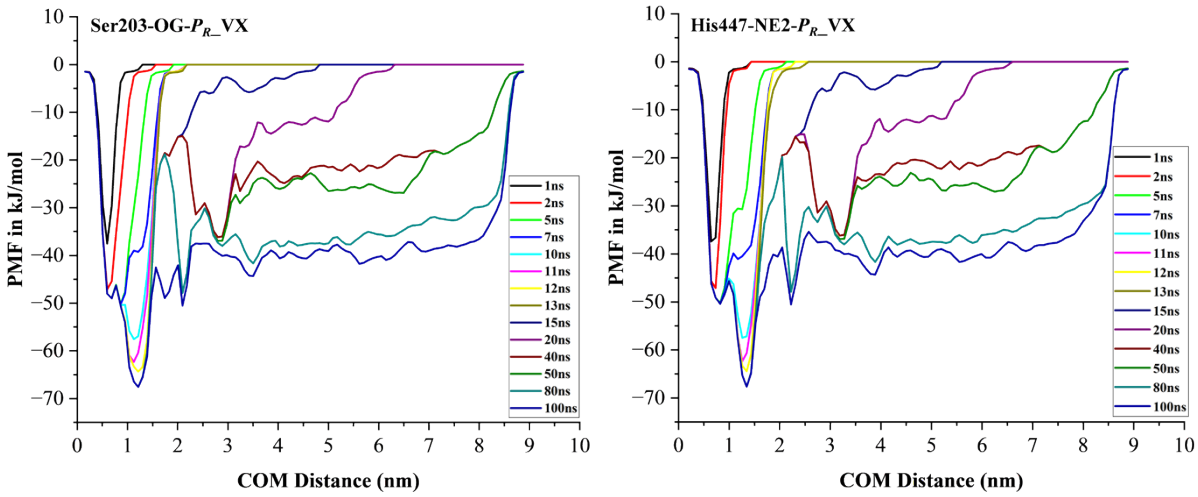

Figure S1. The free energy profile at Basin-I as a function of CV, namely Ser203-OG-P_R_VX and His447-NE2-P_R_VX, are plotted at different time scales and compared with other to access the convergence of a Well-tempered metadynamics simulation.

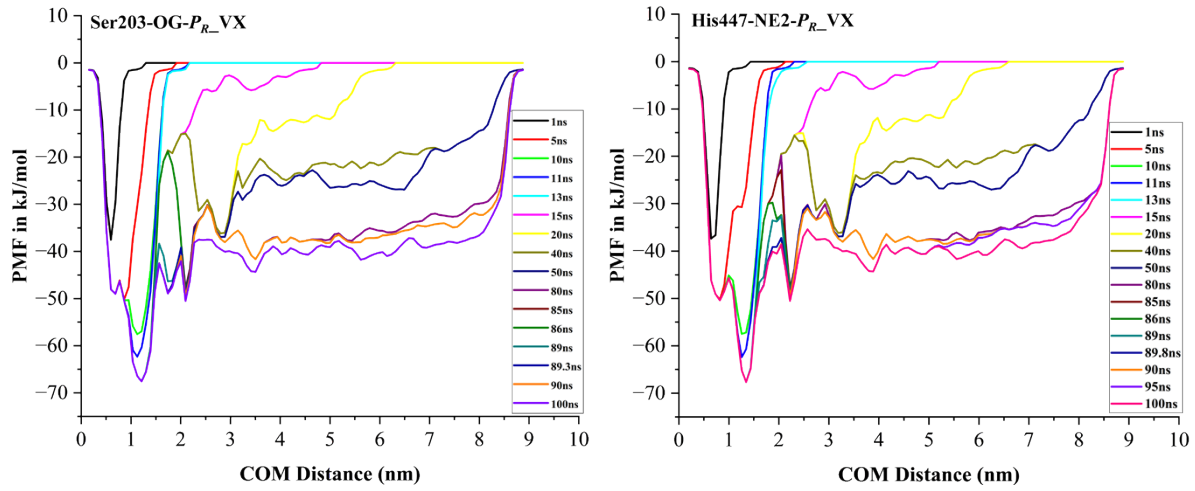

Figure S2. The free energy profile at Barrier-I as a function of CV, namely Ser203-OG-P_R_VX and His447-NE2-P_R_VX, are plotted at different time scales and compared with other to access the convergence of a Well-tempered metadynamics simulation.

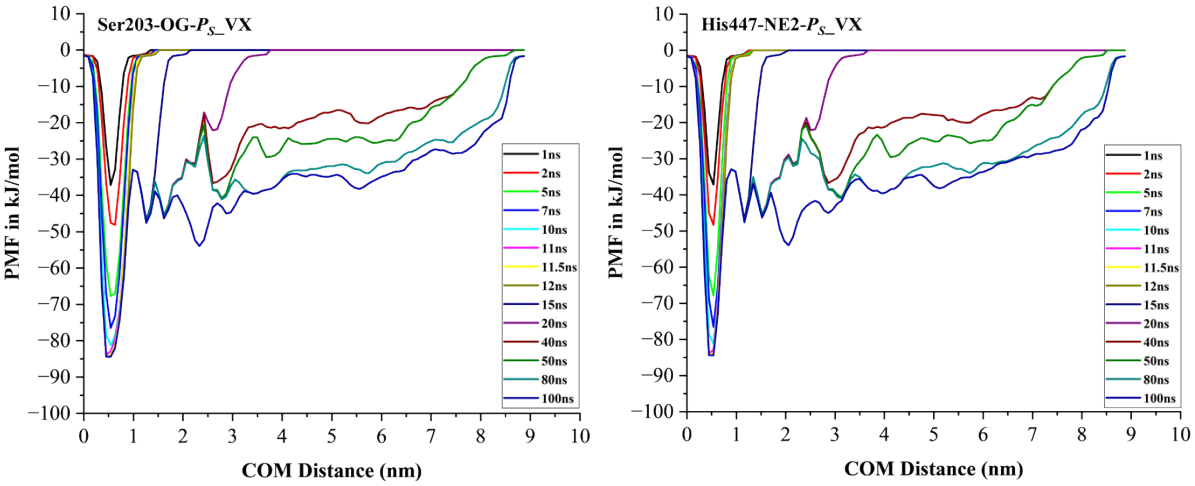

Figure S3. The free energy profile at Basin-I as a function of CV, namely Ser203-OG-P_S_VX and His447-NE2-P_S_VX, are plotted at different time scale and compared other to access the convergence of a Well-tempered metadynamics simulation.

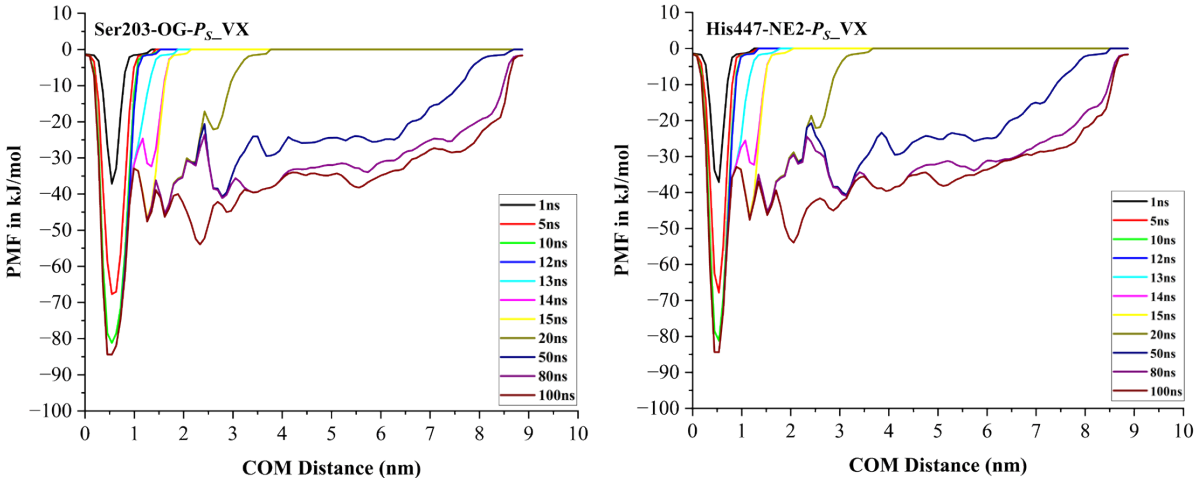

Figure S4. The free energy profile at Barrier-I as a function of CV, namely Ser203-OG-P_S_VX and His447-NE2-P_S_VX, are plotted at different time scale and compared other to access the convergence of a Well-tempered metadynamics simulation.

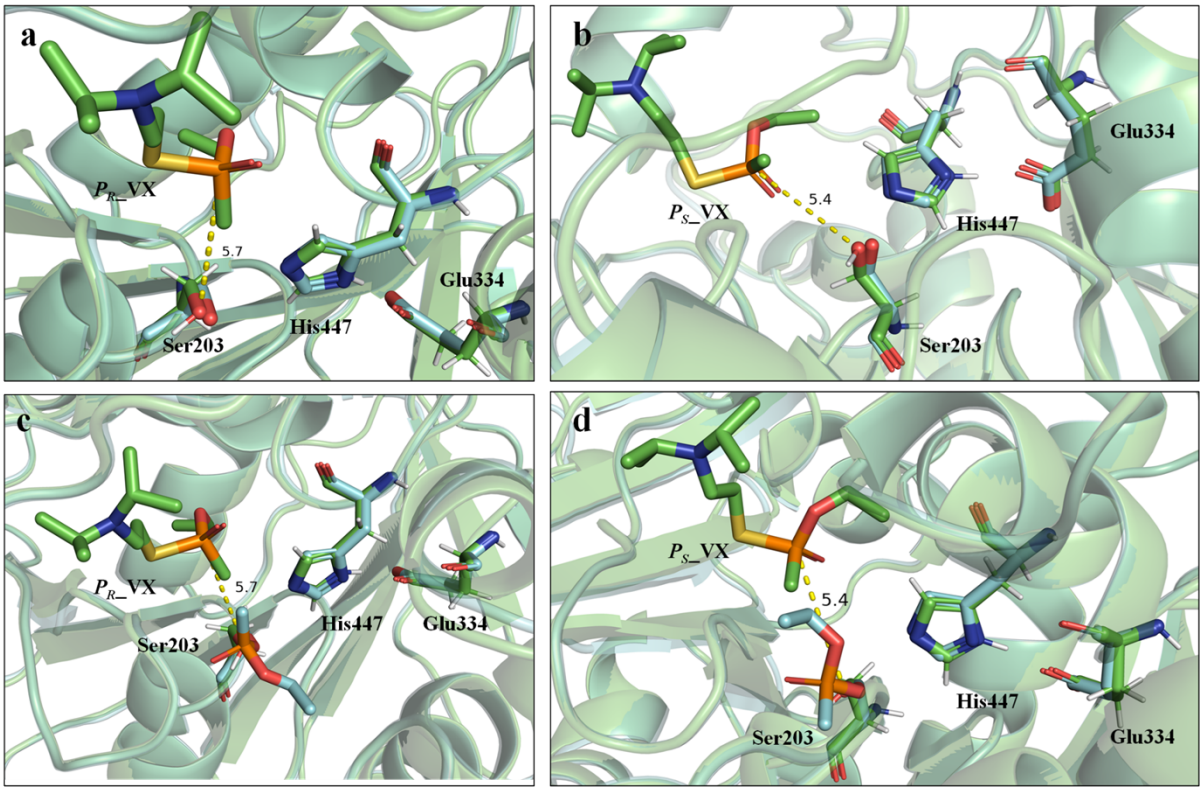

Figure S5. The superimposed structure between the covalently bound stereoisomers VX nerve agent crystal structure (6CQT & 6CQX) with the VX stereoisomers docked apo (4PQE) structure. Above ***P_S*** form and below ***P_R*** form. Distances are shown in Angstrom (Å). a&b) ***P_R*_VX** bound hAChE. b&d) ***P_R*_VX** bound hAChE. In **a** & **b** without covalent adduct, and in **c** & **d** with the covalent adduct bound with Ser203.

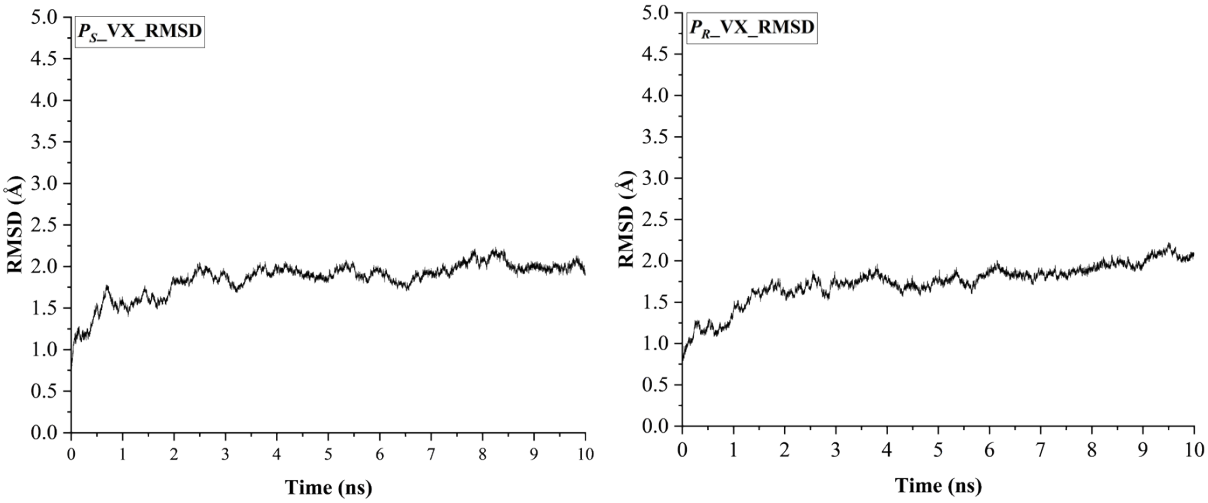

Figure S6. The 10 ns MD simulation equilibration step RMSD plots of VX stereoisomers-bound hAChE.

❖ The Cartesian coordinates of the optimized individual stereoisomeric nerve agent, the B3LYP/6-31G(d) level of theory in the aqueous phase.

P_S_VX			
S	1.32614100	-0.12324300	-1.69739000
P	2.35997700	0.86279800	-0.12736100
O	3.01340100	-0.28576700	0.81545600
O	1.50745400	1.75378200	0.72115900
N	-2.40304900	-0.23987500	0.10262200
C	-2.92085100	0.59107900	1.20659000
C	-3.36639200	-1.01315200	-0.70256000
C	-1.27520800	0.29724700	-0.64655600
C	-0.15508000	-0.74837400	-0.76111900
C	-1.96980600	0.52294400	2.41353600
C	-3.23283200	2.06130200	0.85123600
C	-3.99038800	-2.15872000	0.10891800
C	-4.45406500	-0.18038500	-1.41125800
C	3.73094200	1.68542500	-0.98995100
C	3.92804600	-1.30868700	0.33846200
C	4.09384000	-2.33641200	1.44175700
H	-3.86460100	0.12625600	1.51174500
H	-2.76366900	-1.48273900	-1.49022400
H	-1.55876800	0.63607500	-1.65682500
H	-0.86409600	1.16523900	-0.12858300
H	0.16664300	-1.08177400	0.22843900
H	-0.47723200	-1.63057900	-1.32082600
H	-1.82473700	-0.51548400	2.72948800
H	-2.37398800	1.09120000	3.26002200
H	-0.98707400	0.94428000	2.16874600
H	-3.69984600	2.56042900	1.70878700
H	-2.32251800	2.62096400	0.60676400
H	-3.91705000	2.14028200	0.00178500
H	-3.20944800	-2.77390600	0.56786900
H	-4.59971100	-2.79710400	-0.54139400
H	-4.64507500	-1.78747300	0.90606200
H	-5.02723500	-0.81290200	-2.09970700
H	-5.16147700	0.25278500	-0.69465200
H	-4.01383000	0.63606000	-1.99469300
H	4.38679900	2.13383900	-0.23706300
H	3.33191900	2.47478500	-1.63202600
H	4.31032900	0.98578400	-1.59867600
H	3.51650300	-1.76333400	-0.56886000
H	4.88507900	-0.83635900	0.09208000
H	4.79314200	-3.11358100	1.11550800
H	4.49164600	-1.87246200	2.34980900
H	3.13564200	-2.80895700	1.67948000

P_R_VX			
S	1.28880300	-1.35137700	-1.11647200
P	2.43306100	-0.61611400	0.52202400
O	1.58908900	0.03629300	1.57498700
N	-2.47294300	-0.08061900	0.06351400
C	-2.84133100	0.94053200	1.06263700
C	-3.50483500	-0.53120300	-0.88831500
C	-1.12651200	-0.00111500	-0.48850100
C	-0.42107600	-1.36207000	-0.39163800
C	-2.17454500	0.62669700	2.41251500
C	-2.57124700	2.40536000	0.65432400
C	-4.59597300	-1.35598700	-0.18833400
C	-4.12569700	0.57683400	-1.76355500
H	-3.92295000	0.84101600	1.20487800
H	-2.98377600	-1.21778400	-1.56752000
H	-1.11869000	0.34109000	-1.53658000
H	-0.53556700	0.71741000	0.08205000
H	-0.36376900	-1.68793700	0.64817800
H	-0.94854200	-2.13155800	-0.96265900
H	-2.45784900	-0.37395000	2.75579900
H	-2.47715000	1.35451400	3.17520900
H	-1.08140900	0.65966400	2.33191100
H	-2.97421700	3.08503100	1.41472400
H	-1.49799200	2.61224700	0.57044800
H	-3.03912400	2.65327100	-0.30247300
H	-4.14921600	-2.17460500	0.38546500
H	-5.28343700	-1.78345400	-0.92741700
H	-5.19426500	-0.74566800	0.49841400
H	-4.77714200	0.13620900	-2.52781100
H	-4.73493700	1.26549800	-1.16709100
H	-3.35362400	1.16013400	-2.27813100
C	3.47929300	-1.97972000	1.10220200
H	4.06025700	-2.39862000	0.27680300
H	4.15837700	-1.60134500	1.87235700
H	2.84386900	-2.75906400	1.53048800
O	3.55914900	0.31290500	-0.18015700
C	3.22129800	1.63029700	-0.70023400
H	2.70968500	2.19596400	0.08424800
H	2.53658600	1.50565100	-1.54577200
C	4.51048300	2.30608500	-1.12494000
H	4.28715700	3.29989700	-1.52736700
H	5.18869300	2.42178200	-0.27365000
H	5.01782000	1.72485900	-1.90151800