Supplementary Information

Modulation of alkali metal ions on acetylcholinesterase

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Table S1 Time-averaged geometric distances for ACh-hAChE complex obtained in DFTB/MM-MD simulations.

list	150 mM Li	150 mM Na	150 mM K
Hγ(S200)-Nε2(H444)	2.9±1.0	2.1±0.3	2.1±0.3
Oγ(S200)-C1(ACh)	4.8±1.8	6.2±0.8	5.0±1.4
Hδ1(H444)-Oε2(E331)	3.0±1.6	2.0±0.4	1.8±0.1
O1-H(G118)	3.9±0.9	5.3±0.7	4.2±1.2
O1-H(G119)	2.9±1.2	3.9±0.6	3.8±1.2
O1-H(A201)	3.7±2.0	6.5±0.8	6.1±1.9
N1-W84-ring	4.2±0.2	4.2±0.2	4.2±0.2
N1-Y334-ring	10.2±0.6	9.9±0.4	10.3±0.5
N1-Y446-ring	5.3±0.6	5.5±0.3	5.2±0.4

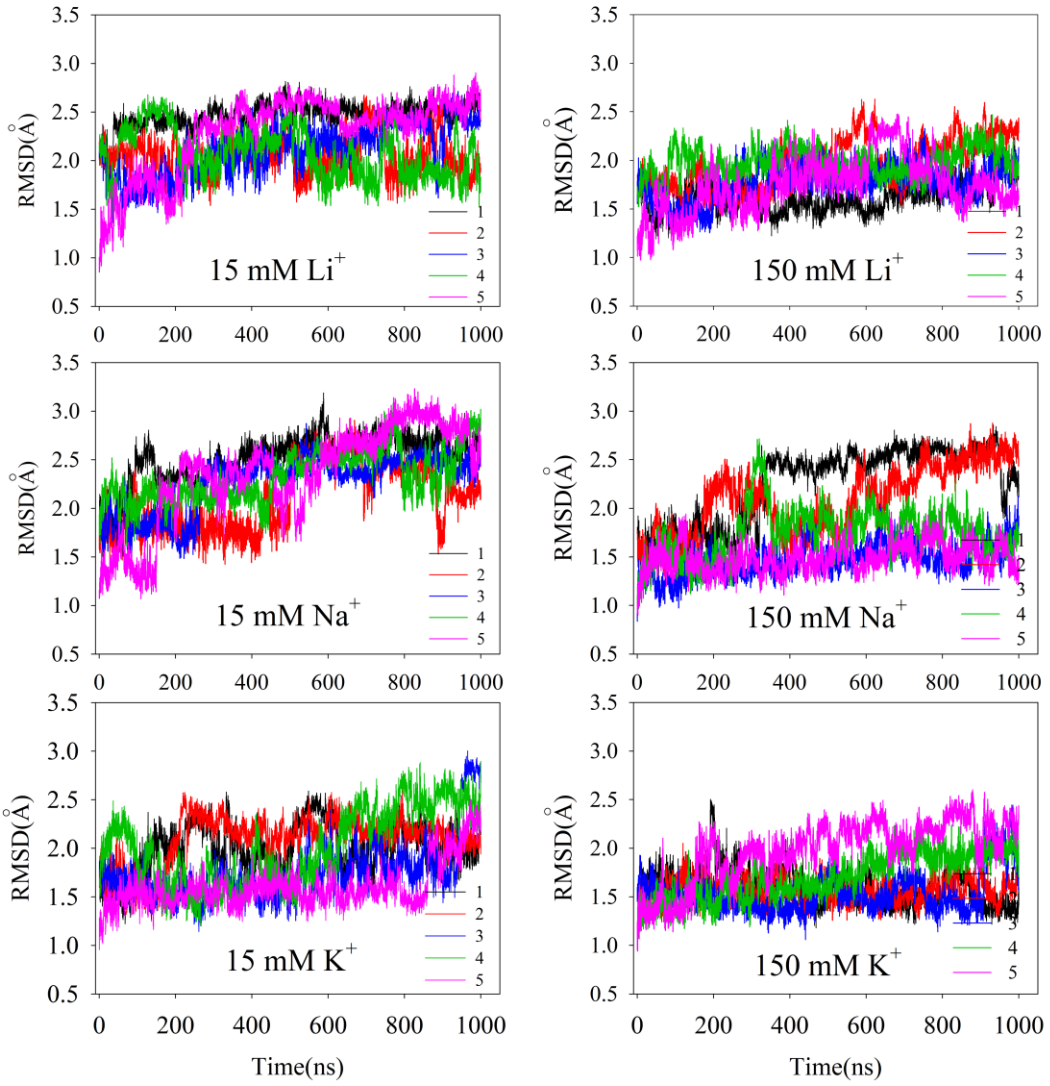

Fig. S1 Time evolution of RMSD of hAChE by Cα alignment on initial structure in Li^+, Na^+, and K^+ systems of 15 mM and 150 mM, respectively. Each system was simulated with five copies.

We examine the conformation and dynamics of hAChE complex in Li^+, Na^+, and K^+ systems of 15 mM and 150 mM, respectively, in 1000-ns MD simulations. Indicated by the root means square deviations (RMSD) of hAChE in Fig. 1, the protein structure reached equilibrium at around 400 ns. Accordingly, we collected the last 200 ns for data analysis. Final RMSD values for the 15 mM systems are 2.51±0.09 Å (Li^+), 2.45± 0.10 Å(Na^+), and 2.17±0.12 Å (K^+), respectively. Overall, hAChE exhibits similar conformations in all 15 mM systems. The Li^+ and Na^+ systems exhibit a slightly higher RMSD value than the K^+ system. The RMSD values for the 150 mM systems are 1.68 ±0.15 Å (Li^+), 1.48 ± 0.15 Å (Na^+), and 1.51±0.14 Å (K^+), indicating the RMSD evolutions of hAChE in three ion systems are similar. In general, the conformation of hAChE in the 150 mM system is more stable than it in the 15 mM system enzyme.

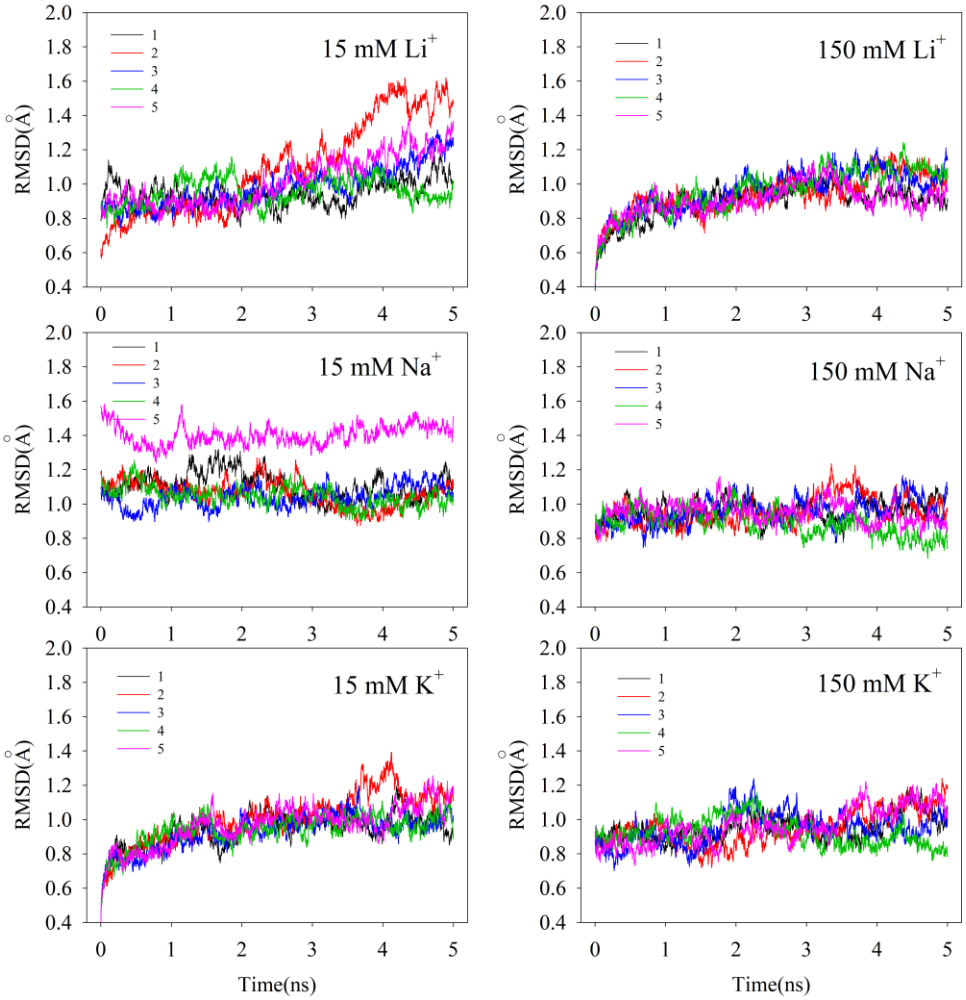

Fig. S2 RMSD results of five QM/MM-MD simulations for all systems.

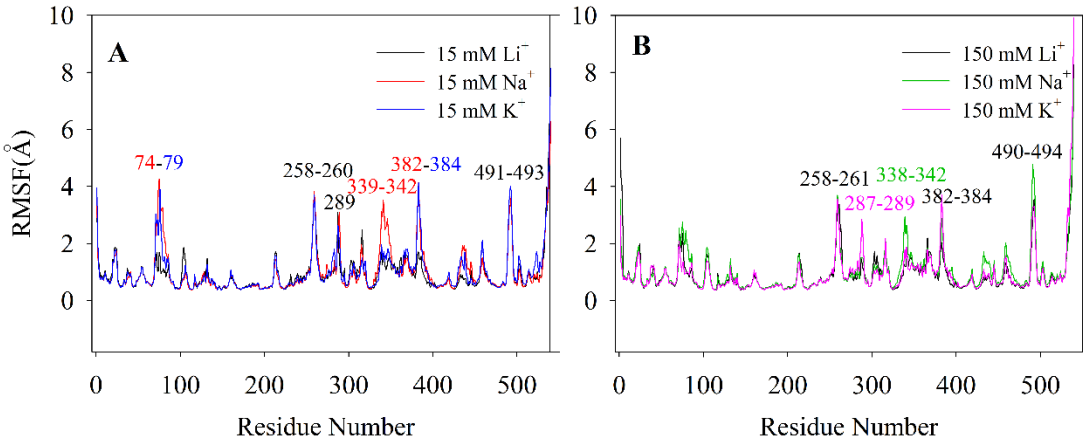

Fig. S3 RMSF per residue of hAChE in Li^+, Na^+, and K^+ systems of 15 mM and 150 mM, respectively. High RMSF regions that exit in all three ion systems are labeled upon the RMSF peaks and colored in black. High RMSF regions that only exit in certain ion

system(s) are labeled upon the RMSF peaks using the same system color(s) as the color scheme to the upper right.

There are six regions that exhibit RMSF peeks of different heights, which locate at res. 74-79, 258-260, 289, 339-342, 382-384 and 491-493. In the 15 mM systems, the Li^+ system displays low RMSF in res. 74-49, 339-342, and 383-384, while the Na^+ system exhibits high RMSF in res. 339-342. In the 150 mM systems, the Na^+ system displays high RMSF in res. 338-342, while the K^+ system exhibits high RMSF in res. 287-289. The structural alignment of hAChE in Na^+ system and in crystal structure is shown in Fig. 3. The res. 338-342 as a loop between two helixes was observed to form helical conformation during the simulation, which is likely attributed to certain potential ion binding sites.

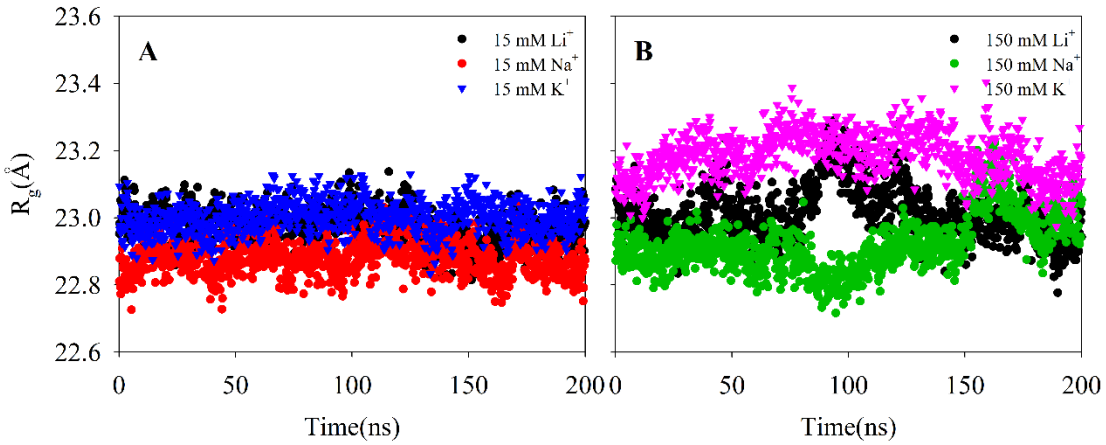

Fig. S4. Radius of gyration (R_g) of hAChE in Li^+, Na^+, and K^+ systems of (A) 15 mM and (B) 150 mM, respectively in the last 200 ns.

The R_g in three 15 mM systems are similar, around 22.9~23 Å, while vary significantly in the 150 mM systems. In the 150 mM systems, hAChE in the Na^+ system exhibits the smallest R_g; hAChE in the Li^+ system shows intermediate R_g, and hAChE in the K^+ system displays the highest R_g. By comparing the R_g in the two concentrations systems, hAChE was affected the most by high concentration of K^+, while less affected by changing concentrations of Li^+ and Na^+, which encourages us to go further into the modulation mechanism of different ion species.

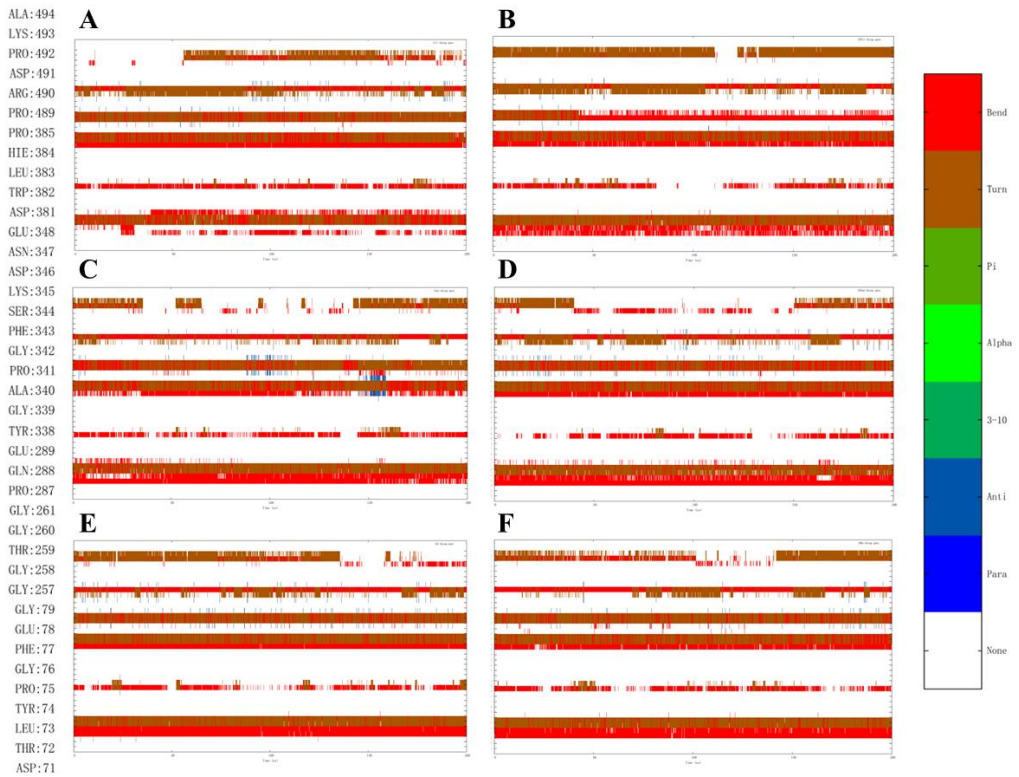

Fig. S5 DSSP secondary structure results of hAChE fragments in Li^+, Na^+, K^+ of 15 mM (in A,C,E) and 150 mM (in B,D,F), respectively in the last 200 ns, the color bar represented different secondary structures. These fragments are residue 71-79, 257-261, 287-289, 338-348, 381-385 and 489-494 in RMSF results.

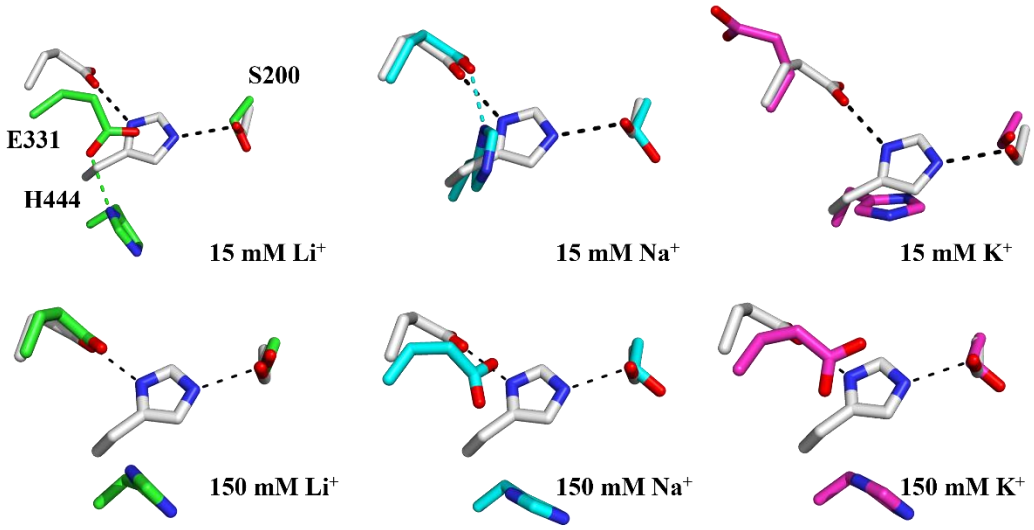

Fig. S6 The alignment view of conformational representative on the crystal structure for the residues at the active site.

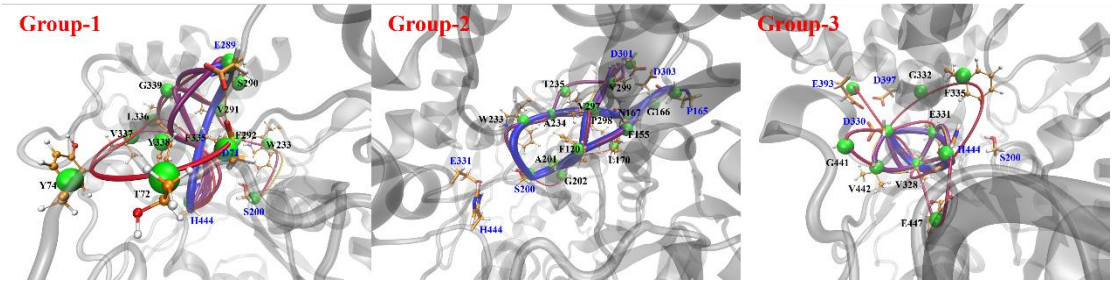

Fig. S7 optimal path from ion binding sites to active sites.

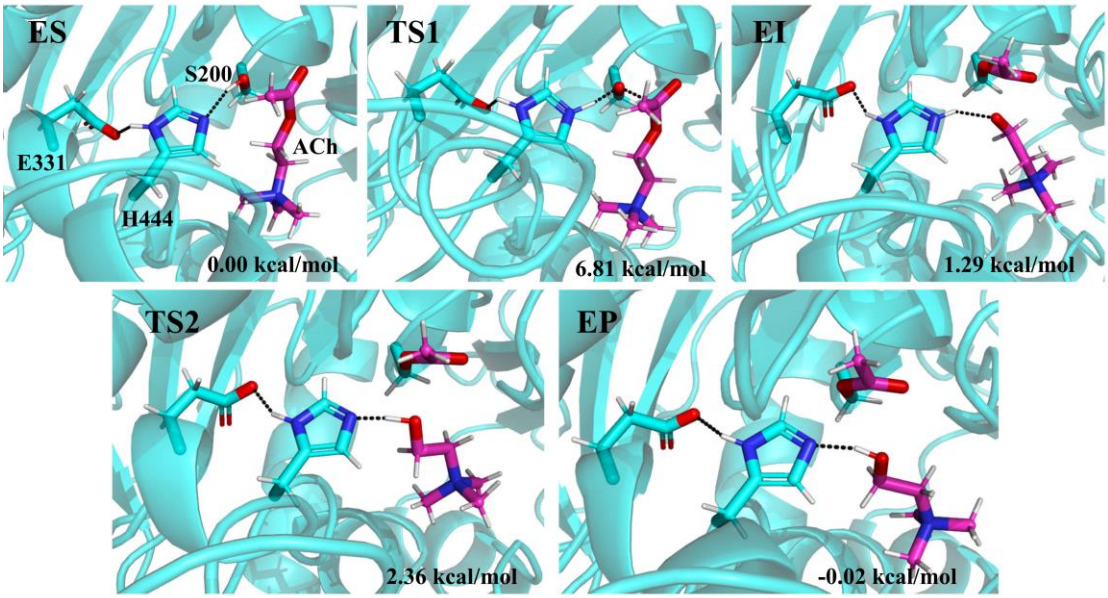

Fig. S8 Snapshot structures of ACh hydrolysis in the 15 mM Na^+ system.

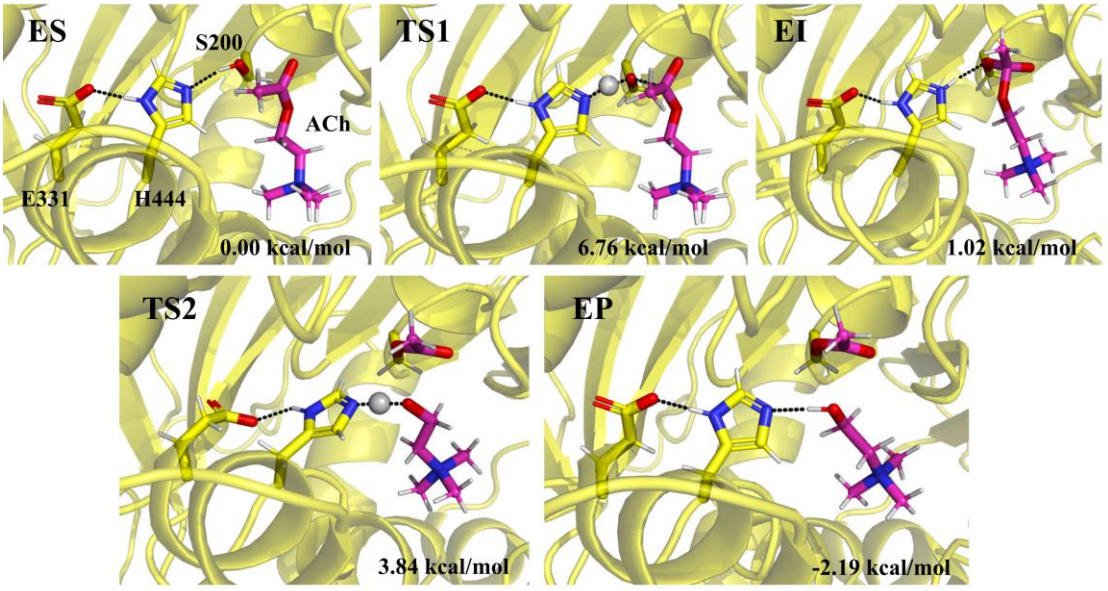

Fig. S9 Snapshot structures of ACh hydrolysis in the 15 mM K^+ system.

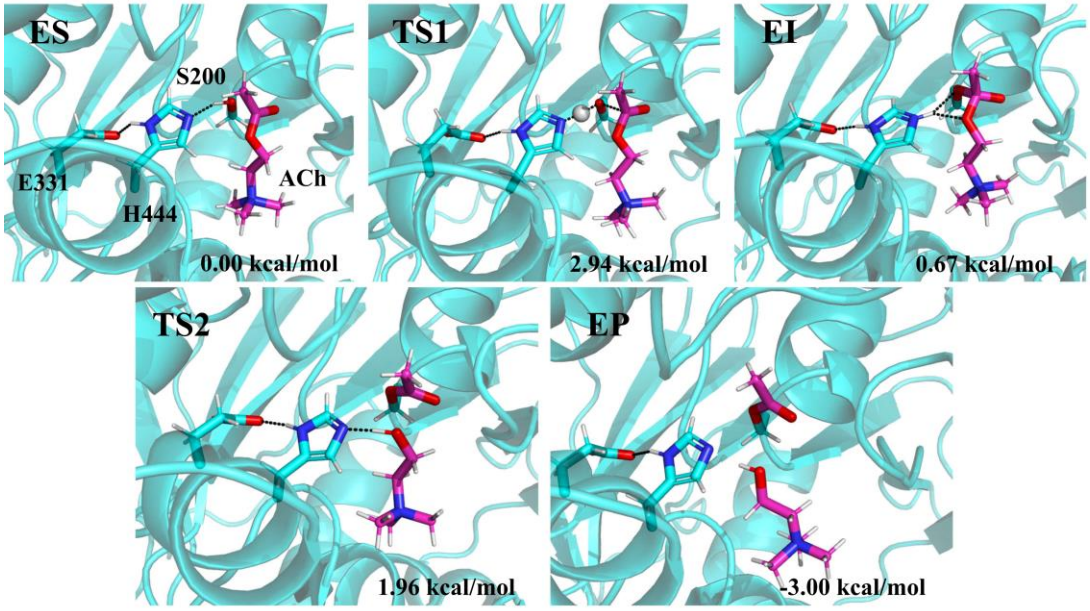

Fig. S10 Snapshot structures of ACh hydrolysis in the 150 mM Na^+ system.

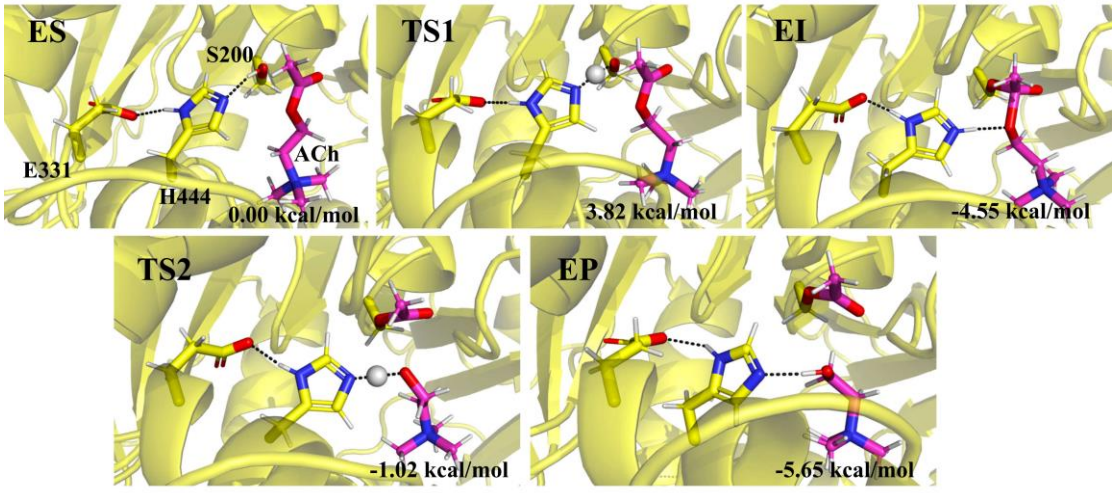

Fig. S11 Snapshot structures of ACh hydrolysis in the 150 mM K^+ system.