# Reaction Pathway and Free Energy Barrier for Reactivation of Dimethylphosphoryl-inhibited Human Acetylcholinesterase

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**Supporting Information Available.** Additional free energy profiles concerning the role of Glu334 and additional geometries optimized in exploring the possible alternative reaction pathway. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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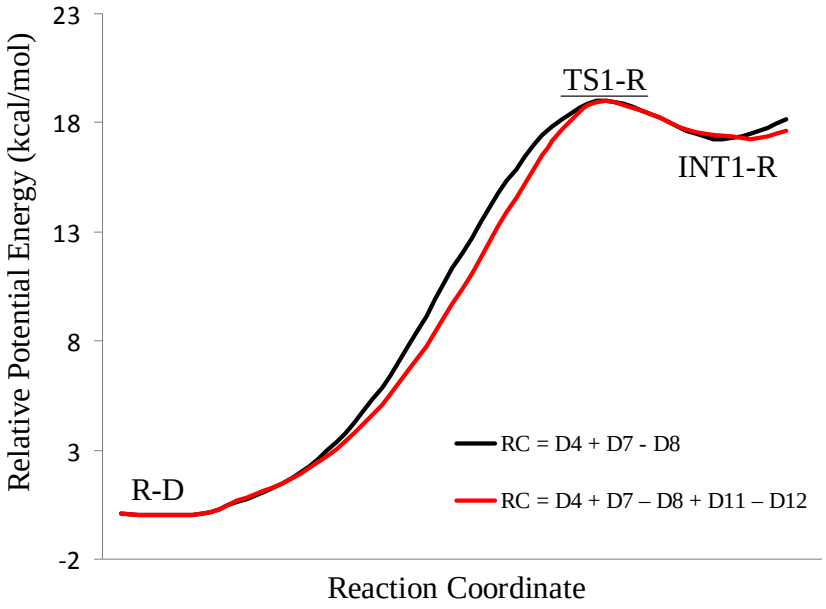


Figure S1. Relative potential energy profiles calculated at B3LYP/6-31G* level for the first reaction step, *i.e.* the nucleophilic attack on the P atom by a water molecule. The energy curve colored in black is obtained with Reaction Coordinate (RC) = D4 + D7 – D8. The energy curve colored in red is obtained with RC = D4 + D7 – D8 + D11 – D12. The two energy curves are almost identical, indicating that the conclusion we made on the role of Glu334 does not change when D11 and D12 are included into the reaction coordinate.

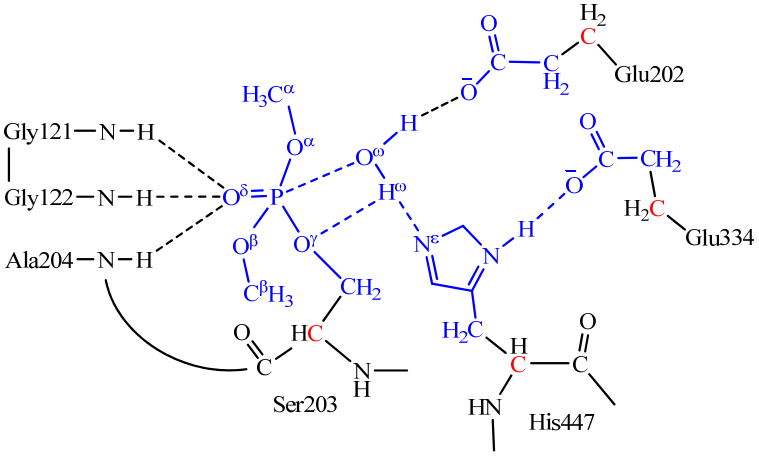


Figure S2. Division of the QM/MM system with Glu202 in the QM subsystem. The atoms in blue are treated by QM method. Four boundary carbon atoms (in red) are treated with the improved pseudobond parameters. All other atoms belong to the MM subsystem.

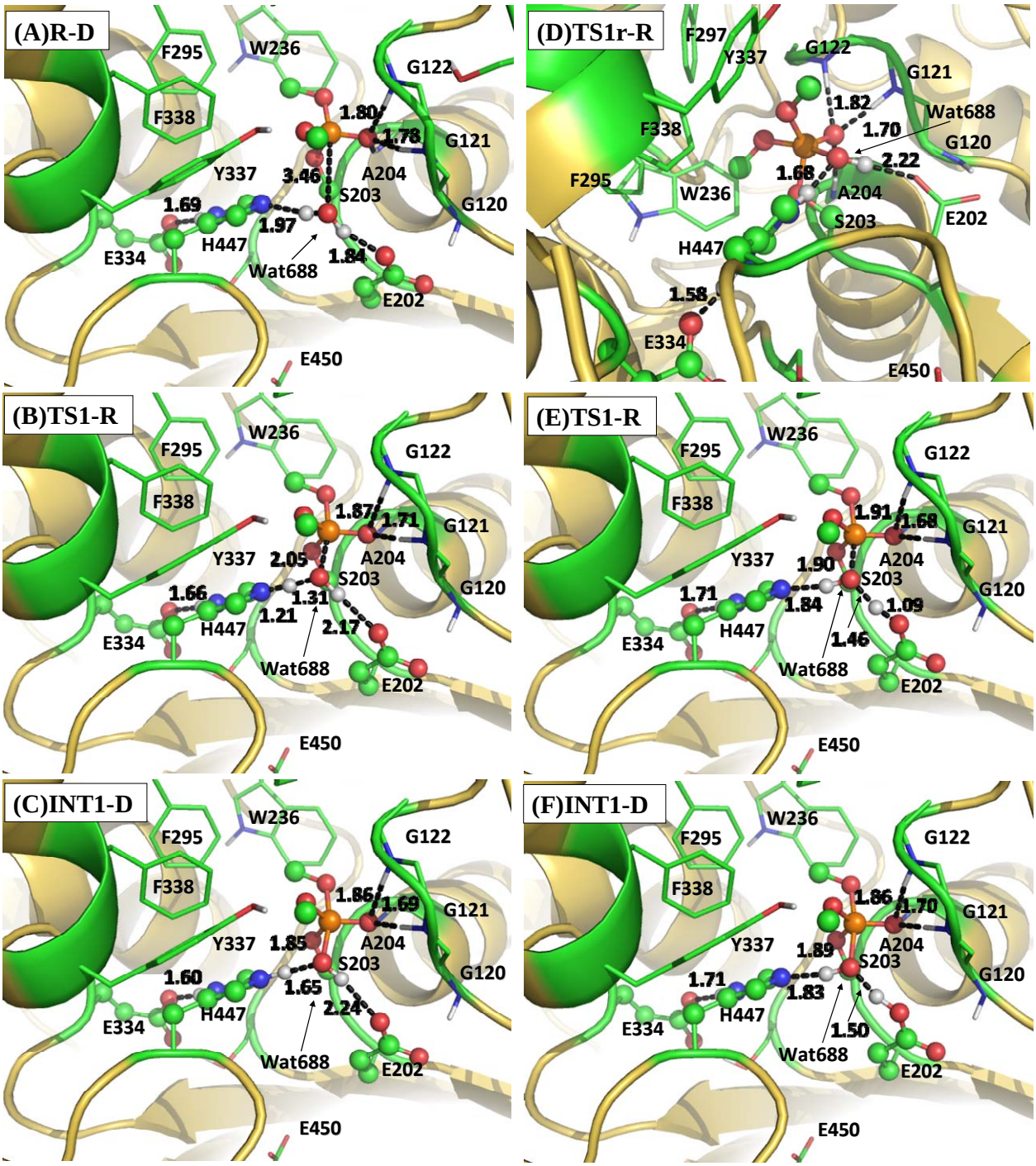


Figure S3. The geometries optimized at the QM/MM(B3LYP/6-31G*:AMBER) level with Glu202 included in the QM subsystem. (A) to (D) refer to the geometries for the reaction pathway where His447 acts as the general base. (E) and (F) refer to the geometries for the reaction pathway where Glu202 acts as the general base.