Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supplemental data

Energetics and Structural Characterization of the "DFG-Flip" Conformational Transition of B-RAF Kinase: A SITS Molecular Dynamics Study

Qiang Shao[1*], Zhijian Xu[1], Jinan Wang[1], Jiye Shi[2*], Weiliang Zhu[1]

[1]Drug Discovery and Design Center, Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai, 201203, China

[2] UCB Biopharma SPRL, Chemin du Foriest, Braine-l'Alleud, Belgium

*To whom correspondence should be addressed. Qiang Shao, Tel: +86 21 50806600-1304, E-mail: qshao@mail.shcnc.ac.cn; Jiye Shi, Jiye.Shi@ucb.com.

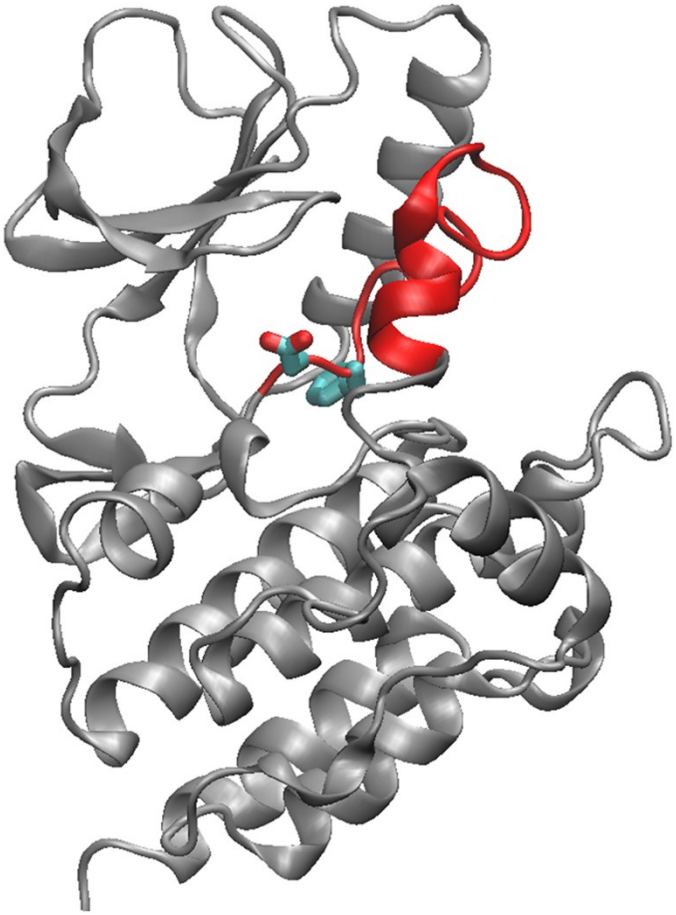

Figure S1. The modeled B-RAF kinase structure with repaired A loop (red). The side-chains of Asp594 and Phe595 are shown with licorice representation.

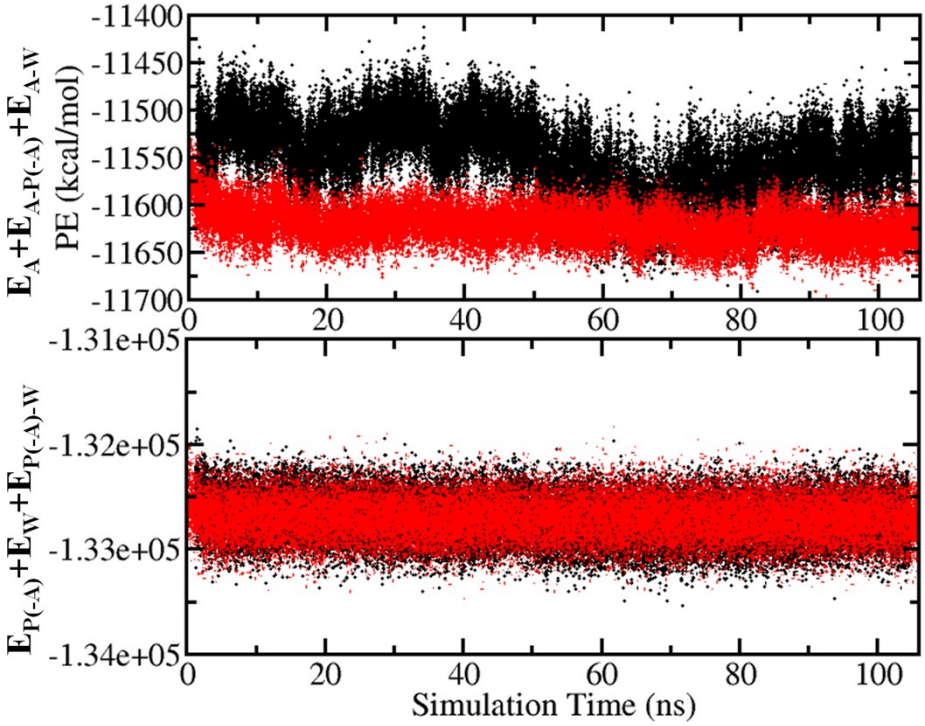

Figure S2. Time series of the potential energy terms (unit: kcal/mol) in a representative trajectory of B-RAF kinase simulated by SITS-MD (black) and conventional MD (red), respectively.

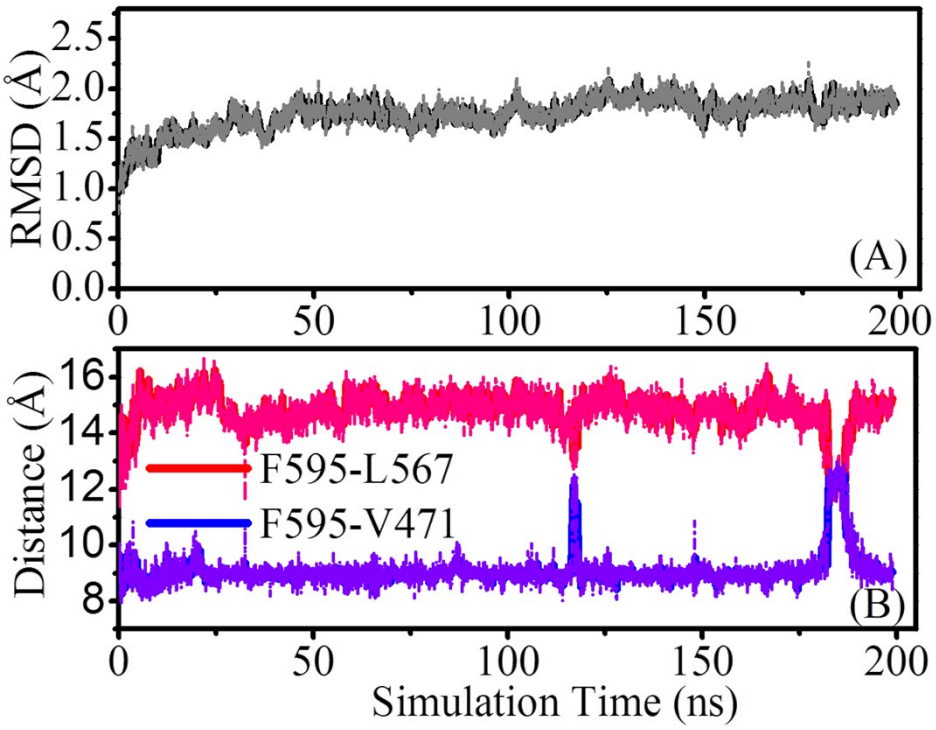

Figure S3. Simulation results for explicit-solvent conventional MD evaluating the stability of SITS-MD identified DFG-out structure of B-RAF. (A) Time series of the overall root-mean-square deviation (RMSD) of B-RAF kinase with respect to the SITS-MD identified DFG-out structure. (B) Time series of side-chain distances of Phe595-Leu567 and Phe595-Val471.

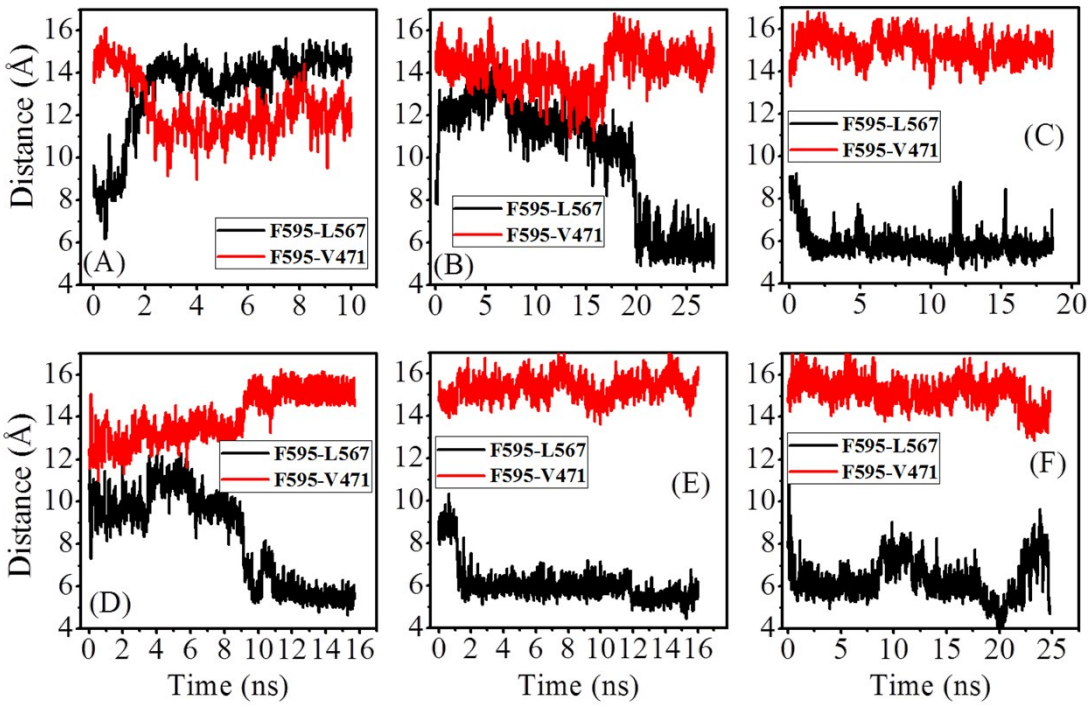

Figure S4. First trial simulation trajectories from selected structure ensembles of the transition (TS) state. (A) Trajectory indicating the transition from TS to DFG-out state. (B-F) Trajectories indicating the transition from TS to DFG-in state.

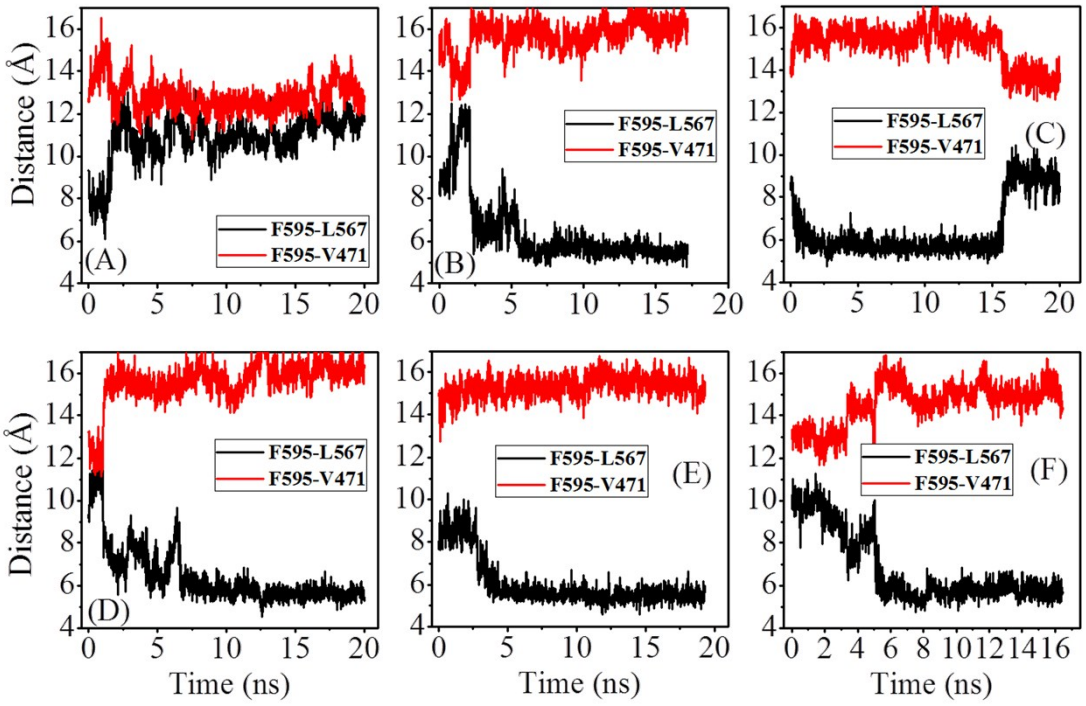

Figure S5. Second trial simulation trajectories from selected structure ensembles of the transition (TS) state. (A) Trajectory indicating the transition from TS to DFG-out state. (B-F) Trajectories indicating the transition from TS to DFG-in state.

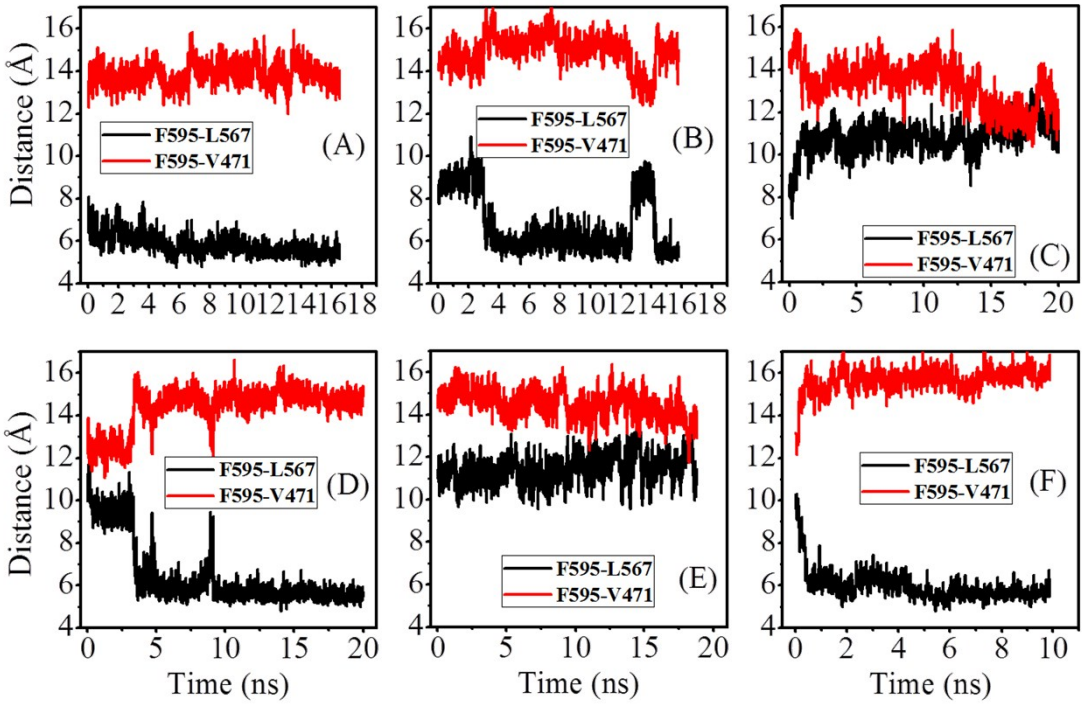

Figure S6. Third trial simulation trajectories from selected structure ensembles of the transition (TS) state. (A-B, D, F) Trajectory indicating the transition from TS to DFG-in state. (C, E) Trajectories indicating the transition from TS to DFG-out state.

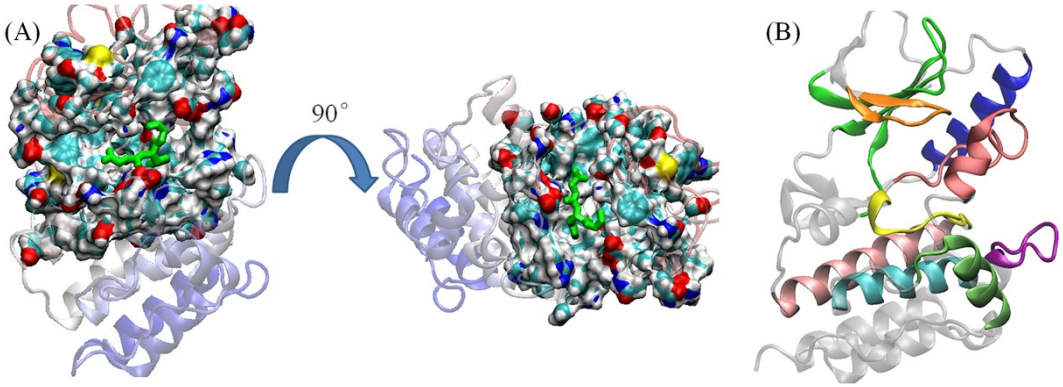

Figure S7. (A) Surface representation of the regions surrounding the DFG-motif of A loop in a front view and a side view with 90° rotation. DFG motif is shown with licorice representation and colored in green. (B) Protein segments nearby A loop (blue: αC helix; orange: P loop; yellow: catalytic loop; pink: αE helix; cyan: αF helix; lime: αG helix; purple: F loop; green: anti-parallel β-strands nearby P loop).