Electronic supplementary information for PCCP paper

A Comparative QM/MM Study of the Reaction Mechanism of the Hepatitis C Virus NS3/NS4A Protease with the Three Main Natural Substrates

Alejandro Rodríguez, Carolina Oliva, and Miguel González*

Stereo view of the active site (NS3/NS4A protease + NS5A/5B substrate; AM1/MM level of calculation), equipotential contour plots of the two-dimensional representation of the AM1/MM PES for the acylation and peptide bond breaking regions for the three substrates, projection of potential of mean force trajectories on the two-dimensional representation of the AM1/MM PES for the acylation and peptide bond breaking regions for the three substrates, and structure and main distances (QM part) of the stationary points located on the AM1/MM PES for the NS4B/5A and NS4A/4B substrates.

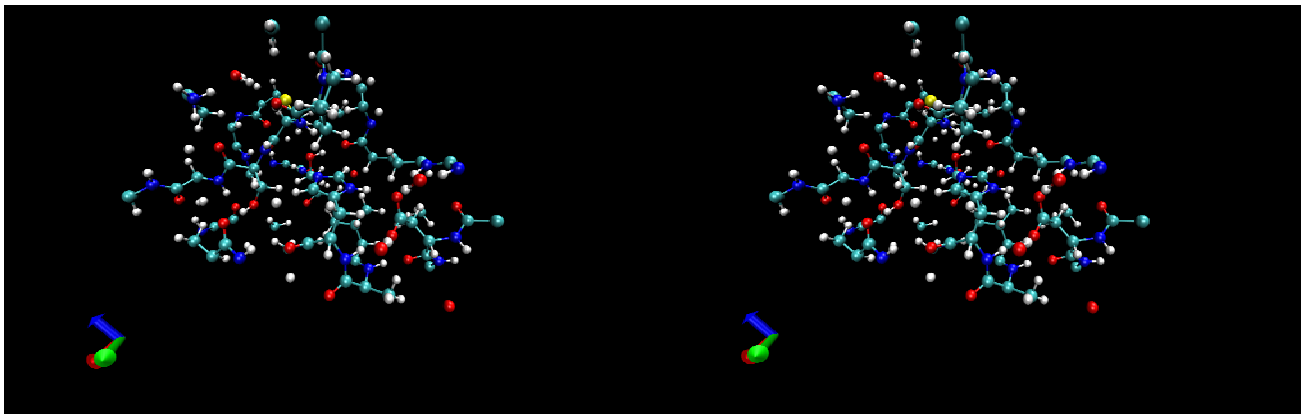


Figure S1. Stereo view of the active site (NS3/NS4A protease + NS5A/5B substrate; AM1/MM level of calculation). Close to the center of this figure the His-57 and Ser-139 residues of the enzyme can be seen

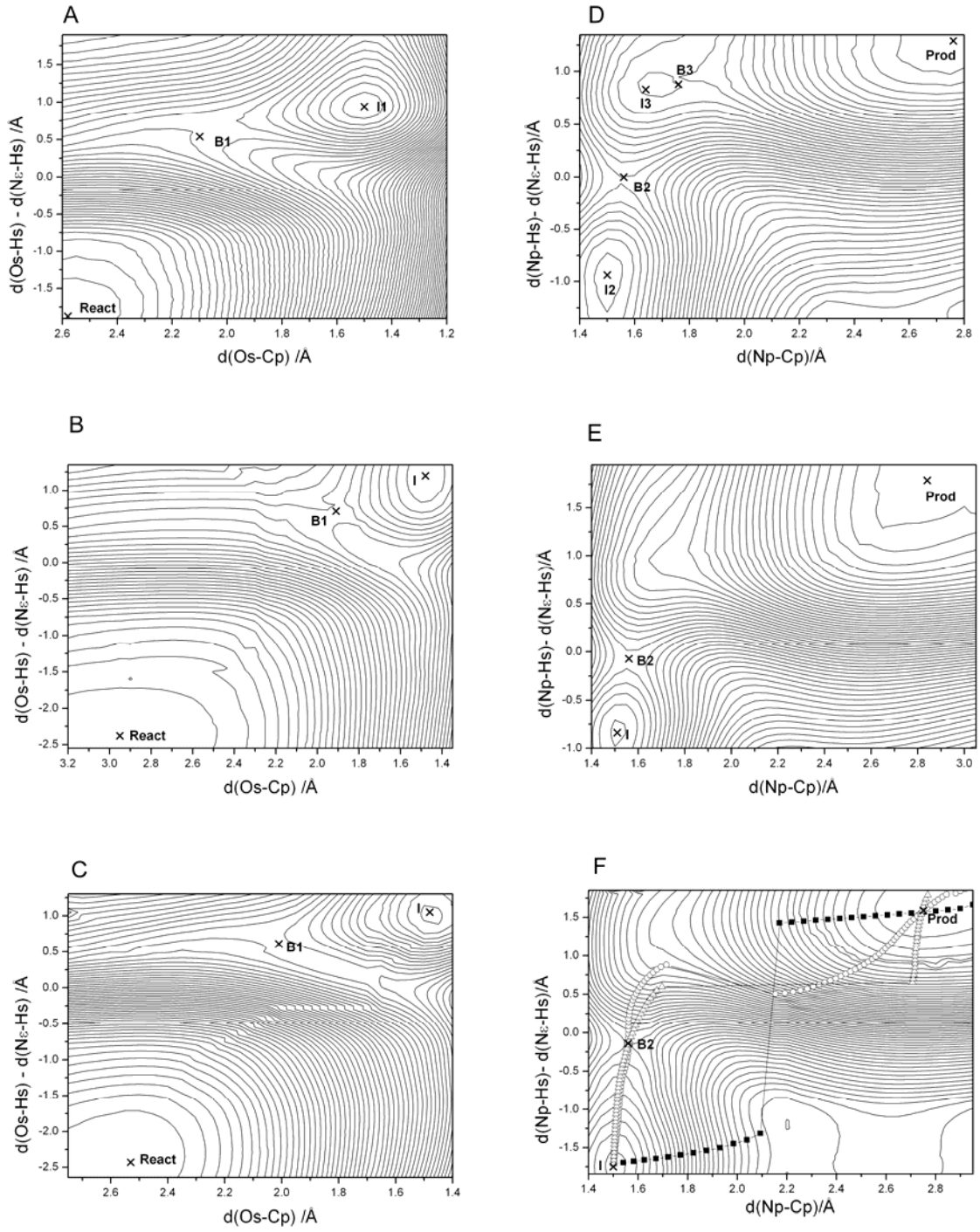


Figure S2. Equipotential contour plots of the two-dimensional representation of the AM1/MM potential energy surface for the acylation region [NS5A/5B **(A)**; NS4B/5A **(B)**; NS4A/4B **(C)**] and for the peptide bond breaking region [NS5A/5B **(D)**; NS4B/5A **(E)**; NS4A/4B **(F)**]. In the last case the one-dimensional distinguished coordinate paths are also given: Np-Cp bond breaking distinguished coordinate "-■-"; proton transfer distinguished coordinate "-Δ-"; symmetric combined distinguished coordinate "-○-" (see text). The curves are given every 1.0 kcal mol^{-1} and the zero of energy is taken in reactants. This figure complements Fig. 2 of the article.

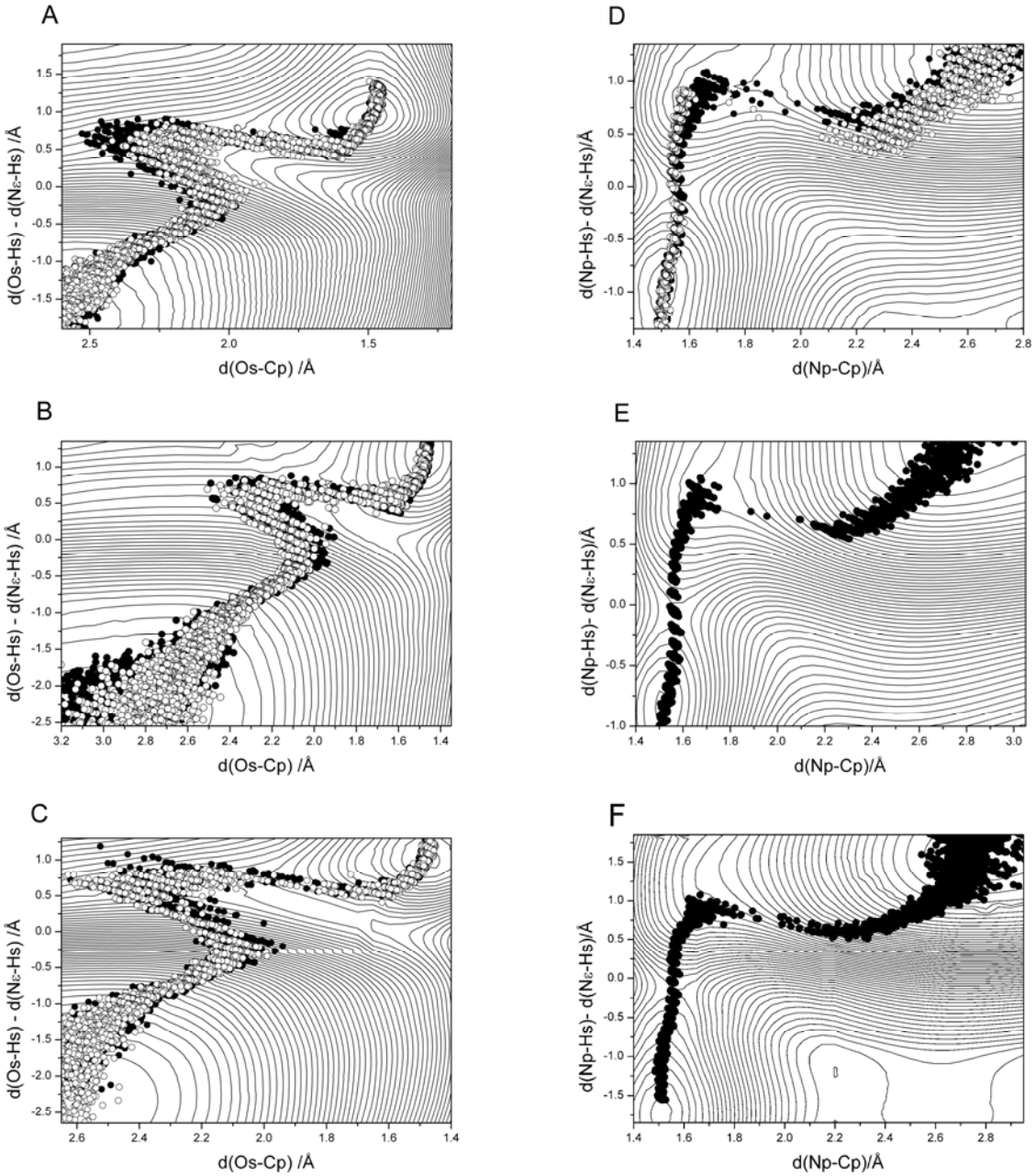
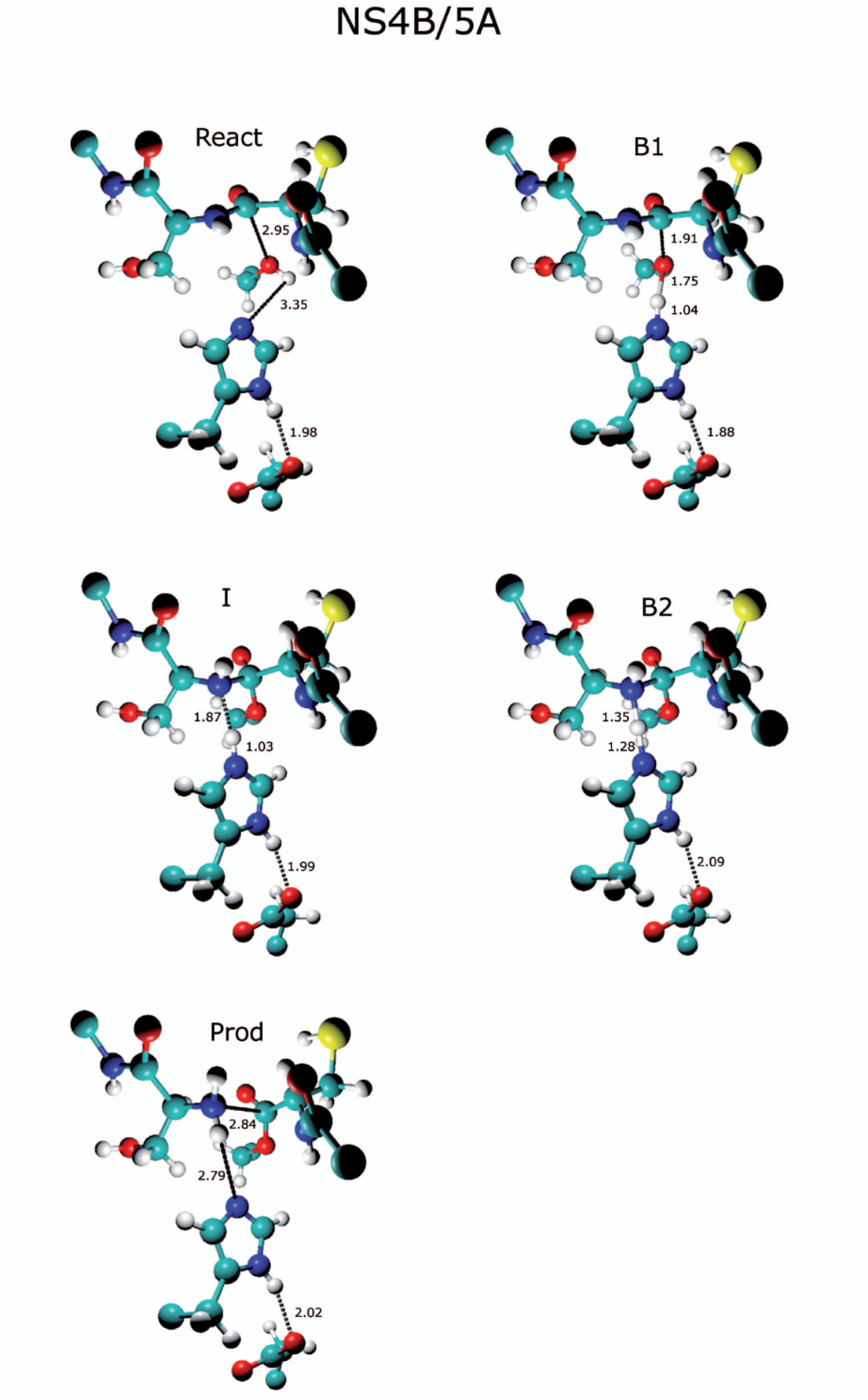


Figure S3. Projection of potential of mean force trajectories on the two-dimensional representation of the AM1/MM potential energy surface for the acylation region [NS5A/5B **(A)**; NS4B/5A **(B)**; NS4A/4B **(C)**] and for the peptide bond breaking region [NS5A/5B **(D)**; NS4B/5A **(E)**; NS4A/4B **(F)**]. The symbol "●" represents geometries obtained through forward simulations while "○" represents the backward ones. This figure complements Fig. 7 of the article.

A



B

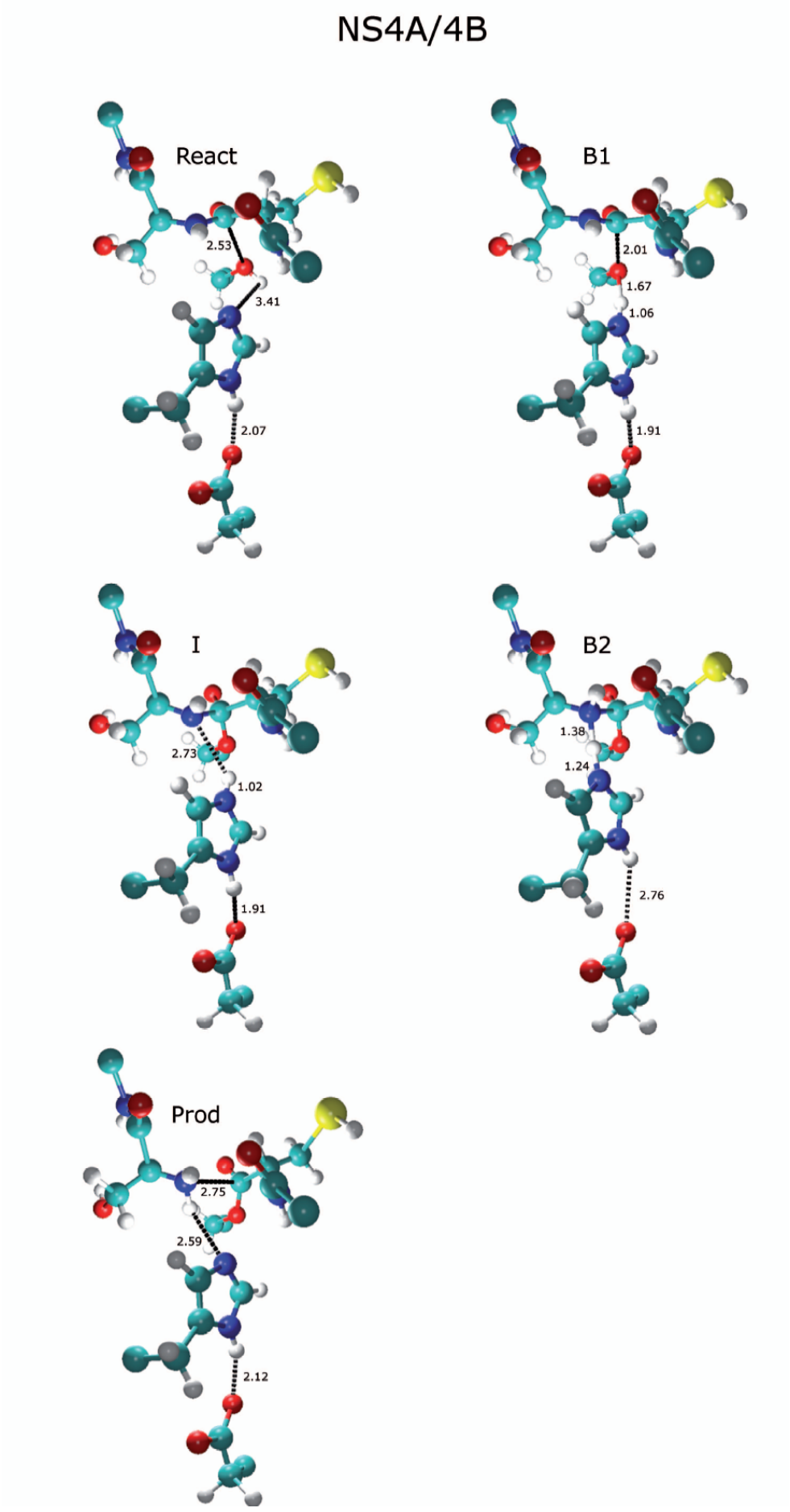


Figure S4. Structure and main distances (QM part) of the stationary points located on the AM1/MM potential energy surface for the reaction of the NS3/NS4A protease with the NS4B/5A **(A)** and NS4A/4B **(B)** substrates.