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

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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 “-∆-”; 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.
**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.