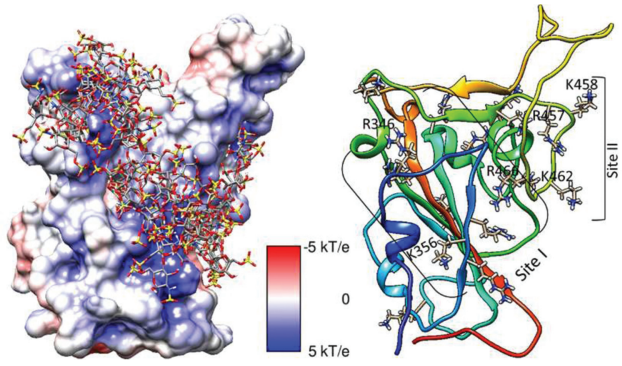
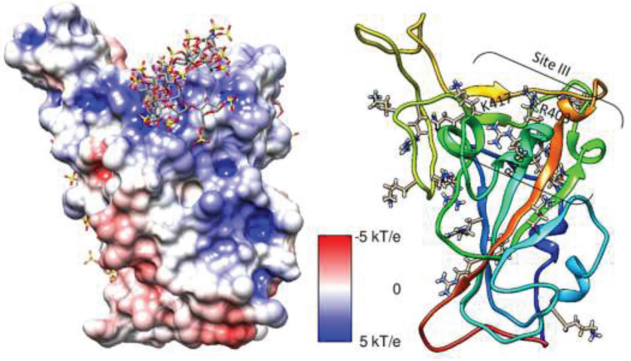
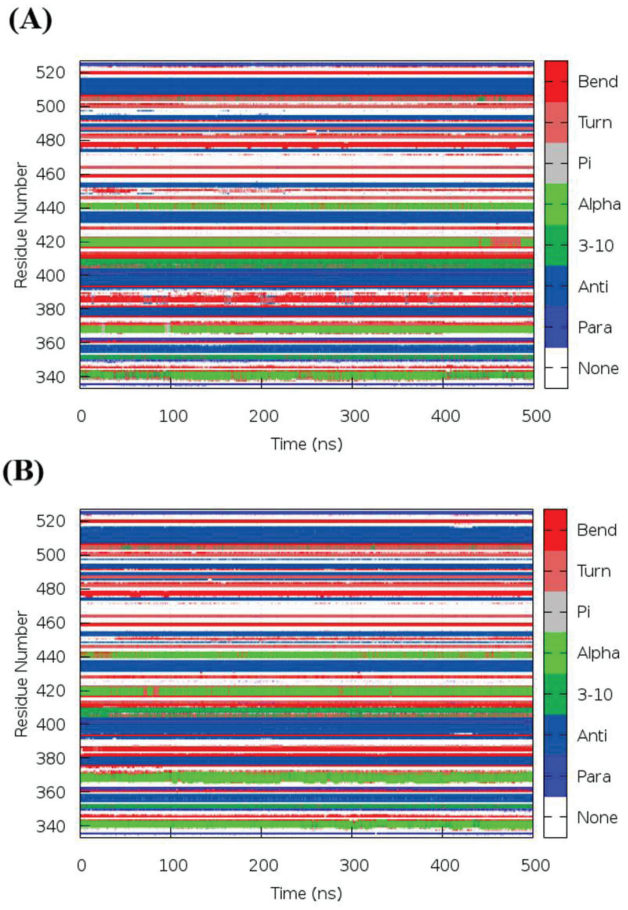


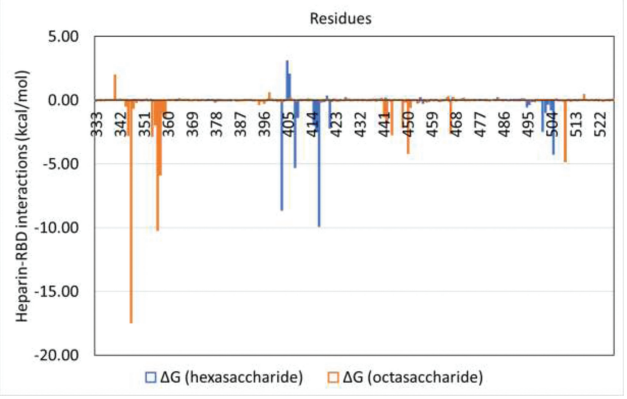
Supplementary Fig. S1 Predicted SARS-CoV-2 RBD interaction with heparin tetrasaccharide. RBD surface was coloured according to the electrostatic potential. *Blue*, *red*, and *white* colours indicate respectively a region of positive (+ 5 kT/e), negative (−5 kT/e), and neutral potential. Heparin tetrasaccharides are shown as stick and CPK colour. RBD structure is presented in cartoon and in the same orientation as the surface. The residues interacting with heparin on sites I and II are shown with indicated numbers. RBD, receptor-binding domain.



Supplementary Fig. S2 Predicted SARS-CoV-2 RBD interaction with heparin tetrasaccharide showing overlap with the receptor binding motif (RBM). Binding of heparin to the receptor binding motif could inhibit receptor binding. RBD surface was coloured according to the electrostatic potential. *Blue*, *red*, and *white* colours indicate respectively a region of positive (+ 5 kT/e), negative (−5 kT/e), and neutral potential. Heparin tetrasaccharides are shown as stick and CPK colour. RBD structure is presented in cartoon and in the same orientation as the surface. The residues interacting with heparin at site III are shown with indicated numbers. RBD, receptor-binding domain.



Supplementary Fig. S3 DSSP plots for secondary structure transitions in SARS-CoV-2 RBD during 500 ns MD simulations (**A**) in the presence of heparin hexasaccharide bound to site III and (**B**) in the presence of heparin octasaccharide bound to site I. The horizontal axis is the simulation time, and the vertical axis indicates the amino acid position in the RBD domain. Different secondary structure elements like random coil, parallel and antiparallel β sheets, 310 and α-helices, bends and turns are represented by eight types of colours. Conformational changes are mostly observed in the helical and bend regions. DSSP, Define Secondary Structure of Proteins; MD, molecular dynamics; RBD, receptor-binding domain.



Supplementary Fig. S4 MM/GBSA-binding free-energy decomposition per residue (Δ*G* kcal/mol) for heparin hexasaccharide–RBD interaction (site III) and octasaccharide–RBD interaction (site I). Standard deviations are not shown for clarity. The decomposition approach was helpful for locating residues that contribute to the spike RBD–heparin interaction. RBD, receptor-binding domain.