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Supplementary Materials for

Atomic-scale characterization of mature HIV-1 capsid stabilization by inositol hexakisphosphate (IP_6)

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The PDF file includes:

Other Supplementary Material for this manuscript includes the following:

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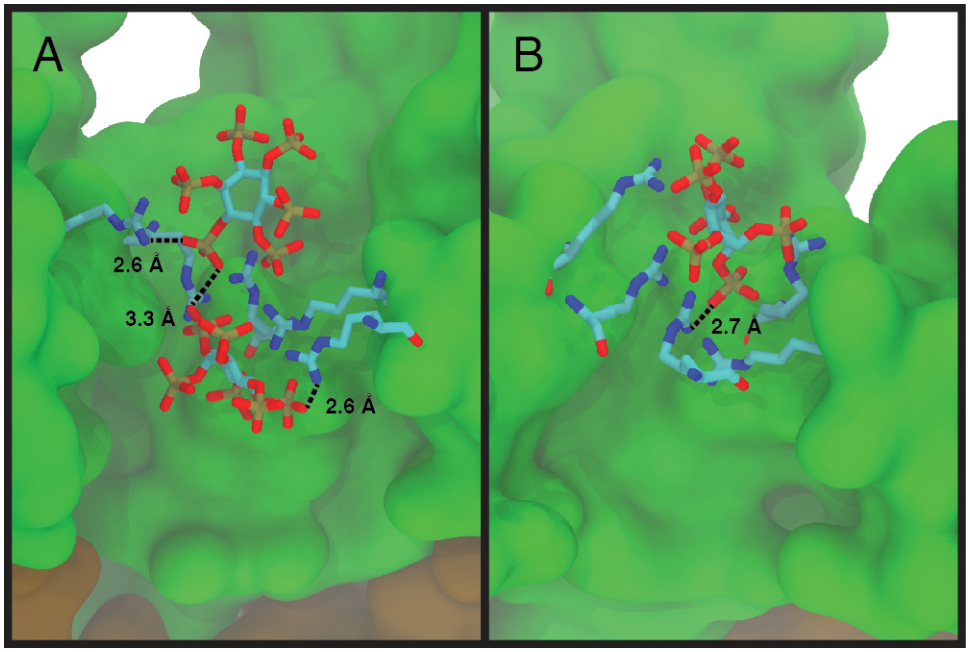

Figure S1: Molecular rendering of CA-IP_6 bound complexes. (A) Snapshot of two IP_6 molecules bound to the CA hexamer during the all-atom molecular dynamics simulations, with 5 of the 6 R18 side chains rendered. 1 of the 6 R18 side chains is not shown for clarity. The closest distance between the two IP_6 molecules is drawn as a black dotted line (3.3 Å), and the two closest distances between IP_6 atoms and R18 atoms is drawn as a black dotted line (2.6 Å). Shape complementarity between IP_6 and CA reflects a ligand contact area of 417 $Å^2$ and 567 $Å^2$ for the IP_6 molecules above and below the R18 ring, respectively. Protein-ligand contacts generally consist of interactions between oxygen atoms of IP_6 phosphates and nitrogen atoms of the R18 sidechain. (B) Snapshot of the IP_6 molecule bound to the CA pentamer during the all-atom molecular dynamics simulations with all 5 R18 side chains rendered. The closest distance between the IP_6 molecule and the R18 side chain is drawn as a black dotted line (2.7 Å). Shape complementarity between IP_6 and CA reflects a contact area of 603 $Å^2$. Protein-ligand contacts generally consist of interactions between oxygen atoms of IP_6 phosphates and nitrogen atoms of the R18 sidechain. The NTD of the CA complex is depicted in surface representation in green, whereas the CTD of the CA complex is depicted in surface representation in brown.

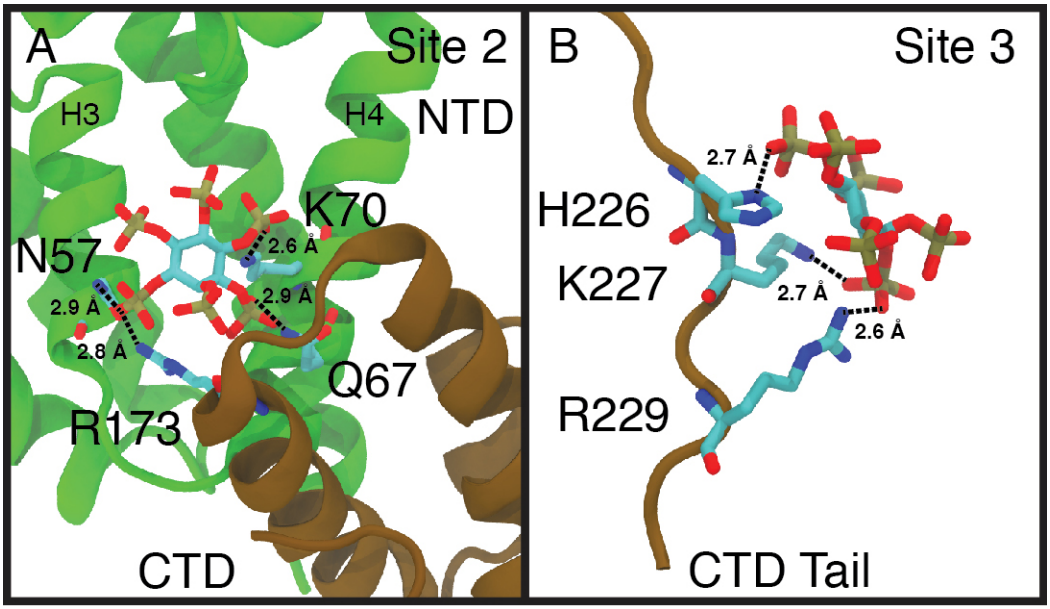

Figure S2: Weaker affinity CA-IP_6 interactions at Site 2 and Site 3. (A) Conformation of the IP_6 molecule bound to CA at Site 2 between helices H3 and H4 during all-atom molecular dynamics simulations. Only the NTD of the CA domain and CTD of the adjacent CA domain are shown for clarity. Oxygen atoms of IP_6 phosphates coordinate the nitrogen atoms of N67, K70, Q67 of the NTD and R173 of the CTD with distances of 2.9, 2.6, 2.9, and 2.8 Å, respectively. Shape complementarity between IP_6 and CA reflects a ligand contact area of 696 $Å^2$. (B) Conformation of the IP_6 molecule interacting with the CA CTD tail during all-atom simulations. Oxygen atoms of IP_6 phosphate groups coordinate nitrogen atoms of residues H226, K227, and R229 with distances of 2.7, 2.7, and 2.6 Å, respectively. Shape complementarity between IP_6 and CA reflects a ligand contact area of 384 $Å^2$.

System	Conformation	H12	Time prior to IP_6 binding (μs)	Total Simulation Time (μs)
CA Hexamer	Open	protonated	0.072 [0.091]	4.0
CA Hexamer	Open	de-protonated	0.333 [0.440]	4.0
CA Hexamer	Closed	protonated	0.643 [0.739]	4.0
CA Hexamer	Closed	de-protonated	0.586 [1.040]	4.0
CA $Pentamer_m$	Open	protonated	0.292	5.0
CA $Pentamer_m$	Open	de-protonated	0.378	7.0
CA Pentamer	Closed	protonated	0.678	9.7
CA Pentamer	Closed	de-protonated	2.959	9.8

Table S1: All-atom MD simulations of IP_6 binding for each initial condition (hexamer/pentamer, open/closed conformation, protonated/de-protonated H12). The subscript $_m$ denotes that the β-hairpin was homology modeled from crystallographically open conformations of the CA hexamer (PDB ID: 5HGL). Square brackets denote the detection of a secondary IP_6 molecule binding to the R18 ring. General trends in the table suggest IP_6 binds quicker to open CA conformations with protonated H12 residues.

Movie S1: Dynamics of inositol hexakisphosphate (IP_6) binding to CA pentamers. Among 10 IP_6 ligands added to bulk solvent, only the ligand that eventually binds to the pore is shown for clarity. Three of the CA domains are rendered in a side view to delineate the pore. The CA system corresponds to the open pentamer with protonated H12 residues. Time points are relative to the start of the initial frame, and a portion of the complete trajectory (Table S1).

Movie S2: Dynamics of inositol hexakisphosphate (IP_6) binding to CA hexamers. Among 10 IP_6 ligands added to bulk solvent, only the two ligands that eventually bind to the pore are shown for clarity. Four of the CA domains are rendered in a side view to delineate the pore. The CA system corresponds to the open hexamer with protonated H12 residues. Time points are relative to the start of the initial frame, and a portion of the complete trajectory (Table S1).