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SUPPLEMENTARY MATERIAL

The SPL7013 Dendrimer Destabilizes the HIV-1 gp120-CD4 Complex

Bidisha Nandy[1,2,+], Suman Saurabh[1,+], Anil Kumar Sahoo[1], Narendra M. Dixit[3,4,*] and Prabal K. Maiti[1,*]

[1]Center for Condensed Matter Theory, Department of Physics, Indian Institute of Science, Bangalore

[2]Department of Physics, Lovely Professional University, Punjab

[3]Department of Chemical Engineering, and [4]Centre for Biosystems Science and Engineering, Indian Institute of Science, Bangalore

[+]Equal contribution

[*]Correspondence: narendra@chemeng.iisc.ernet.in; maiti@physics.iisc.ernet.in

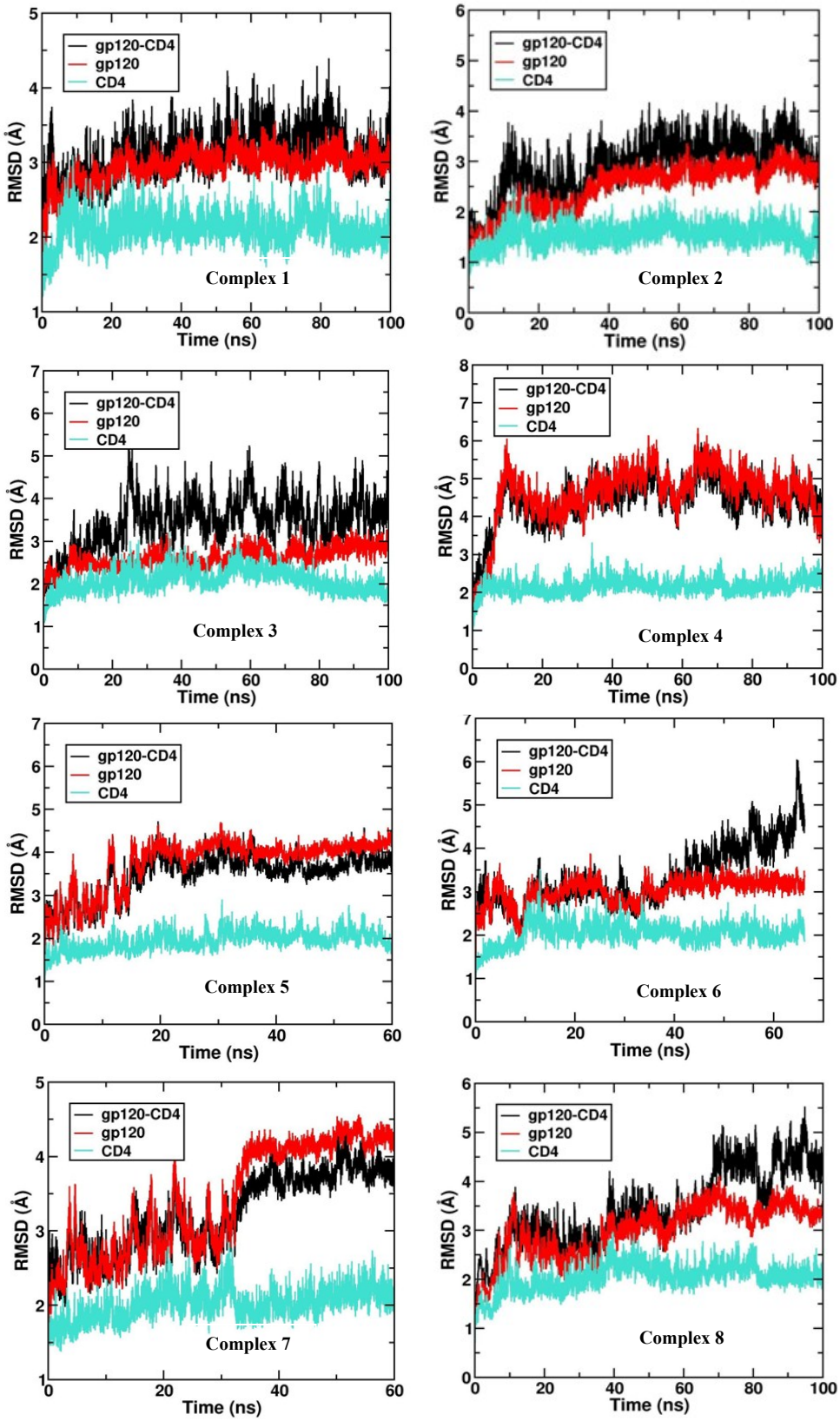

Figure S1. MD simulations of docked structures. The RMSD of gp120, CD4, and the gp120-CD4 complex in the ternary complexes 1 to 8 with respect to their initial configurations, determined using MD simulations.

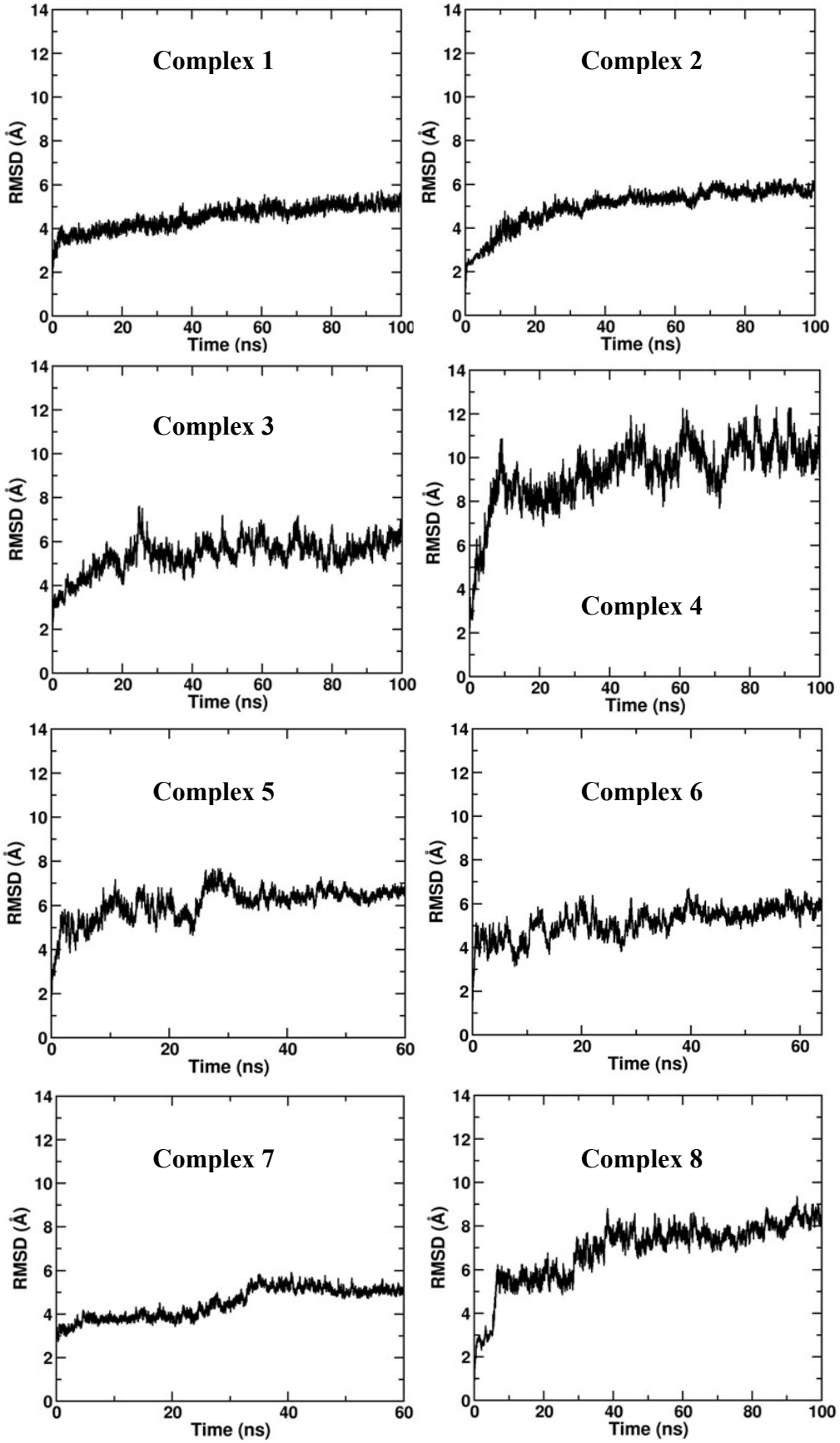

Figure S2. Stability of ternary complexes. RMSD of various ternary complexes with respect to their energy minimized structures.

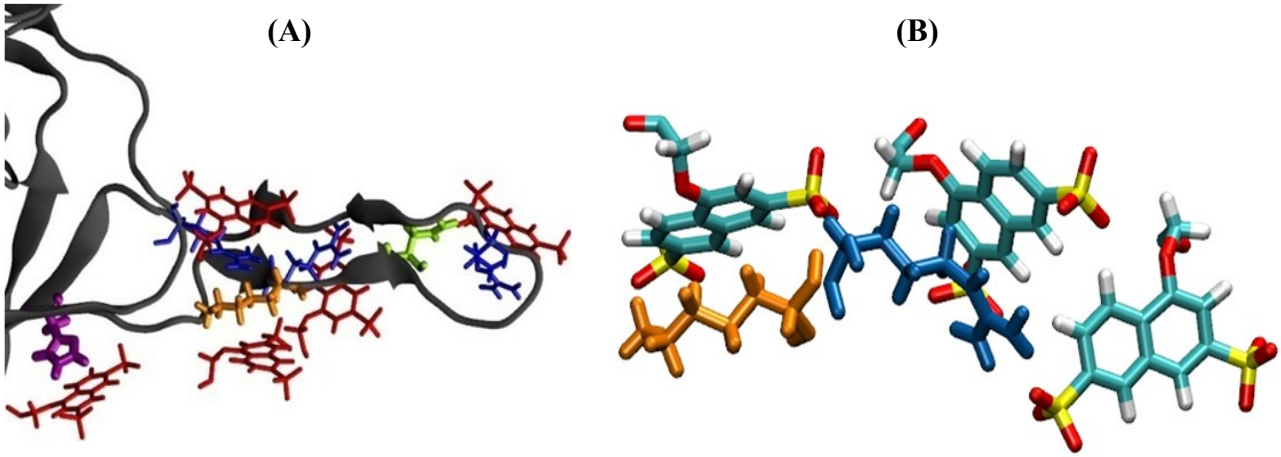

Figure S3. Dendrimer aromatic groups stack on protein residues. (A) Positively charged residues (blue: ARG; orange: LYS) interacting with the aromatic rings of the terminal groups of the SPL dendrimer. **(B)** A close-up view of the interaction. The positively charged residues stack over the aromatic rings providing electrostatic and hydrophobic stability.

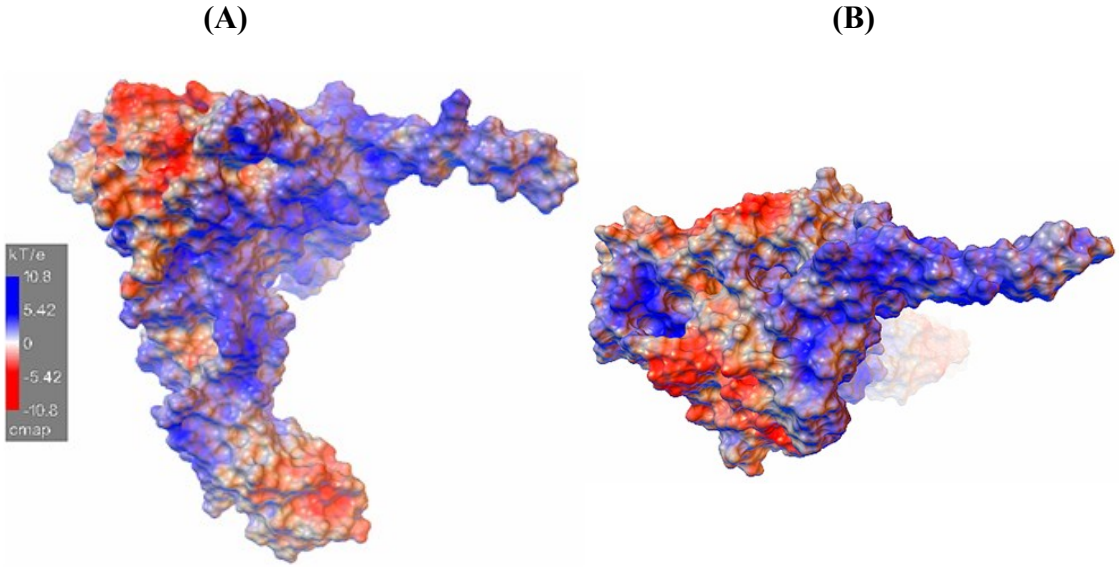

Figure S4. Electrostatic map of the gp120-CD4 surface. (A) Side-view and **(B)** Top-view. Blue corresponds to positive and red to negative electrostatic potential. The V3 loop is strongly positively charged and hence is a preferred binding region for the negatively charged SPL dendrimer.

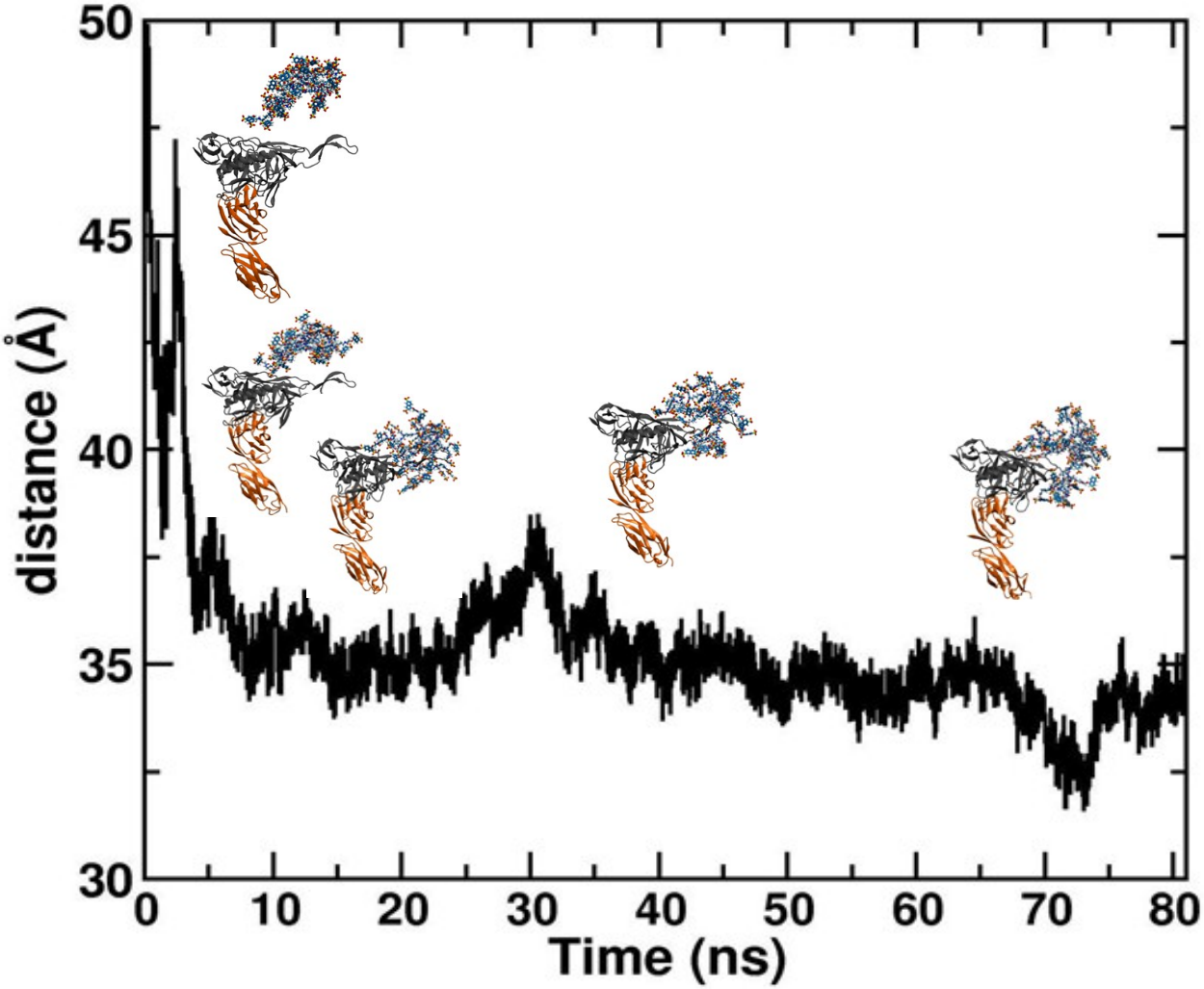

Figure S5. Dendrimer motion towards the gp120-CD4 complex. Time evolution of the distance between gp120 and dendrimer, initially placed 50 Å apart along with snapshots at various times. The dendrimer approaches gp120 and attaches itself to the V3 loop.

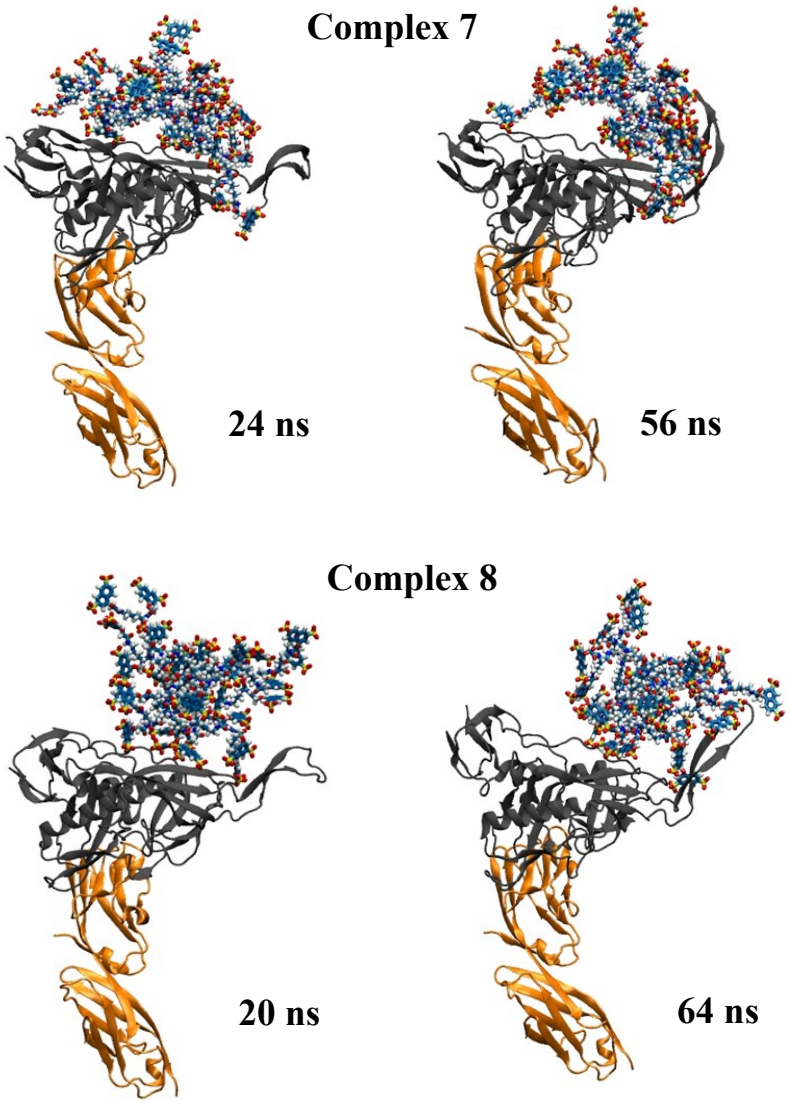

Figure S6. Large amplitude motion of the dendrimer. Snapshots demonstrating large amplitude motion of SPL dendrimer towards the V3 loop in the cases of complex 7 and complex 8.

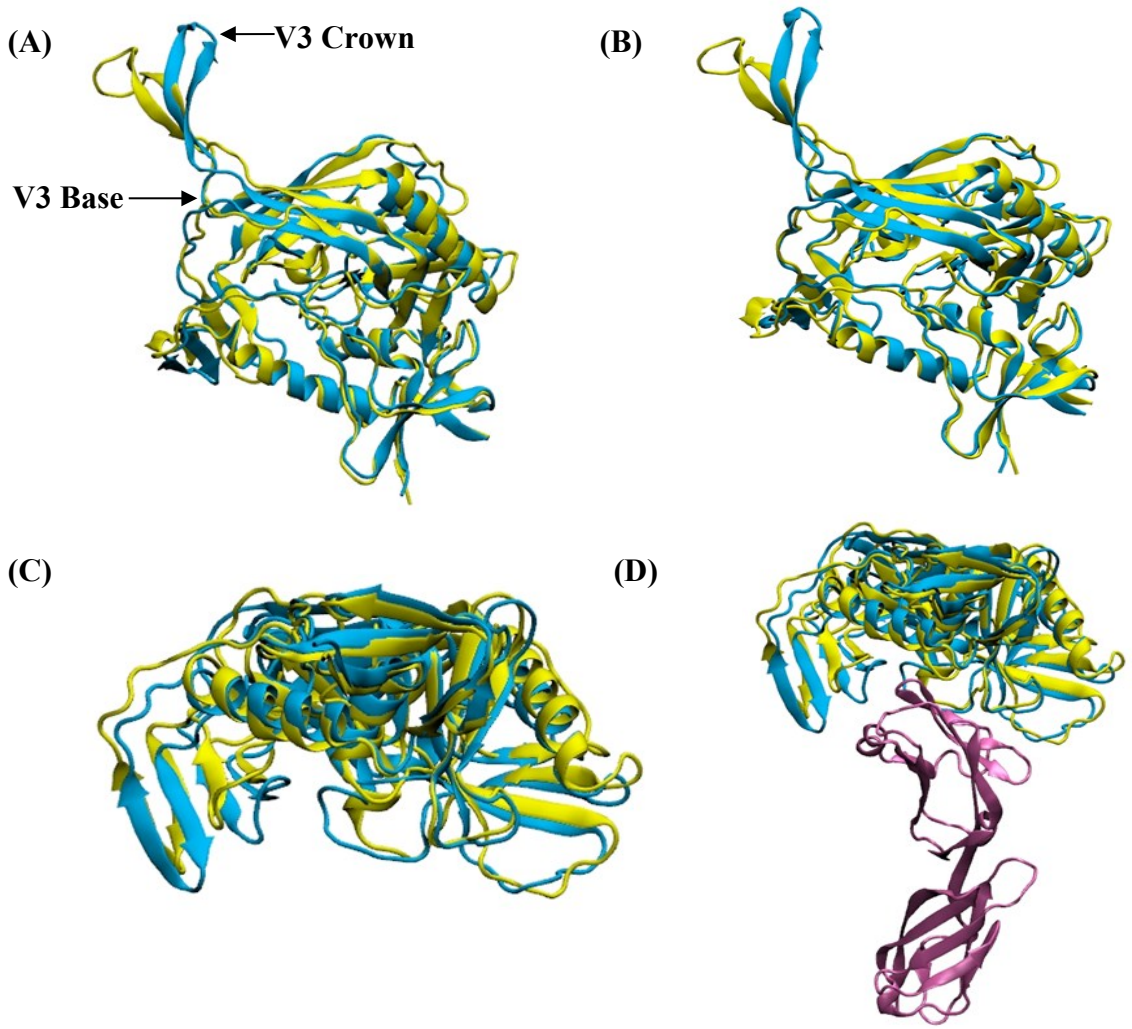

Figure S7. Comparison between the conformations of gp120 in the presence and absence of CD4. (A) gp120 in the presence of CD4 (blue), averaged over 4 ns of MD and aligned with the corresponding structure without CD4 (yellow). **(B)** gp120 in the presence of CD4 averaged over 4 ns of MD, aligned (with V3 loop excluded from alignment) with the corresponding structure without CD4. **(C)** The difference in the loop regions in the presence and absence of CD4. **(D)** The difference in the loop regions must be induced by the presence of CD4 which makes the loops extend towards the CD4 binding region. (CD4 is shown in maroon.) The RMSD between gp120 with and without CD4 is 3.3 Å, whereas the RMSD between the two V3 loops is 8 Å, indicating that the structures are quite different.

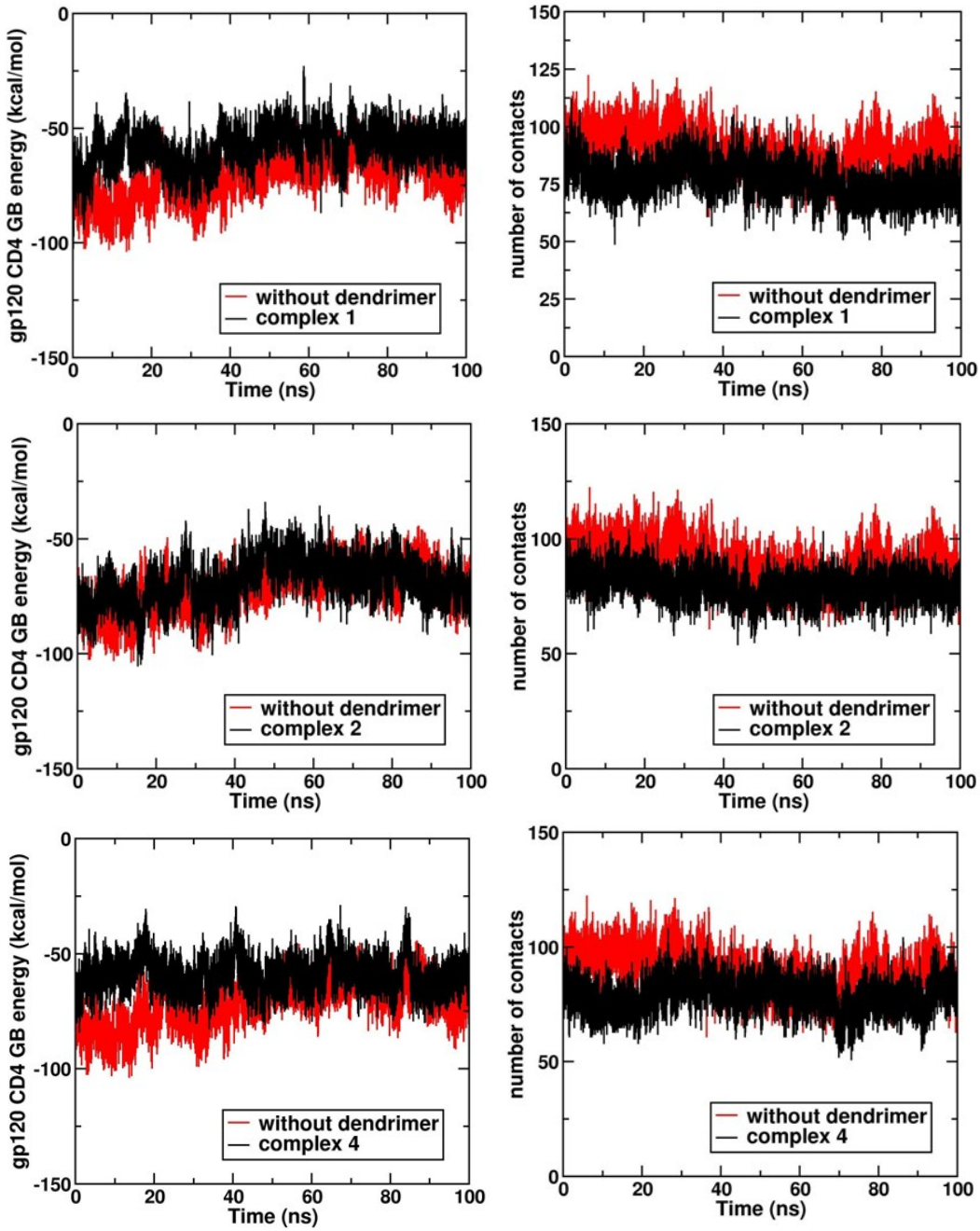

Figure S8. SPL7013 weakens the gp120-CD4 complex. Binding energy and number of contacts between gp120 and CD4 for complexes 1, 2 and 4 compared with those of the gp120-CD4 complex without the dendrimer.

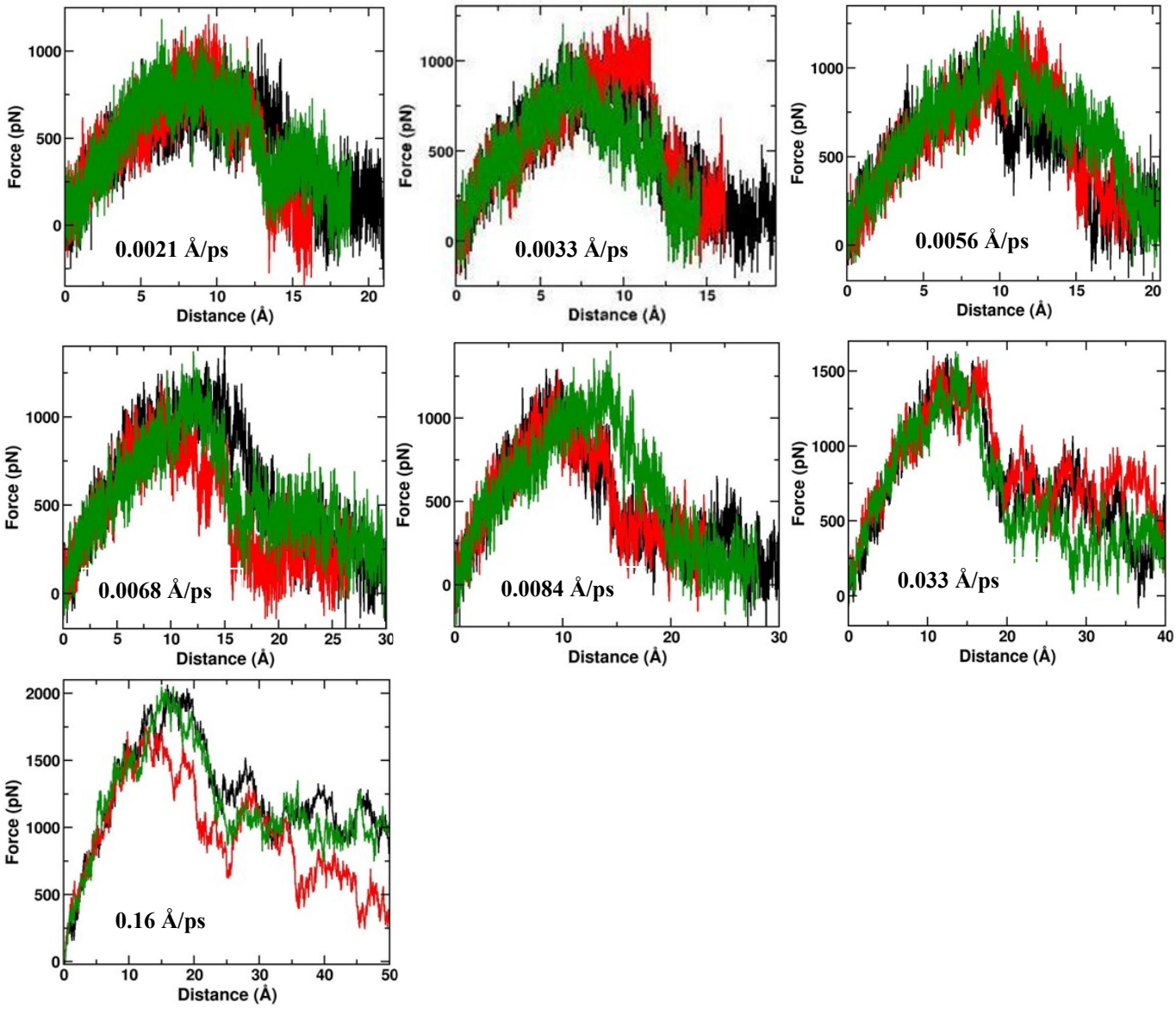

Figure S9. Force versus distance curves in the absence of the dendrimer. Force versus distance curves at different pulling velocities (different panels) for three realizations (different colours) at each velocity.

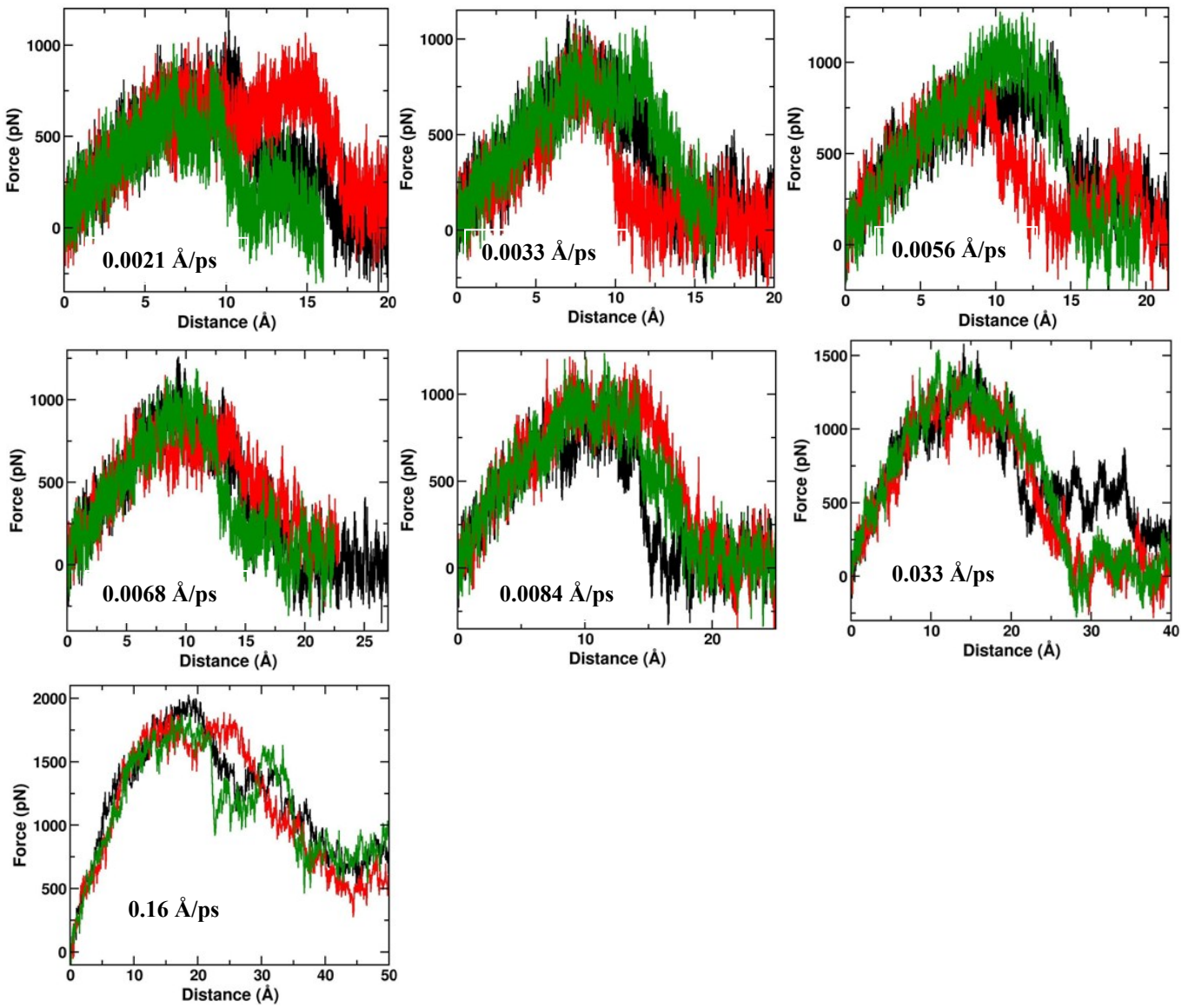

Figure S10. Force versus distance curves for complex 1. Force versus distance curves at different pulling velocities (different panels) for three realizations (different colours) at each velocity.

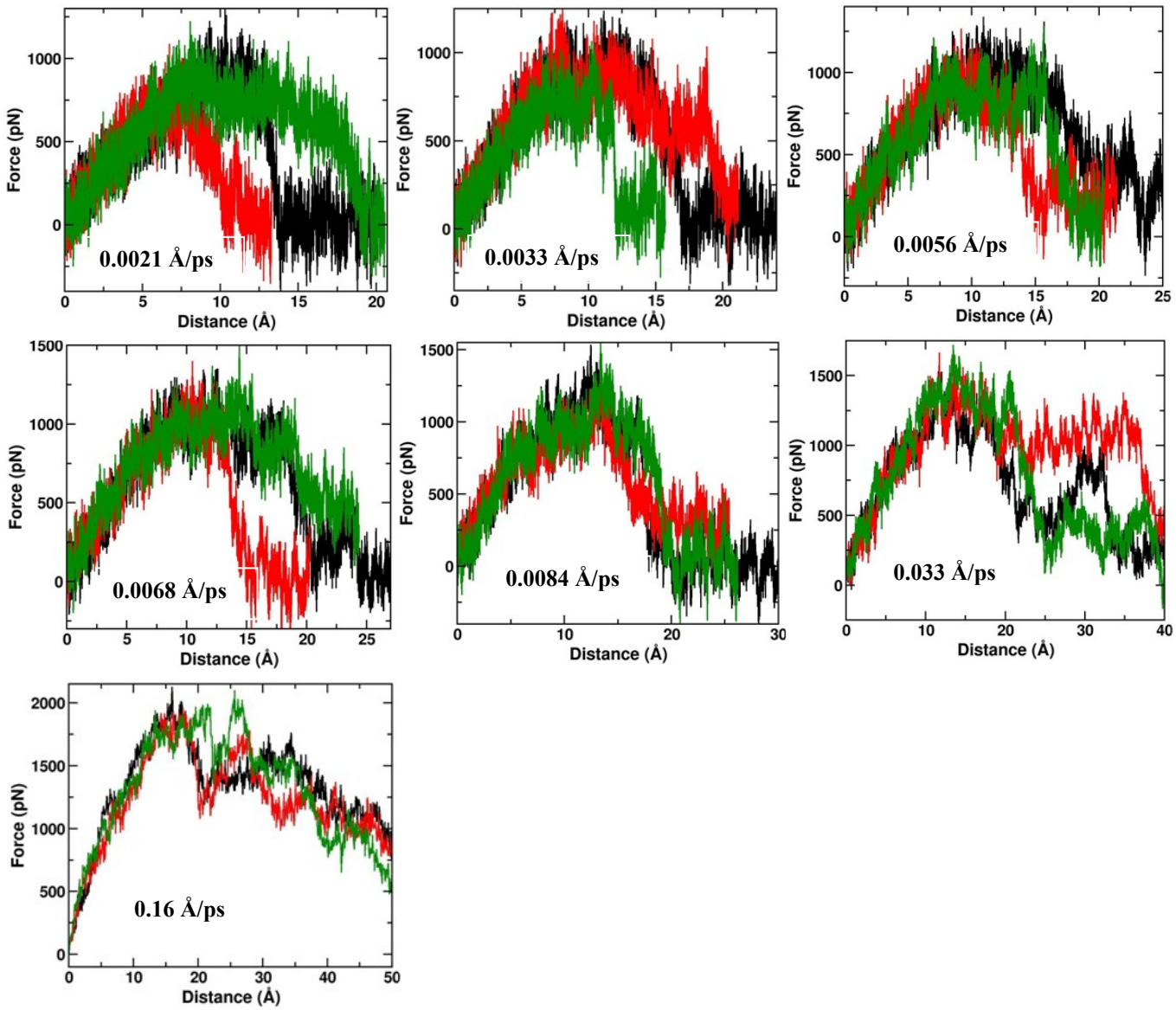

Figure S11. Force versus distance curves for complex 2. Force versus distance curves at different pulling velocities (different panels) for three realizations (different colours) at each velocity.

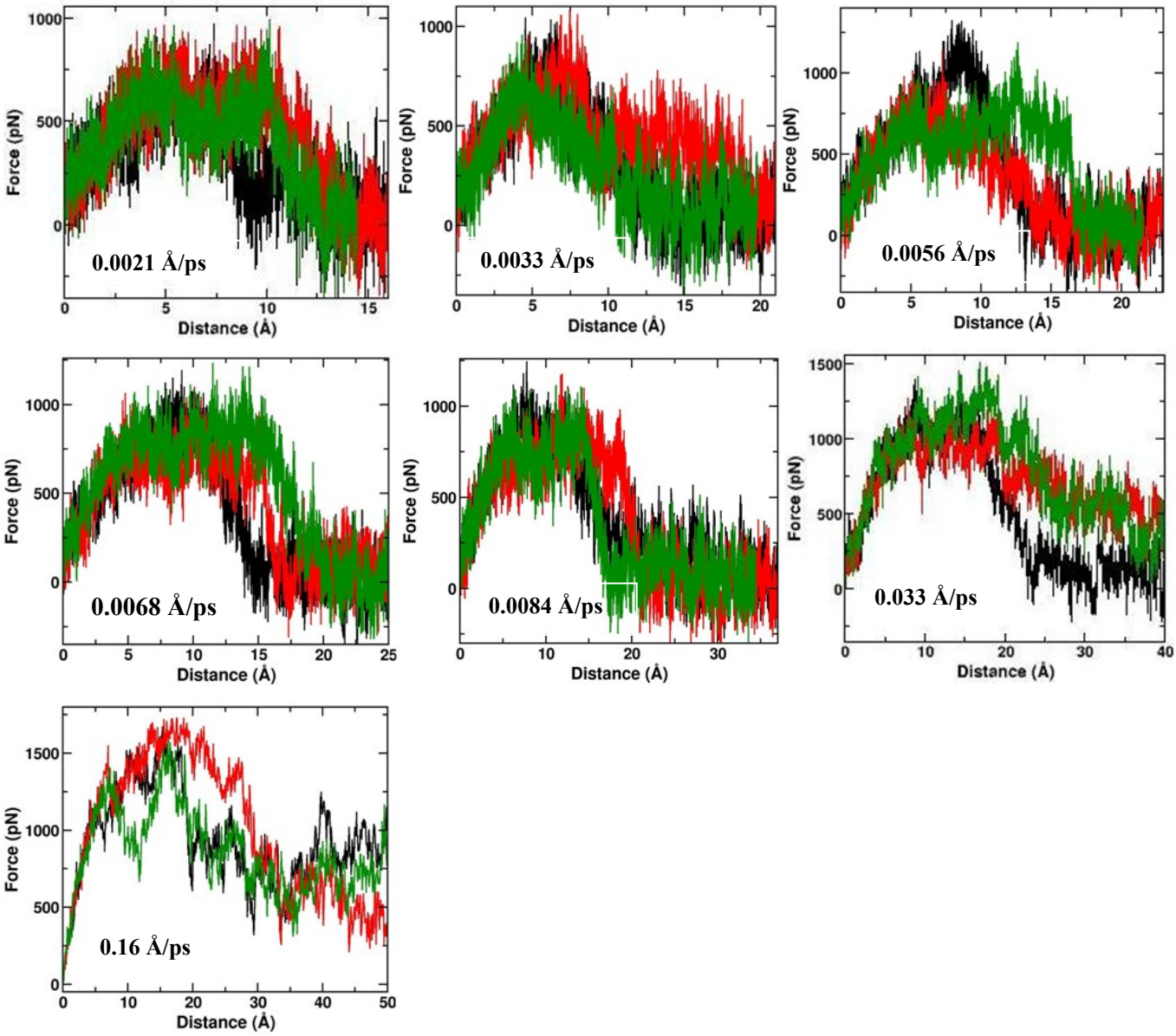

Figure S12. Force versus distance curves for complex 3. Force versus distance curves at different pulling velocities (different panels) for three realizations (different colours) at each velocity.

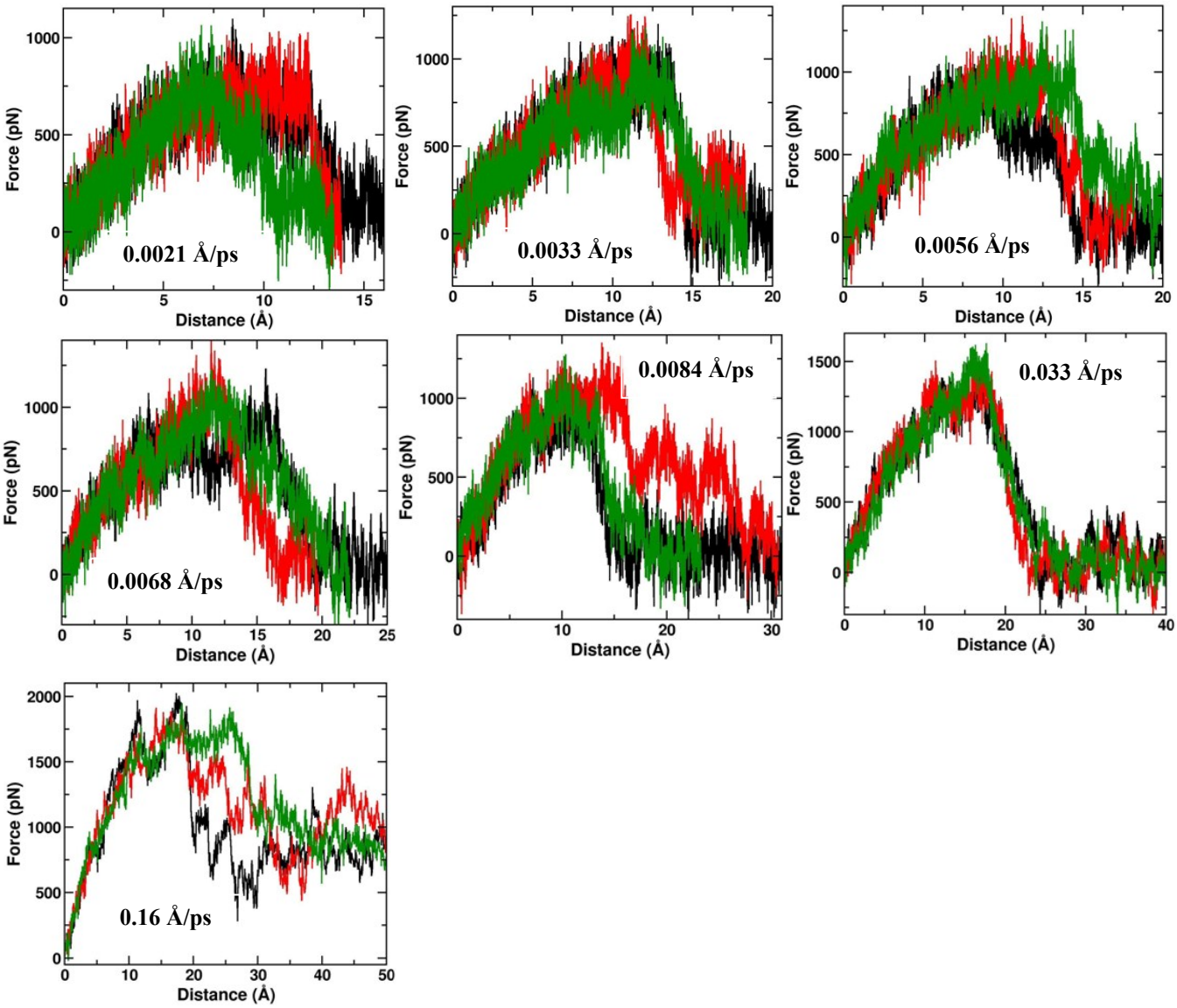

Figure S13. Force versus distance curves for complex 4. Force versus distance curves at different pulling velocities (different panels) for three realizations (different colours) at each velocity.

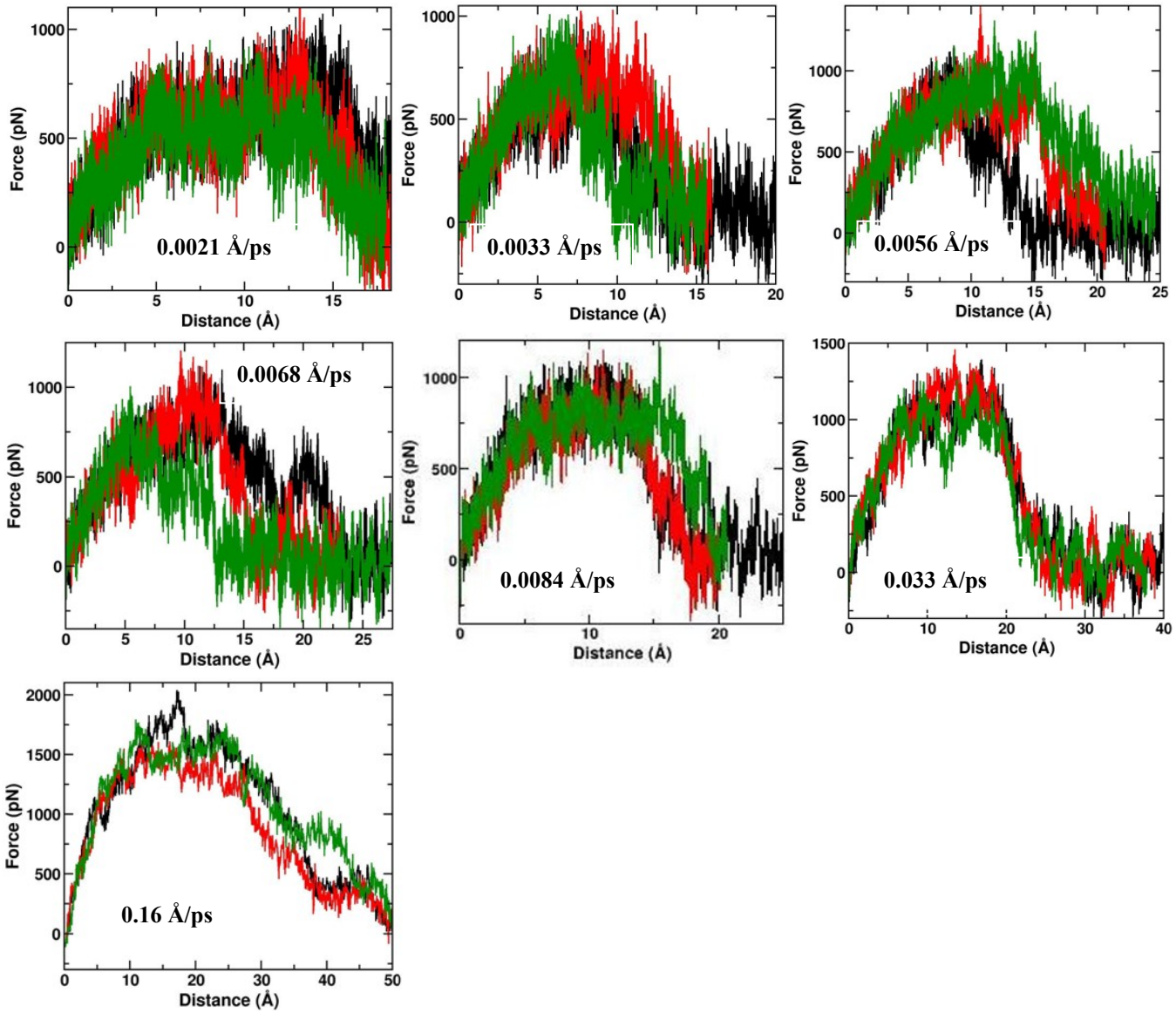

Figure S14. Force versus distance curves for complex 8. Force versus distance curves at different pulling velocities (different panels) for three realizations (different colours) at each velocity.

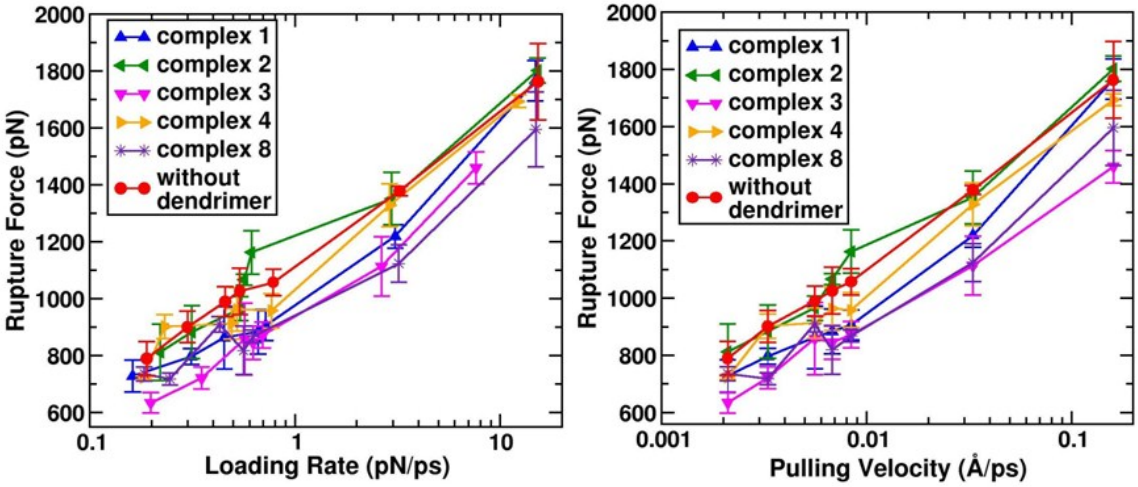

Figure S15. SPL7013 lowers the rupture force of the gp120-CD4 complex. Rupture force as a function of loading rate and pulling velocity for various ternary complexes compared to that for the binary protein complex without the dendrimer.

Table S1: GAFF atom types and RESP charges for the de-capped residues forming the SPL dendrimer.

ATOM S. no.	aaa (Core)		bbb (Branching unit)		ccc (Terminal)	
	ATOM NAME	**CHARGE**	**ATOM NAME**	**CHARGE**	**ATOM NAME**	**CHARGE**
1	**c3**	0.00988	**c3**	0.00988	**ca**	-0.09462
2	**h1**	0.073488	**h1**	0.073488	**ca**	-0.37204
3	**c3**	0.024934	**c3**	0.024934	**ca**	0.190216
4	**C**	0.544235	**c**	0.544235	**ca**	0.05548
5	**Hc**	-0.004064	**hc**	-0.004064	**ca**	-0.107086
6	**Hc**	-0.004064	**hc**	-0.004064	**ca**	-0.093372
7	**c3**	-0.010071	**c3**	-0.010071	**ha**	0.136291
8	**O**	-0.552841	**o**	-0.552841	**ha**	0.189820
9	**Hc**	0.021252	**hc**	0.021252	**ca**	0.104162
10	**Hc**	0.021252	**hc**	0.021252	**ca**	-0.241275
11	**c3**	-0.018747	**c3**	-0.018747	**ha**	0.140089
12	**Hc**	0.042172	**hc**	0.042172	**ca**	-0.163122
13	**Hc**	0.042172	**hc**	0.042172	**ca**	-0.096968
14	**c3**	-0.043216	**c3**	-0.043216	**ha**	0.202363
15	**h1**	0.088912	**h1**	0.088912	**ha**	0.126635
16	**h1**	0.088912	**h1**	0.088912	**s6**	1.327313
17	**N**	-0.527189	**n**	-0.527189	**s6**	1.362443
18	**Hn**	0.331003	**hn**	0.331003	**o**	-0.744329
19	**N**	-0.402096	**n**	-0.402096	**o**	-0.744329
20	**Hn**	0.274077	**hn**	0.274077	**o**	-0.744329
21	**--**	--	**--**	--	**o**	-0.741481
22	**--**	--	**--**	--	**o**	-0.741481
23	**--**	--	**--**	--	**o**	-0.741481
24	**--**	--	**--**	--	**os**	-0.337101
25	**--**	--	**--**	--	**c3**	-0.132460
26	**--**	--	**--**	--	**h1**	0.128842
27	**--**	--	**--**	--	**h1**	0.128842
28	**--**	--	**--**	--	**c**	0.677961
29	**--**	--	**--**	--	**o**	-0.674984

Table S2: Details of the system sizes employed in our simulations. The complexes are indicated by their ranks based on ΔG of dendrimer binding. The ZDOCK rankings are indicated inside the brackets.

Complex	System size (no. of atoms)	Box dimensions
1	303953	152Å × 122Å × 168Å
2	304175	125Å × 149Å × 168Å
3	286376	132Å × 147Å × 153Å
4	371312	140Å × 161Å × 169Å
5	340433	126Å × 144Å × 193Å
6	281900	129Å × 148Å × 151Å
7	313187	149Å × 125Å × 172Å
8	325190	122Å × 149Å × 184Å

Table S3. **Break-up of the dendrimer-protein binding energies**. The energy contributions are the sum over the contributions from each individual residue of gp120 that forms atomic contacts with the dendrimer. A total of 40 gp120 residues for complex 1 and 36 gp120 residues for complex 3 formed atomic contacts with the dendrimer. We obtained the residue-wise energy contributions of these residues towards van der Waals, electrostatic, polar solvation and non-polar solvation energies.

Complex	vdW (kcal/mol)	Electrostatic (kcal/mol)	Polar solvation (kcal/mol)	Non-polar solvation (kcal/mol)
Complex 1	-66.4	-3684.8	3614.5	-13.1
Complex 3	-66.2	-3022.0	2977.2	-10.8

Table S4. Top 8 docking positions (ZDOCK rankings) corresponding to various dendrimer structures. The complexes selected for further MD simulation and energy calculations are indicated (*).

Complex	Docking position				
	68ns	**72ns**	**76ns**	**78ns**	**80ns**
1	Near α1 helix	Hanging on the V3 loop and touching the bridging sheet	Hanging on the V3 loop and touching the bridging sheet*	Hanging on the V3 loop and touching the bridging sheet	Hanging on the V3 loop and touching the bridging sheet
2	V3 loop*	On top of gp120	Near α1 helix	Near α1 helix	V3 loop
3	Near α1 helix	Towards inner domain	Near α1 helix	Near α1 helix	Hanging on the V3 loop and touching the bridging sheet
4	V3 loop	V3 loop	Near V3 loop	V3 loop	On top of gp120
5	On top of gp120	V3 loop*	CD4	Hanging on the V3 loop and touching the bridging sheet	Near α1 helix
6	Near V3 loop	Near α1 helix	Near α1 helix	V3 loop*	V3 loop
7	V3 loop	On top of gp120	Crown region of V3 loop	Hanging on the V3 loop	On top of gp120
8	Hanging on the bridging sheet	Hanging on the V3 loop and touching the bridging sheet	Towards inner domain	Hanging on the crown region of the V3 loop	V3 loop

Table S5. Dendrimer-gp120 binding-energy for the 4 complexes with different initial dendrimer conformations. The average dendrimer-gp120 binding energy over different dendrimer conformations (indicated in Table S4) is very close to the one for the 80 ns conformation.

No.	Dendrimer structure	Docking position	Binding Energy (kcal/mol)
1	68 ns	V3 loop (ZDOCK rank 2)	-139 ± 10
2	72 ns	V3 loop (ZDOCK rank 5)	-168 ± 12
3	76 ns	Hanging on the V3 loop and touching the bridging sheet (ZDOCK rank 1)	-168 ± 19
4	78 ns	V3 loop (ZDOCK rank 6)	-132 ± 9