Electronic Supplementary Material (ESI) for Nanoscale.

Supporting Information: Citrate stabilized Gold Nanoparticles interfere with Amyloid Fibril formation: D76N and $\triangle$N6 β2-microglobulin Variants

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MD Refinement of Dimers in Solution

Starting with the most representatives dimeric complexes obtained from rigid-body BD docking, the stability of the dimeric interface is examined by using 400 ns of standard MD simulations in solution. The simulation time was effective in sampling different orientations and positions of the two monomers with respect to each other. Simulations are repeated four times using a different seed for the initial velocity distribution (d1, d2, d3, d4) for each system to improve the statistics of the search of the energy minima on the Potential Energy Surface.

The results are summarized in Tab. S1. A detailed discussion of the MD refinement is presented below.

From Tab. S1, the four independent MD runs revealed the propensity of the D76N dimeric complex A to evolve towards a more stable situation, in two cases over four. Such complex could in fact be easily converted into different dimeric complexes not identified from rigid docking. Better stability is found for the ΔN6 dimeric complex I, resulting to be stable in the initial orientation in three cases over four. This result partially reflects the fact that the population and stability of the encounter complexes crucially rely on the flexible conformation of the monomeric variants. Such conformation can be affected differently by the relaxation during MD refinement, as a function of the different involved modifications, i.e. mutation in the EF-loop for D76N and N-TER deletion for ΔN6, respectively.

Table S1: Orientations of D76N and ΔN6 dimers obtained following the refinement MD runs. A series of four indipendent simulations (400 ns at 300 K) were performed on the most representative protein-protein complex of the two variants, each with different initial velocities. The final global orientation of the systems after the simulation is reported. Nomenclature: "Zipped" refers to the formation of a "salt bridge zipper" between the two monomers due to the pivotal role of a number of conserved charged residues at the protein-protein interface

Complex Num	Init. Vel.	Global orientation	
D76N Dimer A	d1	converted to zipped	
D76N Dimer A	d2	converted to zipped	
D76N Dimer A	d3	stable	
D76N Dimer A	d4	stable	
ΔN6 Dimer I	d1	converted to zipped	
ΔN6 Dimer I	d2	stable	
ΔN6 Dimer I	d3	stable	
ΔN6 Dimer I	d4	stable	

Salt-bridges analysis

The interaction between D76N dimers and the cit-Au essentially brings about dimer detachment; cit-AuNP are shown to be able to break intersubunit salt-bridges which are observed to be stable during the same 20 ns of T-REMD in water Fig. S1 (a left). The glutamate residues are clearly essential for dimer formation, but it is difficult to explain how they could be controlled towards citAuNP interaction. Salt bridges which are broken during the T-REMD simulation of the D76N A-d1, zipped dimer, on cit-AuNP are GLU36-ARG97, GLU69-ARG97 and ASP59-LYS48. The dissociation between the proteins is mainly regulated by an inter-subunit salt bridge. The same trend of salt-bridge breaking is even more pronounced for D76N A-d4, unzipped dimer,on cit-AuNP were simulation are able to detect a clear protein-protein detachment i.e. the disruption of the very first step of aggregation Fig. S1 (a right). A similar but less pronounced trend is observed for ΔN6 dimers in Fig. S1 (b), even if the interaction occurs less efficiently, i.e. with reduced turnover frequency, with citAuNPs. A detailed description of the dimerization interface and the mechanism of interface formation in absence of the NP, will be expanded into an upcoming publication.

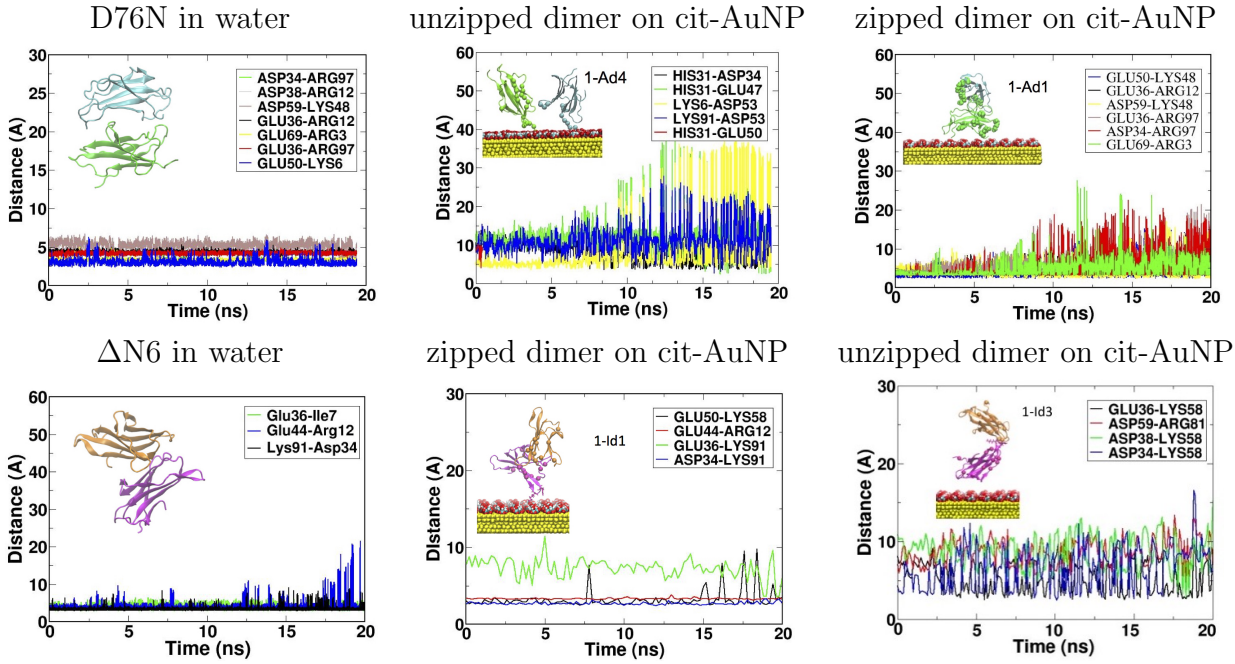

Figure S1: Analysis of the salt-bridges between the dimers in the absence and in the presence of citAuNPs. Inter monomers salt bridges are evaluated during the total 20 ns T-REMD on citAUNP for both D76N and ΔN6 more relevant and stable dimers. The effect of the interaction with the cit-AuNP is that of breaking some of the salt-bridges respect to the dimer in water solvent. the effect is more pronounced for D76N than ΔN6

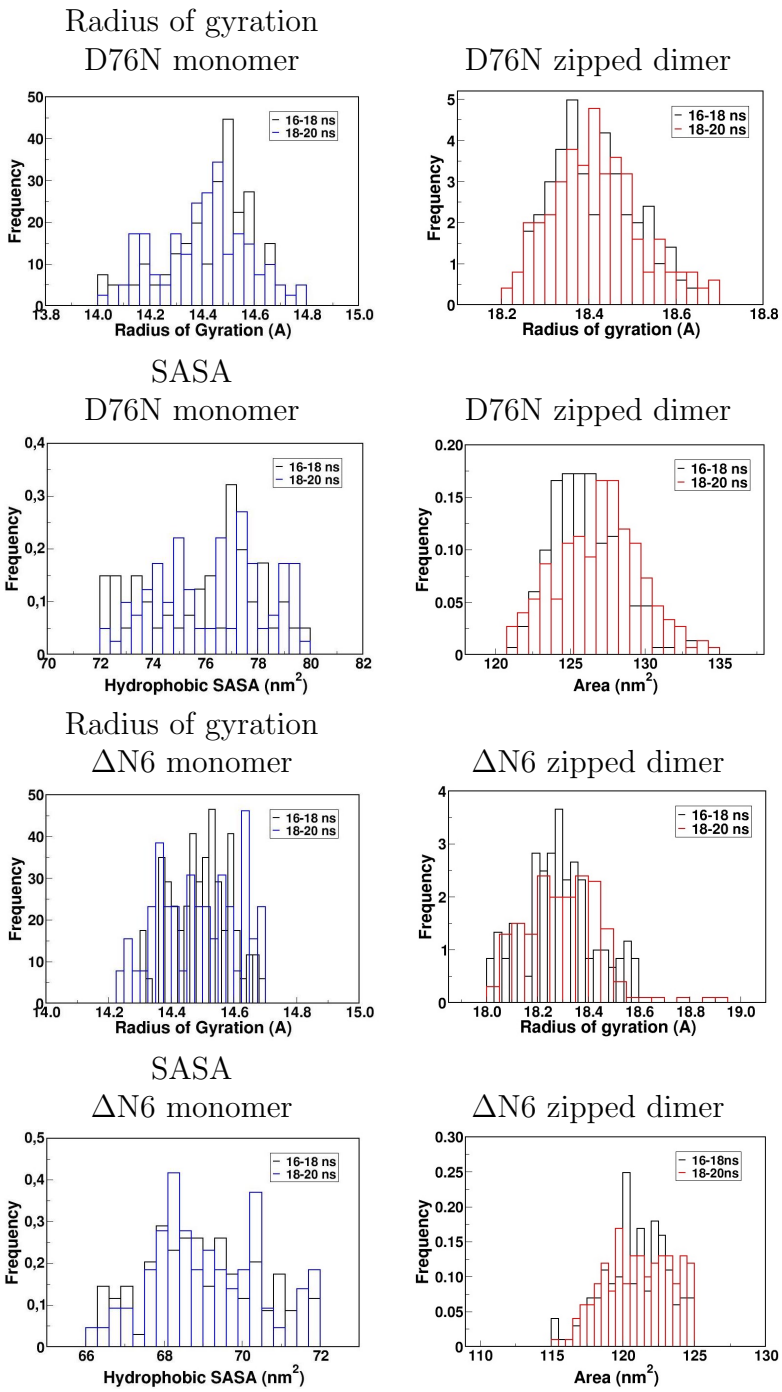

Figure S2: Analysis of the distribution of the radius of gyration and of the SASA for both D76N and DeltaN6 monomer/dimer, within two independent time windows. The data show that the distributions are very stable for both dimeric system on cit-AuNP validating the occuring convergence of the T-REMD simulations.

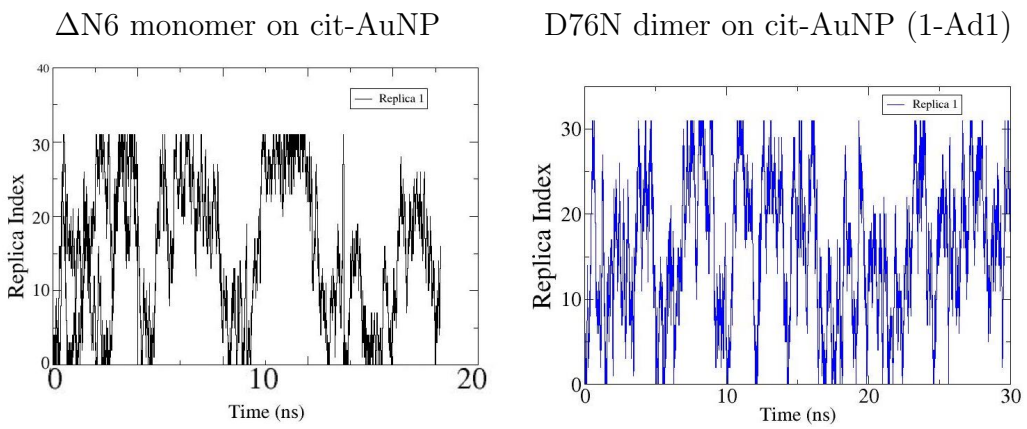

Figure S3: The time evolution of the replica 1 in temperature space for both ΔN6 monomer and D76N zipped dimer on citAUNP.