Supporting Information to the Manuscript "On the *cis* to *trans* Isomerization of Prolyl-Peptide Bonds under Tension"

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Methods

Our model system is the peptide Ala1-Ala2-Pro3-Ala4 (AAPA) in an initial type VIa β-turn conformation (shown schematically in Figure 1 of the main article). The tetrameric peptide was immersed within a cubic box of 2.5 nm side length with 479 TIP4P[1] water molecules with periodic boundary conditions applied. Free MD simulations of AAPA solvated in explicit water molecules were performed equilibrate the system. Classical MM MD simulations were performed with Gromacs 3.3.1[2] and the OPLS-AA force field,[3] the MD step size was 2 fs, bonds involving hydrogens were constrained by the LINCS algorithm.[4] The van der Waals interaction was counted within a cutoff value of 1.0 nm and the Particle-Mesh Ewald method was used to estimate the electronic interaction.[5] The simulations were carried out in a NPT ensemble coupling to a Nosé-Hoover thermostat[6,7] of 300 K and to a Parinello-Rahman barostat of 1 atm.[8] The initial system was prepared by performing a free MD simulation in equilibrium for 50 ns.

Force-clamp Molecular Dynamics simulations

External stretching force was applied to the C_α atoms of residues Ala1 and Ala4 (highlighted in Figure 1B of the main article). A series of force clamp MD (FCMD) simulations[9] has been performed with constant forces ranging from 0.1 nN to 3 nN, a list with all forces for which *cis* to *trans* isomerization occurred can be found in the Supporting Information Table S1. In the OPLS-AA force field (as implemented in Gromacs 3.3.1[2]) a pair of improper dihedrals, regarding the atoms of the peptide bond (C, O, N, H) and the flanking C_α, is dedicated to keeping the peptide bond planar. These constraints were not changed and collide with a correct description of a peptide bond isomerisation by MM.

Force-clamp QM/MM simulations

The combined QM/MM simulations under tension were performed with Gromacs-3.3.1[2] and Gaussian03.[10] As shown in Figure 1B of the main article, the tetrapeptide AAPA was divided into a QM

region and a MM region by cutting the carbon-carbon bonds, as the dashed line shows. The QM region has total 16 atoms and is simulated with B3LYP/6-31G* hybrid density-functional theory [11,12] as implemented in Gaussian03, the carbon carbon bonds connecting QM and MM part were capped with hydrogens on the QM side. [13] The QM part of the system was modeled under a Coulomb field of all MM atoms. The MM part of the tetrameric peptide and the water molecules were treated with the OPLS-AA force field and the TIP4p water model, respectively. The force-clamp QM/MM simulations have been carried out with constant forces from 2 nN to 5 nN with the integration step reduced to 1 fs.

Equilibrium MD simulation

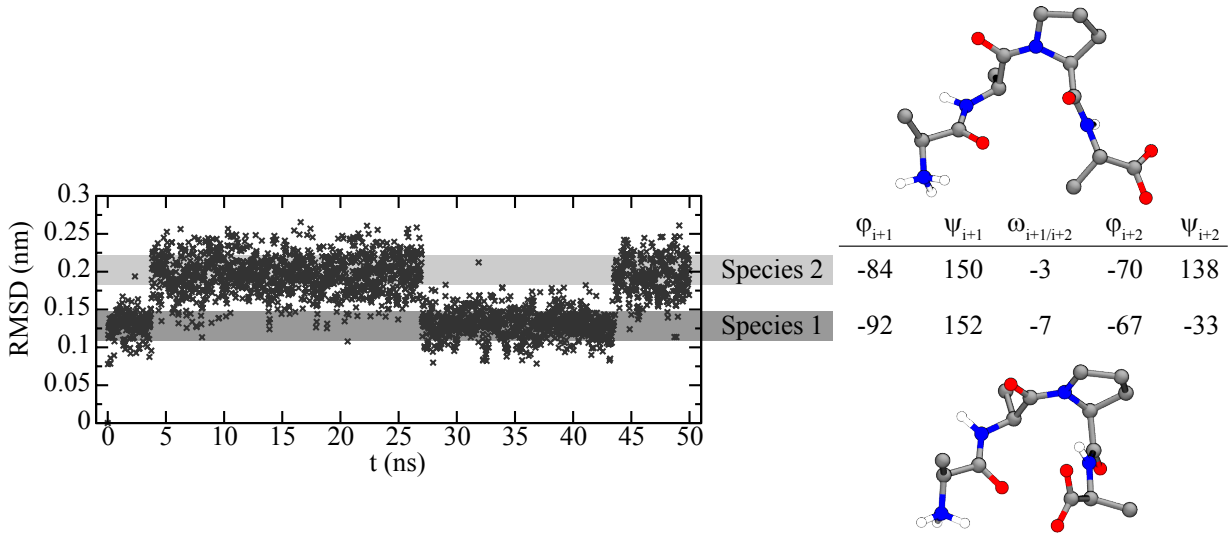

Figure 1: Pure MM equilibrium MD simulation of AAPA for 50ns, RMSD versus simulation time. Most conformations of the equilibrium trajectory can be assigned to one of two species shown here. Clustering and analysis of the representative structures revealed that both conformers are approximate βVI turns characterized by a *cis* peptide bond between Ala2 and Pro3, while a $i \leftarrow (i+3)$ hydrogen bond is not necessarily formed.

Life times

Table 1: Stretching forces and life times for the *cis* to *trans* isomerization to occur in pure MM FCMD simulations.

F (nN)	3	2.6	2.4	2.2	2	1.9	1.8	1.7	1.6	1.5	1.4	1.3	1.2	1.1
t (ps)	13	4	16	11	62	20	80	382	512	1233	3098	5144	7746	26170

Table 2: Stretching forces and 'waiting times' for the *cis* to *trans* isomerization to occur in QM/MM FCMD simulations.

F (nN)	5	4.3	4	3.9	3.8	3.7	3.65	3.4	3
t (ps)	0.58	0.78	1.25	0.93	2.63	10.2	0.78	7.39	364

Transition states

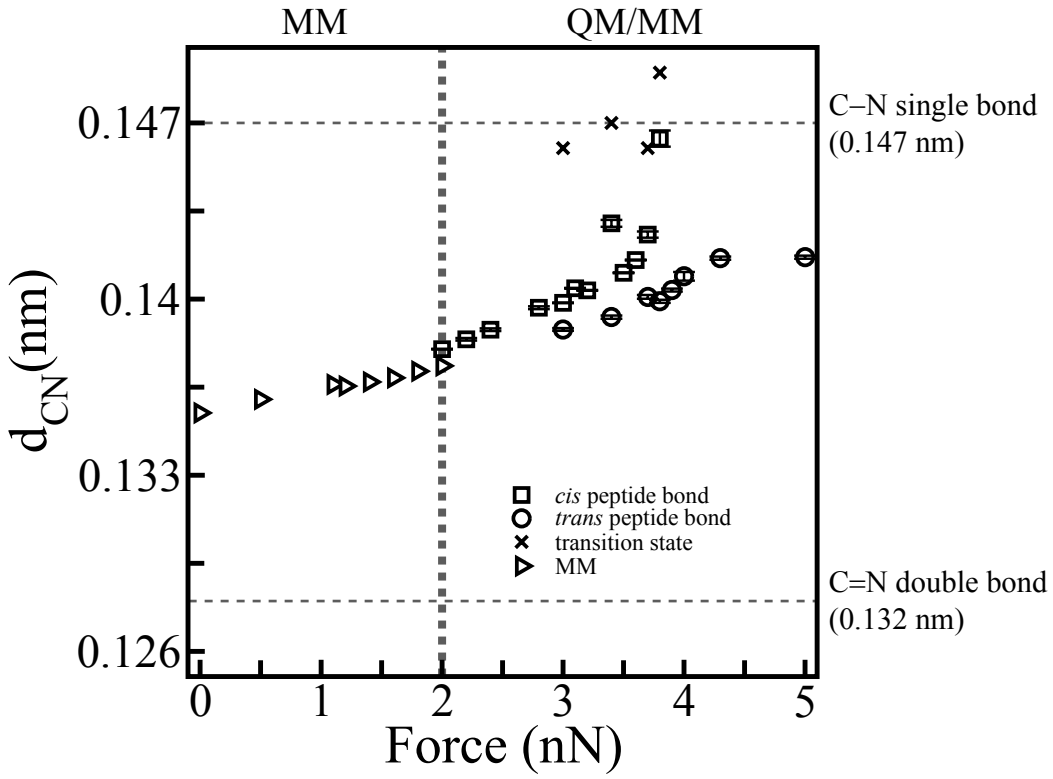

Figure 2: This plot summarizes the d_{CN} bond distances of the prolyl peptide bond in the *cis*, *trans*, and transition state over a range of applied forces. Standard values for C−N and C=N bonds at equilibrium are drawn as guide to the eye.

Order parameters studied by MM simulations

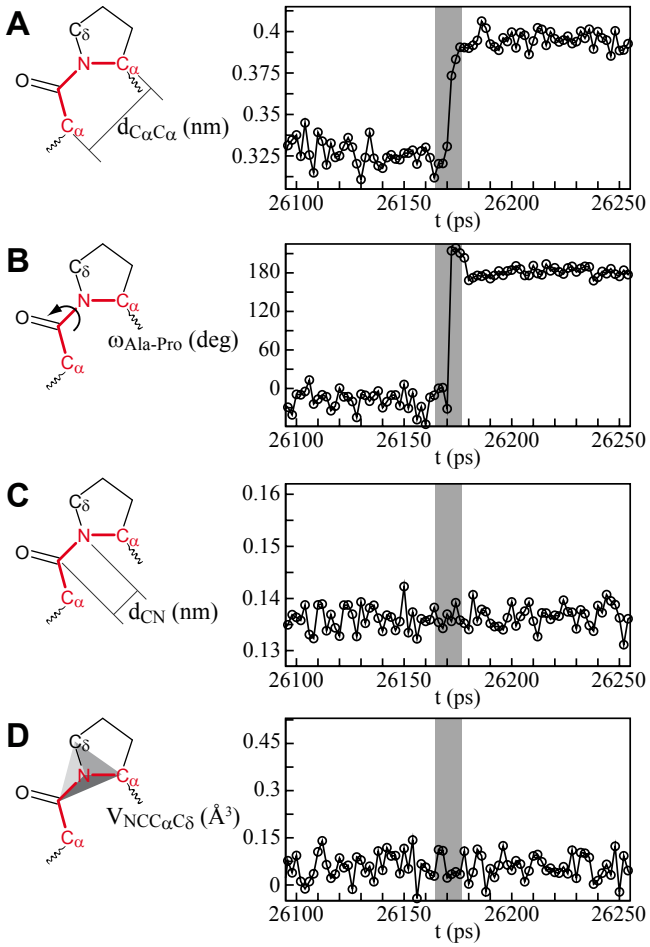

Figure 3: Order parameters of a pure MM FCMD simulation (F=1.1 nN) plotted with respect to simulation time: **A**: Distance of C_α atoms of Ala2 and Pro3 ($d_{C\alpha C\alpha}$); **B**: Torsion angle of the peptide bond between Ala2 and Pro3 ($\omega_{Ala-Pro}$); **C**: Length of the peptide bond between Ala2 and Pro3 (d_{CN}); **D**: Volume $V_{NCC\alpha C\delta}$ of the tetrahedron defined by the atoms C (of Ala2), N, C_α, and C_δ (of Pro3). The time range of the isomerization is highlighted by gray rectangles. The time range plotted here is similar (about 150 ps) as in the plots for the QM simulation (see Figure 2 in the manuscript), though less data points were collected per time in the significantly longer MM simulations at low force.

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