Supporting Information

Unraveling the impact of cyclic peptide primary structure on rotaxane formation through umbrella sampling molecular dynamics simulations

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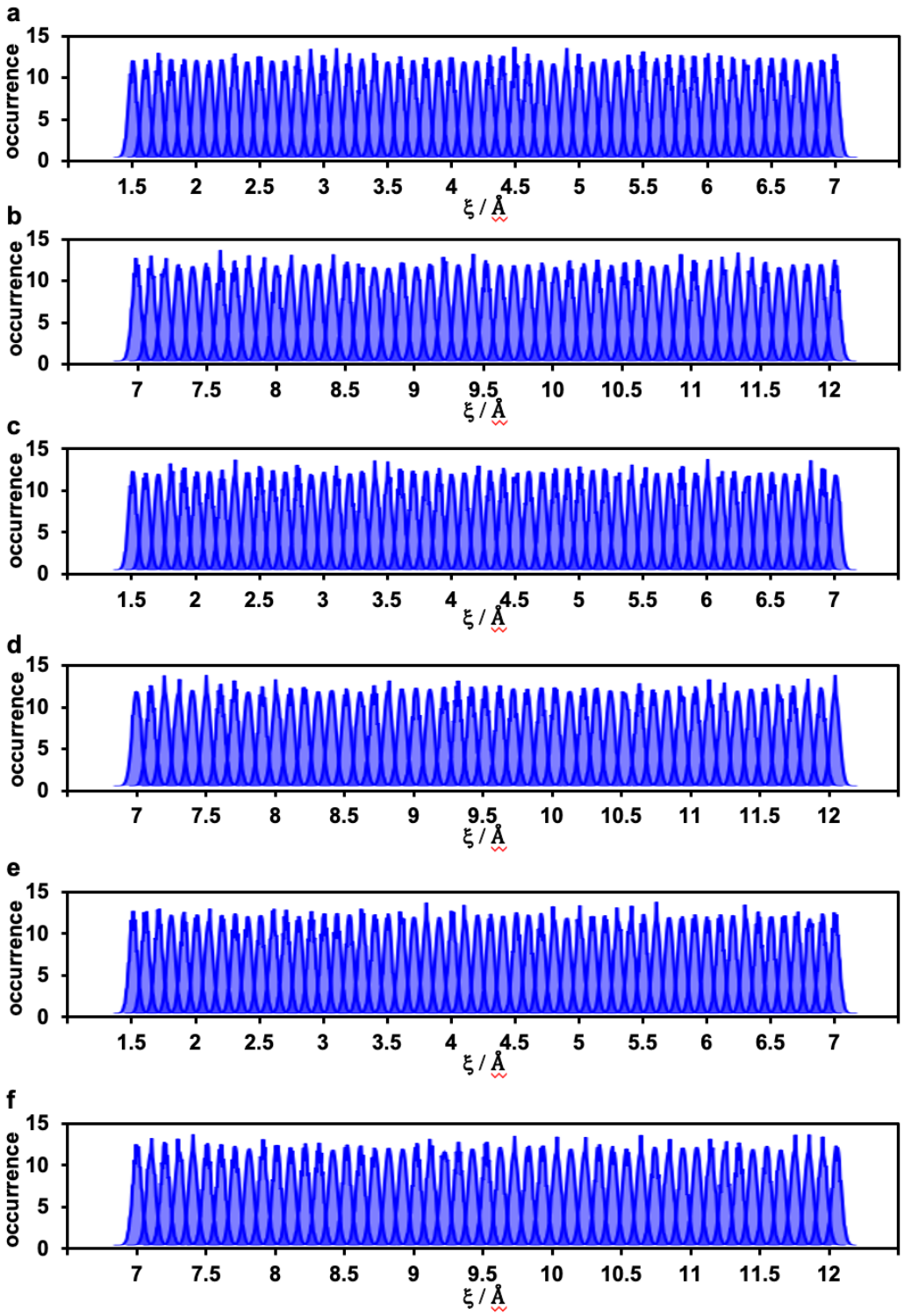

Fig. S1. Histogram from the umbrella sampling simulations of the rotaxane system, presented in two subpanels per system: (a, b) cyclo(PG)$_4$, (c, d) cyclo[(PG)$_3$PC(StBu)], and (e, f) cyclo[GC($\Psi^{Me,Me}$Pro)(GP)$_3$].

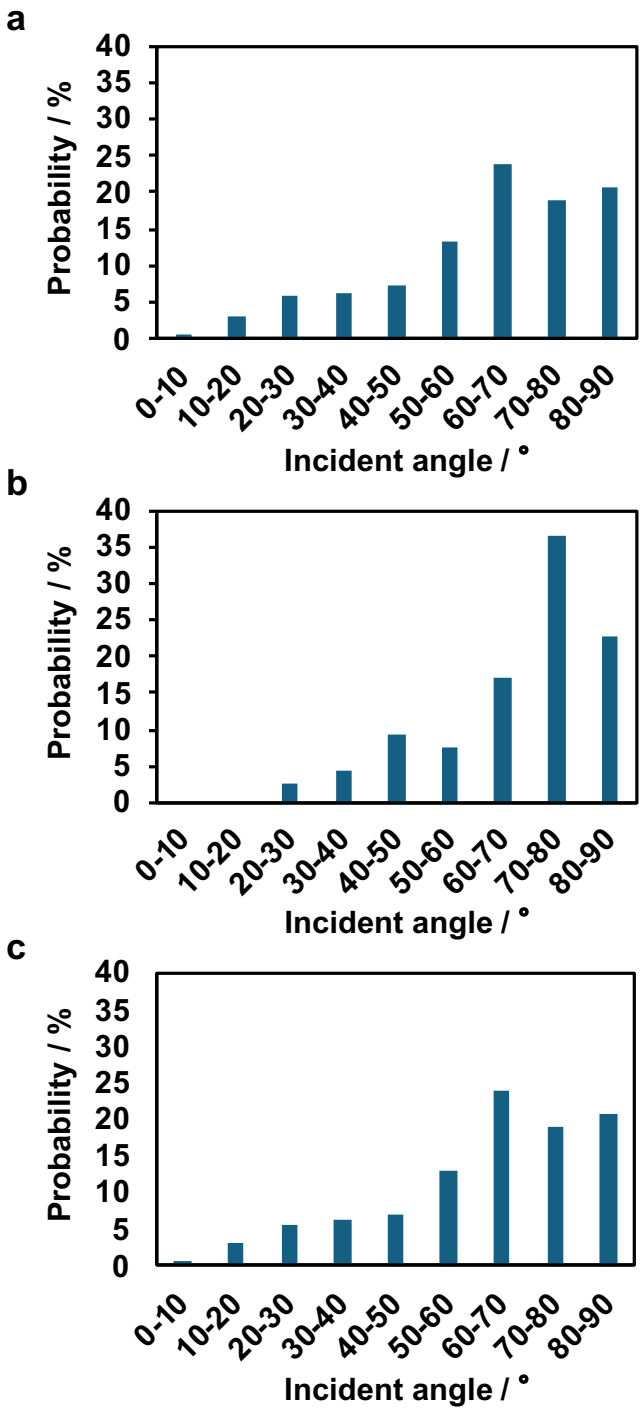

Fig. S2. Angular distributions of the incident angle in the pre-contact region for (a) cyclo(PG)$_4$, (b) cyclo[(PG)$_3$PC(StBu)], and (c) cyclo[GC($\Psi^{Me,Me}$Pro)(GP)$_3$].

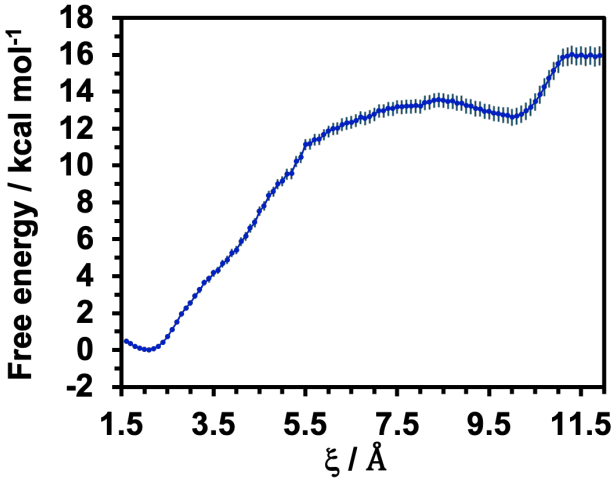

Fig. S3. Free energy profile for the rotaxane system composed of cyclo$(PG)_4$ and the thread using different initial structure from Fig 2. The vertical bars indicate the standard error.

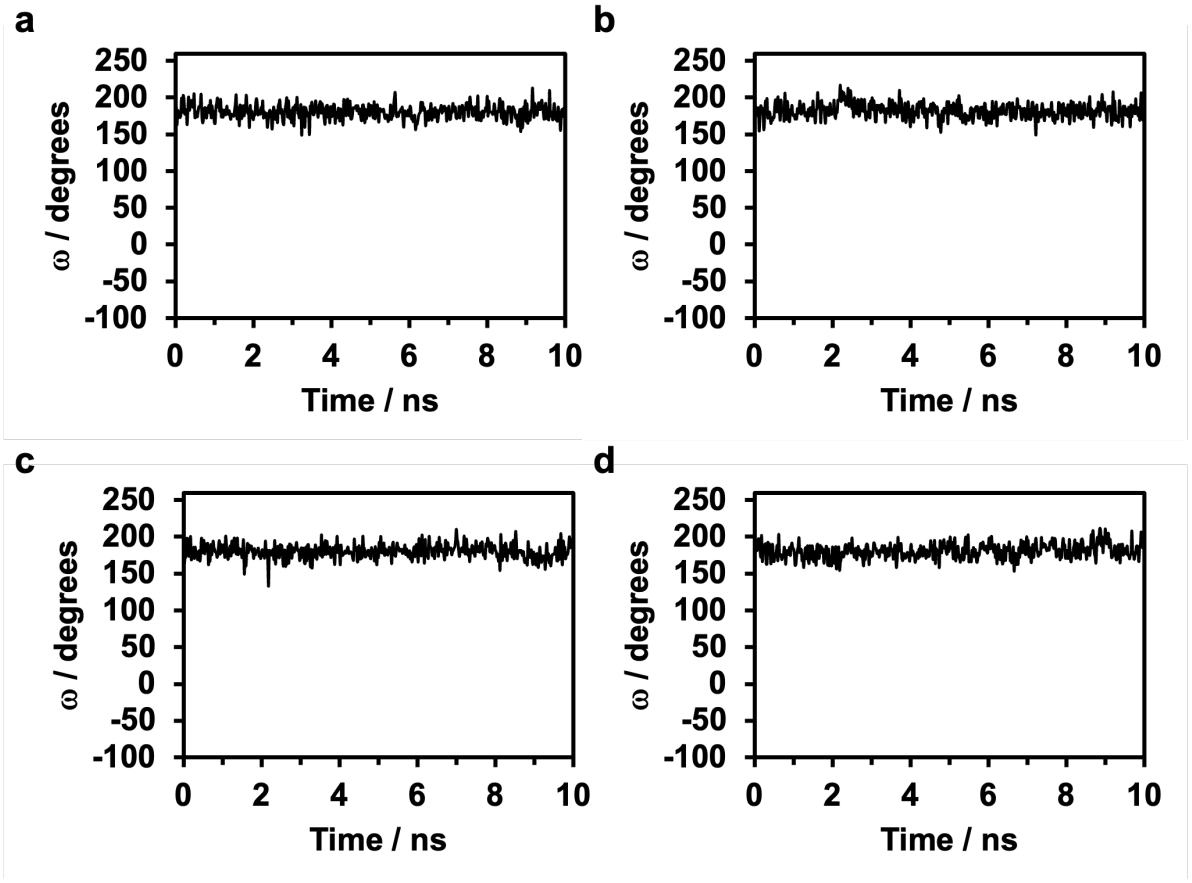

Fig. S4. Time courses of the ω angle for the amide bond preceding each proline in cyclo(PG)$_4$ during 10 ns of umbrella-sampling MD simulation (ξ = 2.1 Å). ω is defined as the dihedral $C\alpha_{\{i-1\}}$-$C_{\{i-1\}}$-N_i- $C\alpha_i$ about the amide bond $C_{\{i-1\}}$-N_i; *trans* and *cis* correspond to ω ≈ 180° and ω ≈ 0°, respectively. Subpanels report the ω time series for the specified Gly-Pro peptide bond: the amide bond (a) between Gly8 and Pro1, (b) between Gly2 and Pro3, (c) between Gly4 and Pro5, and (d) between Gly6 and Pro7.

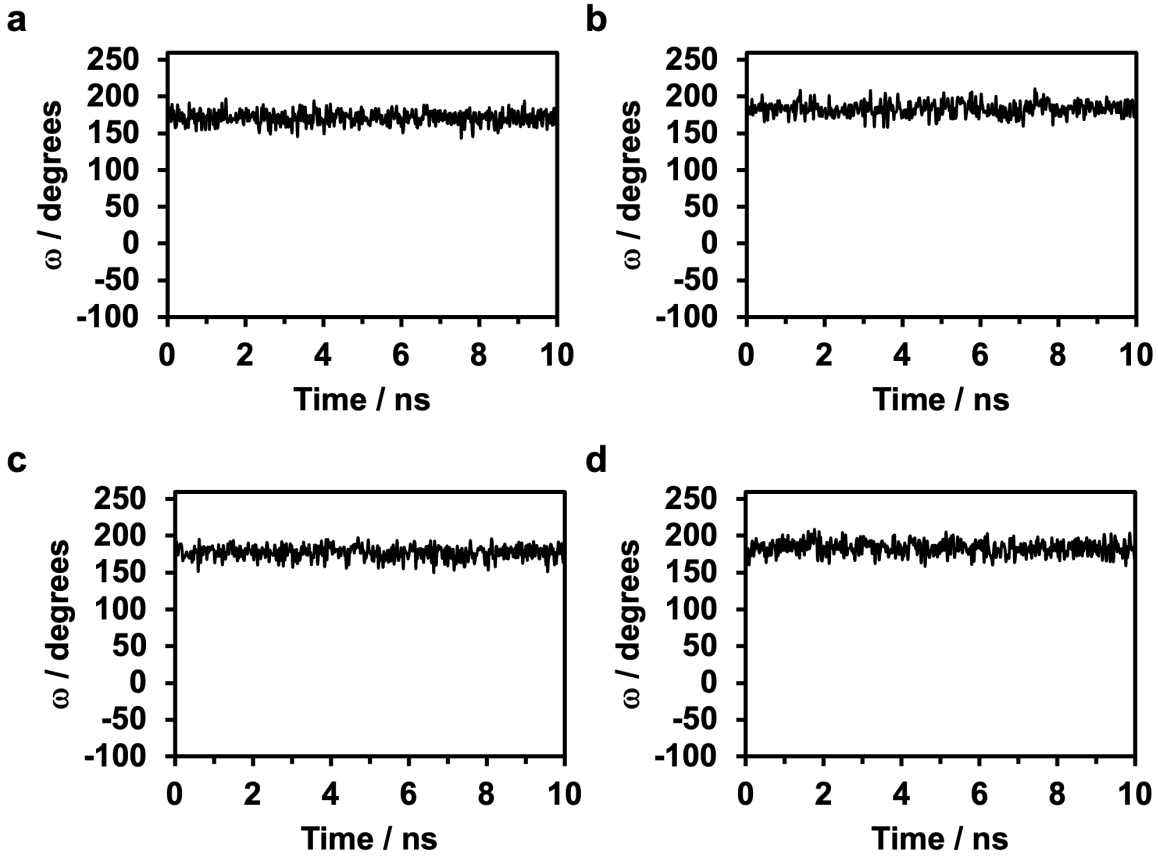

Fig. S5. Time courses of the ω angle for the amide bond preceding each proline in cyclo[(PG)$_3$PC(StBu)] during 10 ns of umbrella-sampling MD simulation (ξ = 1.6 Å). ω is defined as in Fig. S3. Subpanels report the ω time series for the specified amide bond (a) between Gly8 and Pro1, (b) between C(StBu)2 and Pro3, (c) between Gly4 and Pro5, and (d) between Gly6 and Pro7.

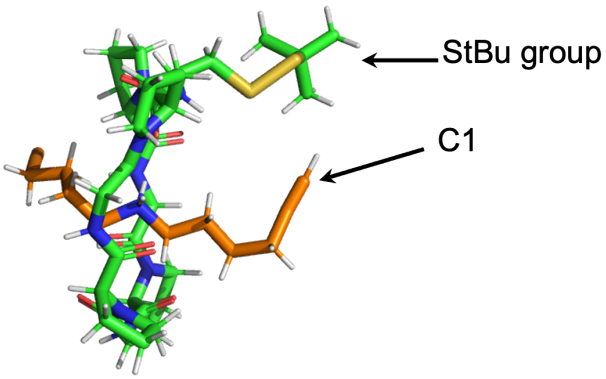

Fig. S6. Schematic representation of steric hindrance induced by C(StBu) residue on the C1 atom of the thread.

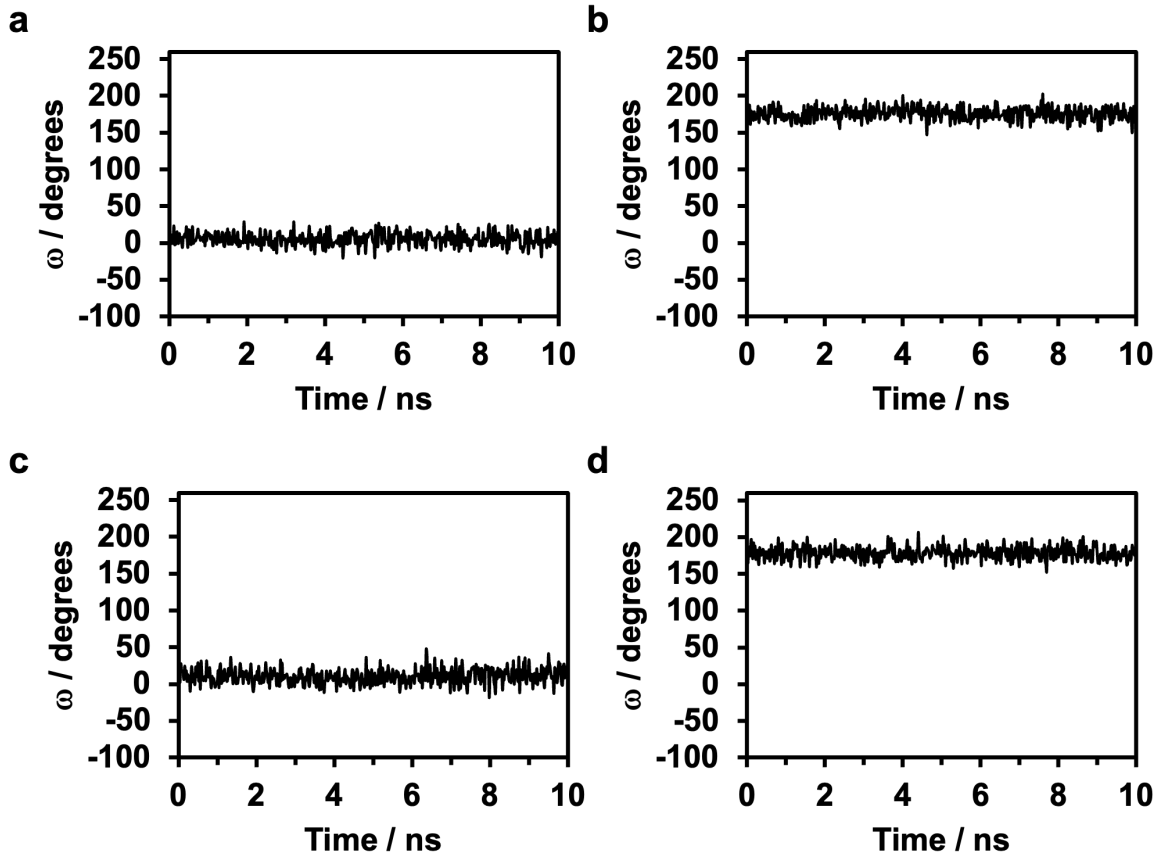

Fig. S7. Time courses of the ω angle for the amide bond preceding each proline (including C($\Psi^{Me,Me}$Pro)) in cyclo[GC($\Psi^{Me,Me}$Pro)$(GP)_3$] during 10 ns of umbrella-sampling MD simulation (ξ = 4.0 Å). ω is defined as in Fig. S3. Subpanels report the ω time series for the specified amide bond (a) between Gly8 and C($\Psi^{Me,Me}$Pro)1, (b) between Gly2 and Pro3, (c) between Gly4 and Pro5, and (d) between Gly6 and Pro7.

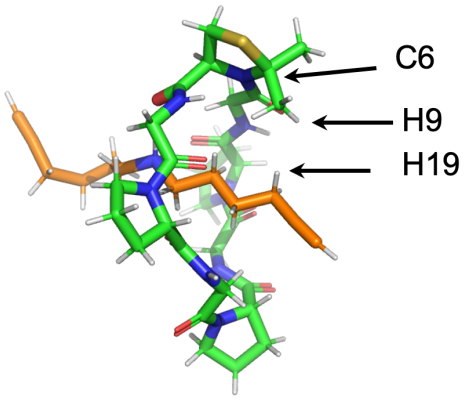

Fig. S8. Schematic representation of steric hindrance induced by C($\Psi^{Me,Me}$Pro) residue on the H19 atom of the thread.

Table S1. Average distances between the atoms of the dimethyl group in cyclo[GC($\Psi^{Me,Me}$Pro)$(GP)_3$] and the atoms on the thread.

Atom in cyclo[GC($\Psi^{Me,Me}$Pro)$(GP)_3$]	Atom in thread	Percentage of atoms within 4 Å / %	Average distance / Å
C6	H19	100	3.05
H6	H19	95.6	2.90
H9	H19	94.0	2.84
H11	H19	92.0	3.00
H9	C10	65.4	3.49
C6	H15	63.0	3.76
H9	H15	58.6	3.37
H11	C10	53.4	3.49
H9	H18	45.6	3.55
H11	H15	44.8	3.34
H11	H18	38.0	3.54
H11	C8	16.4	3.79

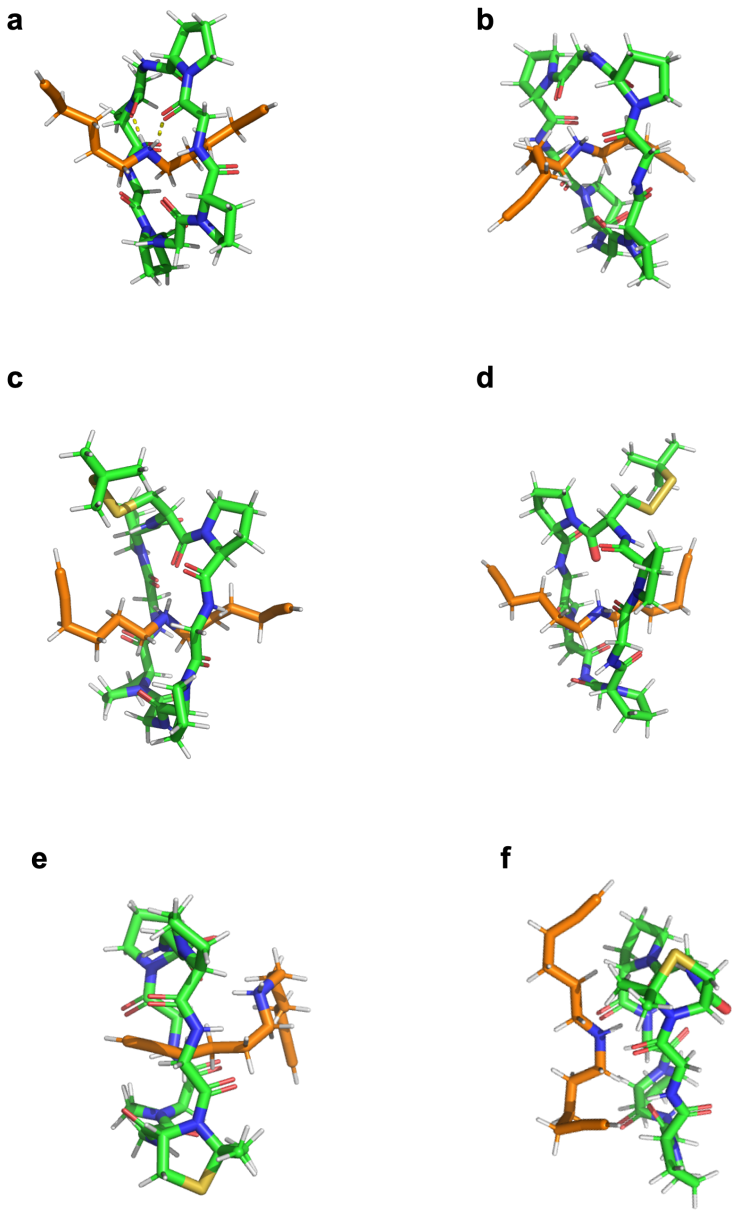

Fig. S9. Snapshots of three rotaxane system at the start (before) and end (after) of conventional MD runs initiated from umbrella-sampling minima: cyclo(PG)$_4$ (a) before (t = 0) and (b) after (t = 1 μs); cyclo[(PG)$_3$PC(StBu)] (c) before (t = 0) and (d) after (t = 1 μs); cyclo[GC($\Psi^{Me,Me}$Pro)(GP)$_3$] (e) before (t = 0) and (f) after (t = 50 ns). Solvent and ions omitted for clarity.

Table S2. MM-PBSA energy decomposition of binding between the thread and the cyclic peptide in cyclo(PG)$_4$ and cyclo[(PG)$_3$PC(StBu)], based on 1 μs conventional MD simulations. All energies are in kcal/mol. ΔE_{VDW}: van der Waals energy, ΔE_{ELE}: electrostatic energy, ΔE_{EPB}: polar solvation energy, $\Delta E_{ENPOLAR}$: nonpolar solvation energy, ΔG_{GAS}: total gas phase energy (ΔE_{VDW} + ΔE_{ELE}), ΔG_{SOLV}: total solvation energy (ΔE_{EPB} + $\Delta E_{ENPOLAR}$), ΔG_{TOTAL}: binding free energy (ΔG_{GAS} + ΔG_{SOLV})

Energy Component	cyclo(PG)$_4$	cyclo[(PG)$_3$PC(StBu)]
$\Delta E_{VDWAALS}$	-14.2	-16.0
ΔE_{ELE}	-80.7	-72.8
ΔE_{EPB}	38.9	38.1
$\Delta E_{ENPOLAR}$	-1.1	-1.2
ΔG_{GAS}	-95.0	-88.8
ΔG_{SOLV}	37.8	36.9
ΔG_{TOTAL}	-57.2	-51.9