Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supplementary information

Energetic contributions of residues to the formation of early amyloid-β oligomers

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Table S1. Characterisation of the secondary structure of oligomers according to DSSP (last 100 ns of each simulation) [1]

	Monomers	Dimers	Trimers	Tetramers	Octamers
β-sheet	6±12	7±5	2±2	3±2	2±1
α-helix	5±9	9±6	17±7	19±7	17±4
Turn	20±11	18±5	19±6	32±4	23±4
Coil	67±15	66±6	62±11	46±6	58±4

[1] Time evolution of secondary structure elements can be found in Figure S3, S4, S5, S6 and S7.

Table S2. The 6 most significant intramonomeric electrostatic stability energies (ΔE_{ele}^{intra}) between residues separated by more than four consecutive residues, in kcal/mol.

	Dimers	Trimers	Tetramers	Octamers
K28-D23	0.0±1.3	-4.5±1.3	-8.9±1.7	-14.7±1.3
K16-E11	0.0±1.3	-2.3±0.1	-9.5±2.3	-11.7±1.1
K28-E22	0.0±0.4	2.2±0.7	-4.9±1.8	-11.0±1.3
M35-E11	0.0±0.3	0.1±0.1	-0.6±0.4	-8.0±0.1
D23-K16	0.0±1.8	-2.7±1.7	4.1±0.5	-6.0±0.9
E22-K16	0.0±0.8	-22.7±4.5	0.7±2.3	-3.0±1.1

Table S3. Decomposition of the stability free energy (ΔG_{total}) and its decomposition into intramonomeric and intermonomeric contributions, in kcal/mol.[a]

		ΔE_{int}	ΔE_{ele}	ΔE_{vdw}	$\Delta G_{sol,pol}$	$\Delta G_{sol,apol}$	ΔG_{total}
Dimers	Global	0.0 ± 10.7	-71.9 ± 30.9	-35.4 ± 8.1	86.5±29.3	-5.7±0.8	-26.4±12.1
	Intra	0.0 ±10.7	0.0 ± 36.8	0.0 ± 9.9	0.0±36.0	0.0±1.3	0.0±13.7
	Inter	0.0 ± 0.0	-71.9 ± 32.8	-35.4 ± 5.9	86.5±32.3	-5.7±1.1	-26.4±6.3
Trimers	Global	5.6 ± 8.5	-121.0 ± 24.7	-46.4 ± 8.0	135.1±22.6	-7.5±1.0	-34.3±10.4
	Intra	5.6 ± 8.5	-42.3 ± 33.1	-5.2 ± 7.2	36.6±32.6	-1.0±1.1	-6.4±10.5
	Inter	0.0 ± 0.0	-78.7 ± 28.5	-41.2 ± 8.6	98.5±29.2	-6.4±1.3	-27.8±4.5
Tetramers	Global	5.0 ± 7.3	-96.9 ± 23.7	-49.5±6.0	116.7±23.2	-7.8±0.6	-32.6±8.7
	Intra	5.0 ± 7.3	-27.0 ± 22.4	-6.1±5.9	23.6±20.8	-0.9±0.8	-5.3±9.0
	Inter	0.0 ± 0.0	-70.0 ± 18.2	-43.4±7.8	93.0±19.2	-6.9±1.1	-27.3±6.4
Octamers	Global	5.5 ± 5.2	-103.1 ± 23.3	-59.7±4.8	132.0±23.0	-9.8±0.7	-35.2±6.8
	Intra	5.5 ± 5.2	-30.0 ±12.5	0.5±4.6	26.1±11.7	-0.2±0.7	1.9±6.1
	Inter	0.0 ± 0.0	-73.1 ±25.5	-60.2±4.1	105.8±24.1	-9.6±0.5	-37.1±3.6

[a] All energy terms are referenced to the averaged energy profile of both monomers of the dimer and consequently the intramonomeric terms of the dimer are computed to be null.

Table S4. Residue decomposition splitted by intra and inter contributions of the vdW stability energy (ΔE_{vdw}) for all oligomers, in kcal/mol.[a]

	Dimers			Trimers			Tetramers			Octamers		
	Total	Intra[b]	Inter	Total	Intra	Inter	Total	Intra	Inter	Total	Intra	Inter
Y10	-4.2	0.0	-4.2	-5.3	-1.6	-3.7	-5.8	-1.3	-4.5	-4.5	-1.2	-3.3
E11	-1.9	0.0	-1.9	-1.7	-0.5	-1.3	-1.9	-0.9	-1.0	-1.8	-0.4	-1.4
V12	-2.8	0.0	-2.8	-4.4	-1.5	-2.9	-3.6	-1.1	-2.5	-2.8	-0.9	-1.9
H13	-1.5	0.0	-1.5	-3.4	-0.3	-3.1	-2.5	-0.5	-2.0	-2.6	-0.3	-2.3
H14	-1.6	0.0	-1.6	-2.8	-0.9	-1.9	-3.2	-1.8	-1.4	-4.1	-1.3	-2.8
Q15	-2.1	0.0	-2.1	-3.2	-1.1	-2.1	-3.8	-1.8	-2.0	-3.6	-1.6	-2.0
K16	-1.8	0.0	-1.8	-2.8	-0.6	-2.1	-2.2	-0.6	-1.6	-2.9	-1.1	-1.8
L17	-2.2	0.0	-2.2	-1.6	0.6	-2.2	-1.6	0.7	-2.3	-2.4	0.4	-2.8
V18	-1.3	0.0	-1.3	-1.1	0.4	-1.5	-2.0	0.0	-2.0	-2.4	-0.1	-2.3
F19	-0.9	0.0	-0.9	-3.1	-0.4	-2.7	-4.0	-0.3	-3.7	-4.8	0.4	-5.2
F20	-1.9	0.0	-1.9	-2.9	-1.2	-1.7	-3.3	-0.7	-2.5	-2.9	0.6	-3.6
A21	-0.3	0.0	-0.3	-1.3	-0.6	-0.7	-0.7	0.2	-0.8	-1.3	-0.1	-1.2
E22	-0.4	0.0	-0.4	-1.6	-0.4	-1.2	-1.3	-0.4	-0.9	-2.3	-0.6	-1.6
D23	-0.3	0.0	-0.3	-0.7	-0.2	-0.6	-1.1	-0.4	-0.8	-1.8	-0.5	-1.3
V24	-0.5	0.0	-0.5	-1.1	-0.1	-0.9	-1.3	-0.2	-1.1	-2.4	-0.6	-1.8
G25	-0.4	0.0	-0.4	-1.2	-0.4	-0.8	-1.0	-0.2	-0.8	-1.5	-0.5	-1.1
S26	-0.5	0.0	-0.5	-0.7	0.1	-0.9	-0.7	0.4	-1.2	-1.5	0.4	-1.9
N27	-0.8	0.0	-0.8	-0.4	0.5	-0.8	-0.6	0.4	-1.0	-2.2	0.5	-2.7
K28	-1.2	0.0	-1.2	0.0	0.9	-0.9	0.1	1.2	-1.1	-1.1	1.1	-2.2
G29	-0.5	0.0	-0.5	-0.5	0.4	-0.9	-0.5	0.4	-0.8	-0.3	0.9	-1.3
A30	-0.8	0.0	-0.8	-0.6	0.5	-1.0	-0.8	0.5	-1.3	-0.7	1.0	-1.6
I31	-1.7	0.0	-1.7	-0.6	0.9	-1.5	-1.3	0.8	-2.2	-1.7	1.6	-3.2
I32	-2.0	0.0	-2.0	-0.7	0.4	-1.1	-1.2	0.2	-1.4	-2.1	1.3	-3.4
G33	-0.9	0.0	-0.9	-0.7	0.2	-0.9	-1.0	-0.1	-0.8	-1.1	0.4	-1.5
L34	-1.8	0.0	-1.8	-2.0	-0.1	-1.9	-1.9	-0.3	-1.6	-3.0	0.4	-3.4
M35	-1.2	0.0	-1.2	-2.0	-0.1	-1.8	-2.1	-0.1	-2.1	-1.8	0.8	-2.7
Total[c]	-35.4	0.0	-35.4	-46.4	-5.2	-41.2	-49.5	-6.1	-43.4	-59.7	0.5	-60.2

[a] Standard deviation is listed Table S5. [b] The intra vdw interaction for dimer is computed to be null since it is taken as a reference structure. [c] The sum of the columns give rise to the total values presented in Table S3.

Table S5. Standard deviation of residue decomposition splitted by intra and inter contributions of the vdW stability energy (ΔE_{vdw}) for all oligomers, in kcal/mol.[a]

	Dimers			Trimers			Tetramers			Octamers		
	Total	Intra	Inter	Total	Intra	Inter	Total	Intra	Inter	Total	Intra	Inter
Y10	1.8	0.9	1.4	1.0	0.8	0.6	1.1	0.7	1.0	0.9	0.5	0.7
E11	1.6	1.0	0.9	0.9	1.0	0.6	0.9	0.8	0.4	0.6	0.6	0.3
V12	1.6	1.0	1.1	1.0	0.9	0.5	1.2	0.7	1.0	0.7	0.5	0.5
H13	1.1	1.1	0.6	1.0	1.1	0.8	0.9	0.6	0.6	0.8	0.4	0.5
H14	1.3	0.9	0.8	1.0	1.0	0.8	1.4	0.7	1.2	0.7	0.5	0.6
Q15	2.1	1.6	0.9	0.9	0.9	0.6	0.9	0.8	0.4	0.7	0.6	0.6
K16	1.2	1.0	1.0	1.1	0.8	0.7	0.8	0.7	0.5	0.6	0.5	0.4
L17	2.2	1.4	1.3	1.6	0.9	1.2	1.3	0.8	1.1	0.7	0.6	0.3
V18	1.0	1.1	0.8	1.1	0.9	0.7	0.9	0.7	0.7	0.6	0.5	0.4
F19	1.6	1.3	0.7	0.9	1.0	1.1	1.3	0.9	1.2	1.3	0.7	1.1
F20	2.4	1.5	1.6	1.1	0.8	0.9	1.1	1.2	1.0	1.2	0.6	0.9
A21	0.7	0.7	0.3	0.6	0.5	0.3	0.7	0.4	0.6	0.4	0.5	0.3
E22	1.0	0.9	0.5	0.9	0.9	0.7	0.8	0.6	0.5	0.7	0.7	0.4
D23	1.0	1.0	0.4	0.9	0.9	0.4	0.8	0.8	0.6	0.7	0.7	0.4
V24	1.3	1.2	0.4	1.2	1.0	0.7	1.0	0.9	0.5	0.7	0.6	0.4
G25	0.7	0.6	0.4	0.8	0.6	0.4	0.6	0.4	0.5	0.4	0.4	0.3
S26	1.3	1.2	0.7	0.8	0.7	0.5	1.2	0.7	0.7	0.7	0.7	0.6
N27	1.7	1.7	0.7	0.8	0.7	0.4	1.0	0.6	0.8	0.9	0.8	0.5
K28	1.4	1.5	0.6	1.0	1.1	0.8	1.0	0.7	0.7	0.8	0.7	0.5
G29	1.2	1.1	0.3	0.7	0.7	0.6	0.6	0.5	0.5	0.4	0.4	0.2
A30	1.0	0.9	0.6	0.8	0.6	0.6	0.7	0.5	0.7	0.5	0.5	0.3
I31	1.7	1.6	1.7	1.3	1.0	0.8	1.2	1.3	0.7	0.9	0.9	0.5
I32	2.0	1.5	1.2	1.1	1.2	0.4	1.3	1.2	0.4	1.3	0.9	0.9
G33	0.7	0.6	0.5	0.6	0.4	0.5	0.7	0.4	0.4	0.4	0.2	0.3
L34	1.3	1.1	0.6	1.1	1.0	0.5	1.2	0.9	0.5	1.0	0.7	0.6
M35	1.5	1.4	0.9	1.2	1.1	1.1	1.0	0.8	0.8	0.8	0.5	0.6

Table S6. Residue decomposition splitted by intra and inter contributions of the total stability free energy (ΔG_{total}) for all oligomers, in kcal/mol.[a]

	Dimers			Trimers			Tetramers			Octamers		
	Total	Intra[b]	Inter	Total	Intra	Inter	Total	Intra	Inter	Total	Intra	Inter
Y10	0.6	0.0	0.6	-0.2	-0.4	0.3	-0.2	-0.2	0.0	0.3	-0.4	0.7
E11	-2.0	0.0	-2.0	-1.3	-0.7	-0.6	-1.3	-0.9	-0.4	0.0	-0.3	0.4
V12	-3.5	0.0	-3.5	-4.4	-1.6	-2.7	-3.8	-1.3	-2.5	-3.0	-1.3	-1.8
H13	-1.7	0.0	-1.7	-2.4	0.1	-2.6	-1.7	-0.2	-1.5	-1.7	0.0	-1.7
H14	-0.8	0.0	-0.8	-1.4	-0.4	-1.0	-2.0	-1.0	-0.9	-2.3	-0.4	-2.0
Q15	-1.9	0.0	-1.9	-3.9	-1.7	-2.3	-3.9	-2.2	-1.7	-1.9	-1.1	-0.8
K16	-1.4	0.0	-1.4	-3.6	-1.6	-2.0	-1.2	-1.1	-0.1	-2.6	-1.4	-1.3
L17	-2.1	0.0	-2.1	-2.4	-0.2	-2.1	-2.2	-0.2	-2.0	-2.6	-0.3	-2.4
V18	-1.4	0.0	-1.4	-1.1	0.1	-1.3	-1.7	0.1	-1.8	-1.6	0.1	-1.8
F19	-0.8	0.0	-0.8	-3.5	-0.9	-2.5	-4.0	-0.6	-3.4	-3.7	0.9	-4.5
F20	-1.7	0.0	-1.7	-2.8	-1.5	-1.3	-2.7	-0.6	-2.1	-3.4	-0.4	-3.0
A21	-0.1	0.0	-0.1	-1.1	-0.6	-0.5	-0.4	0.2	-0.6	-1.5	-0.8	-0.7
E22	0.2	0.0	0.2	-1.2	-0.6	-0.6	-0.1	-0.5	0.4	0.1	-0.5	0.5
D23	0.3	0.0	0.3	-0.4	-0.5	0.0	-0.1	-0.5	0.4	0.1	-0.3	0.4
V24	-0.7	0.0	-0.7	-1.0	-0.4	-0.7	-1.3	-0.3	-1.0	-2.0	-0.6	-1.4
G25	-0.2	0.0	-0.2	-0.3	0.1	-0.4	0.1	0.6	-0.5	-0.2	0.6	-0.8
S26	-0.5	0.0	-0.5	0.0	0.2	-0.3	-0.2	0.5	-0.6	-0.3	0.6	-0.9
N27	-0.3	0.0	-0.3	-0.2	0.0	-0.2	-0.4	-0.2	-0.2	-1.7	0.0	-1.8
K28	-1.0	0.0	-1.0	-0.3	0.0	-0.4	-0.7	-0.1	-0.7	-1.7	-0.3	-1.4
G29	-0.3	0.0	-0.3	0.3	0.8	-0.5	0.5	0.8	-0.3	0.8	1.3	-0.5
A30	-0.6	0.0	-0.6	0.2	0.8	-0.7	-0.5	0.7	-1.1	0.0	1.2	-1.2
I31	-1.5	0.0	-1.5	0.3	1.5	-1.2	-0.9	1.2	-2.1	-1.0	1.9	-2.9
I32	-2.0	0.0	-2.0	0.5	1.3	-0.9	-0.5	0.9	-1.4	-1.2	2.1	-3.2
G33	-0.6	0.0	-0.6	-0.4	0.3	-0.7	-0.3	0.1	-0.4	-0.5	0.4	-1.0
L34	-1.8	0.0	-1.8	-2.7	-0.9	-1.8	-2.1	-0.7	-1.4	-3.2	0.1	-3.2
M35	-0.5	0.0	-0.5	-0.6	0.2	-0.8	-1.1	0.1	-1.2	-0.3	0.8	-1.1
Total[c]	-26.4	0.0	-26.4	-34.3	-6.4	-27.8	-32.6	-5.3	-27.3	-35.2	1.9	-37.1

[a] Standard deviation is listed Table S7. [b] The intra vdw interaction for dimer is computed to be null since it is taken as a reference structure. [c] The sum of the columns give rise to the total values presented in Table S3.

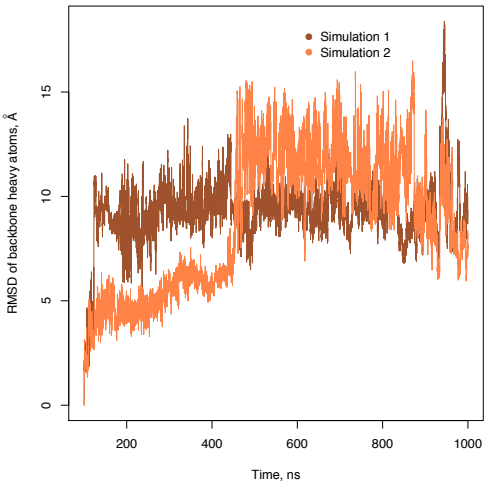
Table S7. Standard deviation of residue decomposition splitted by intra and inter contributions of the *total* stability free energy (ΔG_{total}) for all aggregates, in kcal/mol.[a]

	Dimers			Trimers			Tetramers			Octamers		
	Total	Intra	Inter	Total	Intra	Inter	Total	Intra	Inter	Total	Intra	Inter
Y10	2.8	2.5	1.4	2.4	2.1	1.1	2.0	1.8	1.0	1.5	1.3	0.6
E11	2.5	2.0	1.7	1.7	1.7	0.6	1.5	1.5	0.4	1.2	1.1	0.7
V12	2.6	2.0	1.4	1.8	1.8	0.4	1.9	1.5	1.1	1.2	1.1	0.6
H13	2.2	2.1	0.5	2.0	1.9	0.8	1.5	1.5	0.5	1.4	1.1	0.7
H14	2.2	2.1	0.7	1.9	1.7	0.6	1.9	1.5	1.2	1.3	1.1	0.7
Q15	3.2	2.3	1.5	2.1	1.9	1.1	2.2	1.8	1.0	1.2	1.2	0.5
K16	2.8	2.6	1.3	2.4	2.2	1.1	2.2	1.9	0.7	1.5	1.3	0.6
L17	2.9	2.3	1.4	2.6	1.9	1.1	2.2	1.7	1.1	1.1	1.1	0.3
V18	2.1	2.1	1.1	1.8	1.6	0.7	1.5	1.5	0.7	1.2	1.0	0.4
F19	2.8	2.6	0.8	2.0	1.9	1.1	2.0	1.9	1.2	1.5	1.2	0.9
F20	2.9	2.3	1.6	2.3	2.0	1.0	1.9	1.8	1.0	1.6	1.2	0.9
A21	1.7	1.6	0.3	1.3	1.3	0.4	1.2	1.2	0.6	0.8	0.8	0.3
E22	2.1	2.0	0.4	2.4	1.9	0.9	1.5	1.4	0.4	1.1	1.0	0.5
D23	1.9	1.9	0.3	1.6	1.6	0.6	1.4	1.4	0.4	1.1	0.9	0.6
V24	2.5	2.3	0.6	1.8	1.6	0.6	1.8	1.6	0.5	1.1	1.0	0.4
G25	1.5	1.4	0.4	1.3	1.1	0.3	1.0	1.0	0.5	0.9	0.8	0.4
S26	1.9	1.9	1.1	1.5	1.4	0.4	1.7	1.3	0.9	1.0	0.9	0.7
N27	2.7	2.6	0.6	1.8	1.7	0.5	1.6	1.5	0.4	1.2	1.2	0.8
K28	2.7	2.8	1.3	2.0	2.1	0.6	1.9	1.9	0.6	1.4	1.3	0.7
G29	1.7	1.6	0.4	1.2	1.2	0.6	1.0	1.0	0.5	0.8	0.8	0.2
A30	2.1	1.7	0.8	1.5	1.4	0.5	1.5	1.2	0.9	1.0	0.9	0.4
I31	2.5	2.6	1.5	2.2	2.0	0.8	1.9	2.1	0.8	1.4	1.4	0.5
I32	2.9	2.7	1.1	2.1	2.1	0.5	2.0	1.9	0.6	2.0	1.5	1.1
G33	1.5	1.4	0.6	1.3	1.1	0.5	1.2	1.0	0.5	0.8	0.6	0.5
L34	2.4	2.4	0.7	2.1	2.1	0.6	1.8	1.6	0.6	1.4	1.2	0.6
M35	2.5	2.5	0.9	2.0	2.0	0.8	1.7	1.5	0.8	1.1	1.1	0.5

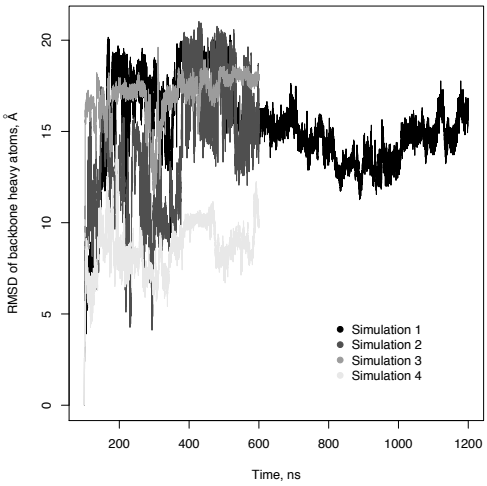
Table S8. The 10th most favourable and the 8th most unfavourable intermonomeric electrostatic stability energies of residue-pairwise interactions, in kcal/mol.[a]

	Dimers	Trimers	Tetramers	Octamers
D23-K16	-15.1±2.0	-53.0±14.1	-50.8±6.3	-117.5±7.9
K28-D23	-24.8±6.4	-31.8±6.8	-45.7±10.3	-112.5±6.8
K28-E22	-38.2±22.2	-34.0±9.2	-45.5±7.9	-109.6±8.5
M35-Y10	-21.3±6.6	-53.2±15.3	-53.4±11.2	-101.8±12.3
M35-K28	-17.4±2.7	-34.8±10.8	-53.0±11.0	-100.9±13.2
M35-K16	-33.8±22.9	-35.7±7.5	-57.6±12.3	-100.3±11.9
E22-K16	-14.7±1.9	-77.0±12.3	-58.3±11.6	-99.4±8.4
K28-E11	-24.3±13.1	-31.3±3.5	-45.1±5.5	-97.5±7.0
D23-Y10	-19.3±5.9	-34.7±3.2	-49.5±4.2	-97.3±9.2
E22-Y10	-21.5±7.9	-34.5±2.9	-52.5±7.7	-94.4±9.4
D23-E22	20.1±4.7	37.9±9.3	41.5±4.9	102.5±5.2
K28-K16	22.7±7.6	37.6±8.0	45.9±4.5	99.6±5.7
K28-Y10	23.4±8.4	32.7±3.2	49.3±5.6	98.6±8.3
M35-E11	19.8±4.3	41.3±6.2	49.3±9.2	95.4±12.6
D23-E11	16.8±4.5	33.2±3.1	44.9±4.0	93.7±7.1
M35-D23	18.6±6.3	29.8±4.0	45.6±4.9	91.9±8.6
M35-E22	18.1±4.5	29.1±3.2	46.3±4.7	90.2±7.2
E22-E11	17.5±4.4	33.2±3.2	46.4±3.0	90.0±4.7

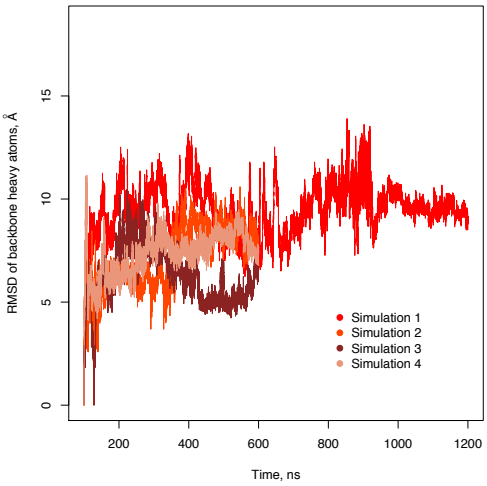
[a] Ranked according the octamer values.



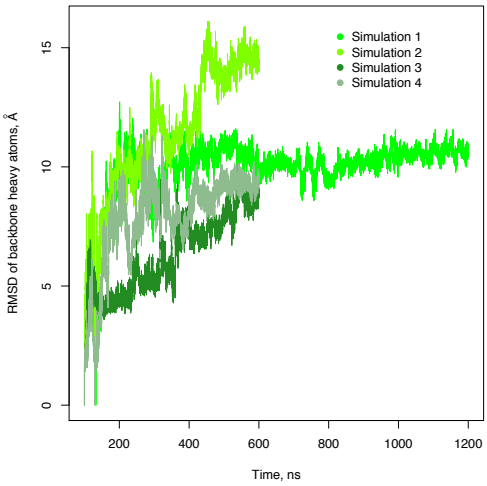
Monomers



Dimers

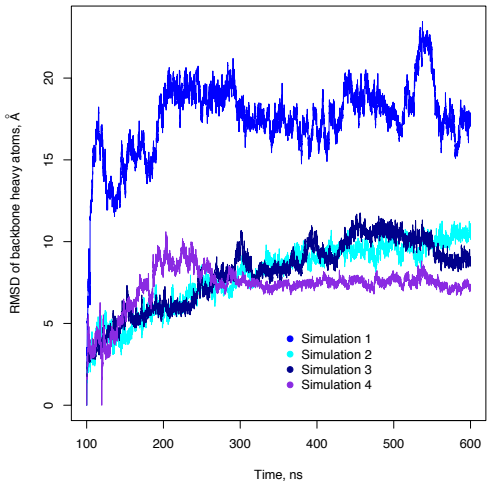


Trimers



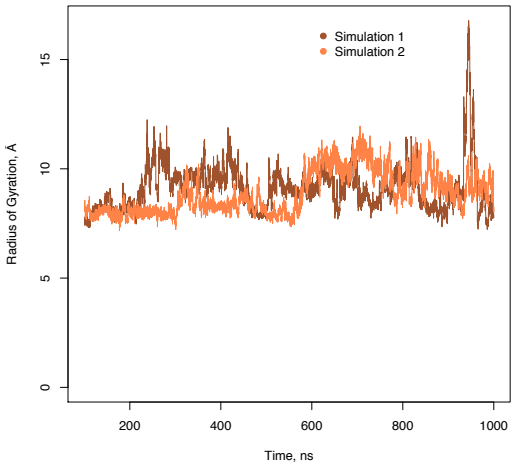
Tetramers

Figure S1. RMSD of backbone heavy atoms of all MD 18 simulations

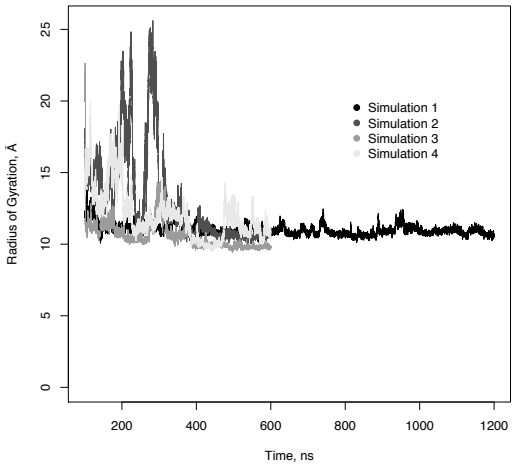


Octamers

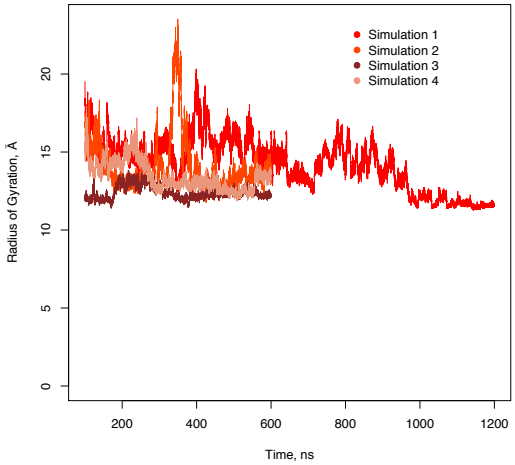
Figure S1 (cont.). RMSD of backbone heavy atoms of all MD 18 simulations.



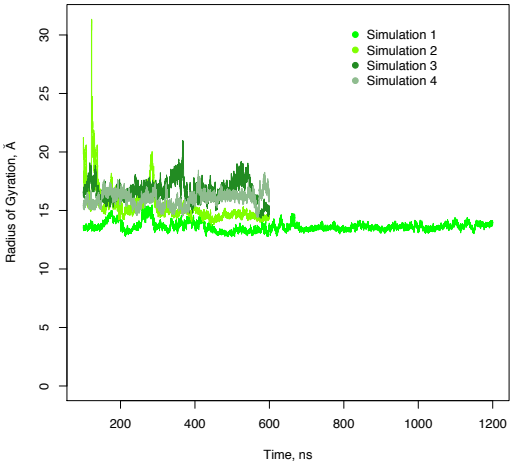
Monomers



Dimers

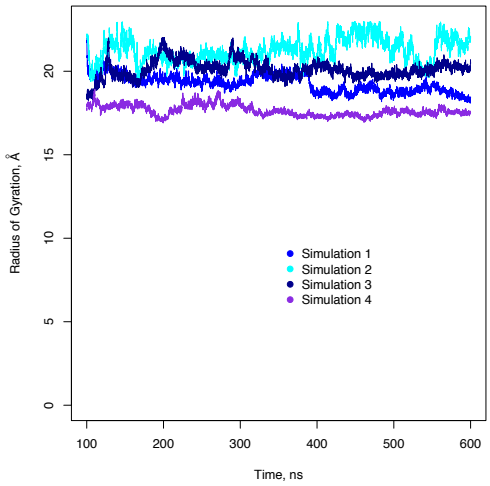


Trimers



Tetramers

Figure S2. Radius of Gyration evolution along the 18 trajectories.



Octamers

Figure S2 (cont.). Radius of Gyration evolution along the 18 trajectories.

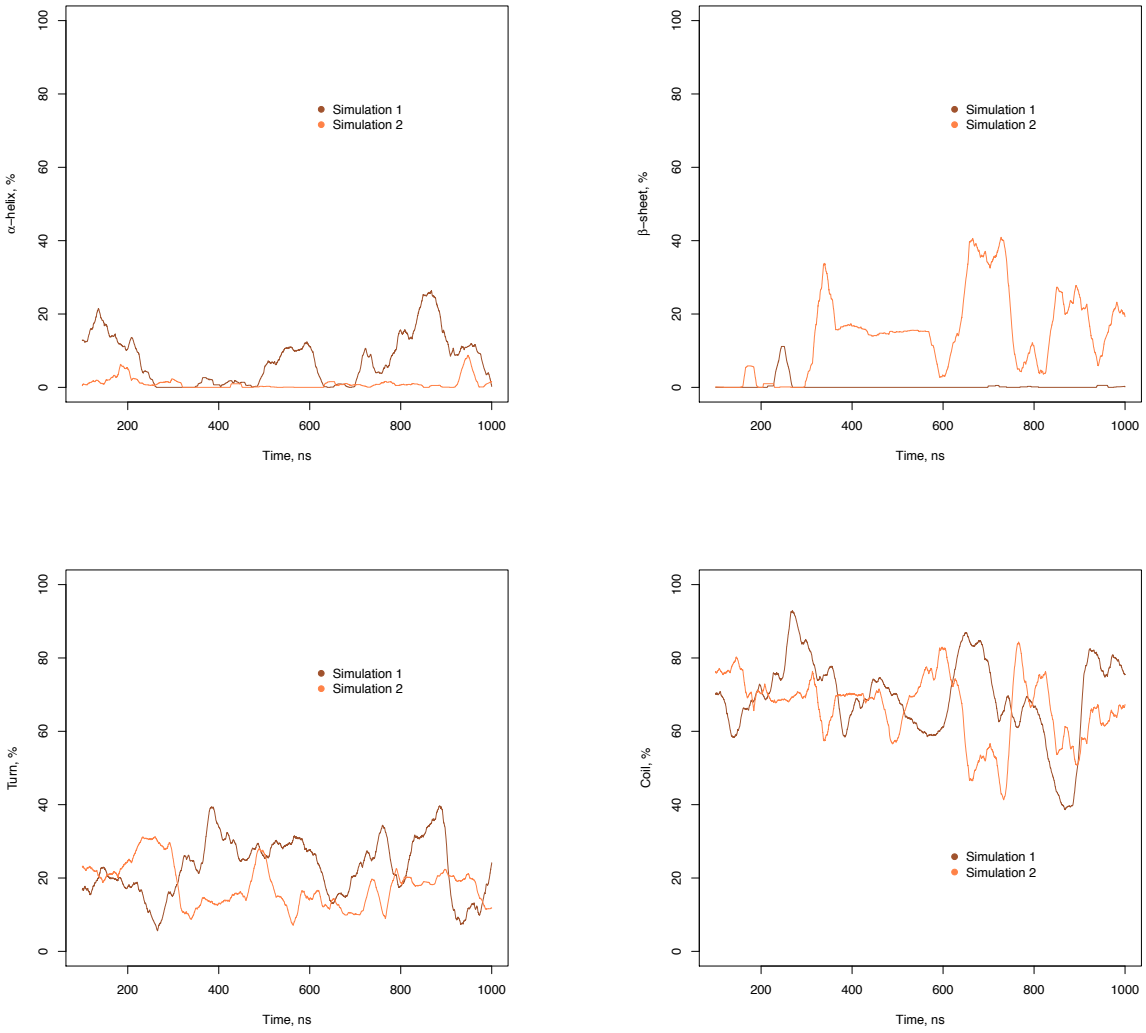


Figure S3. Time evolution of the secondary structure elements for monomers.

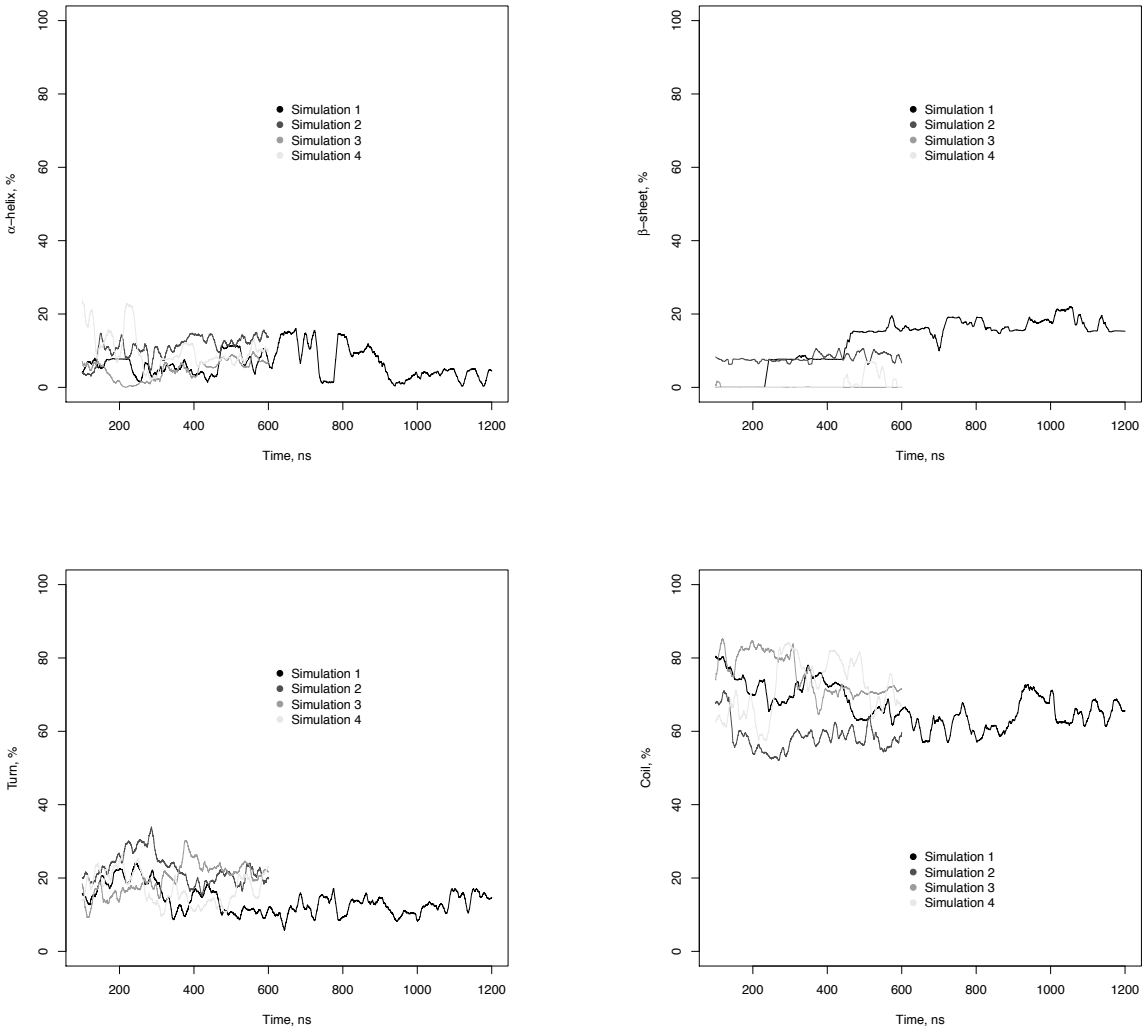


Figure S4. Time evolution of the secondary structure elements for dimer oligomers.

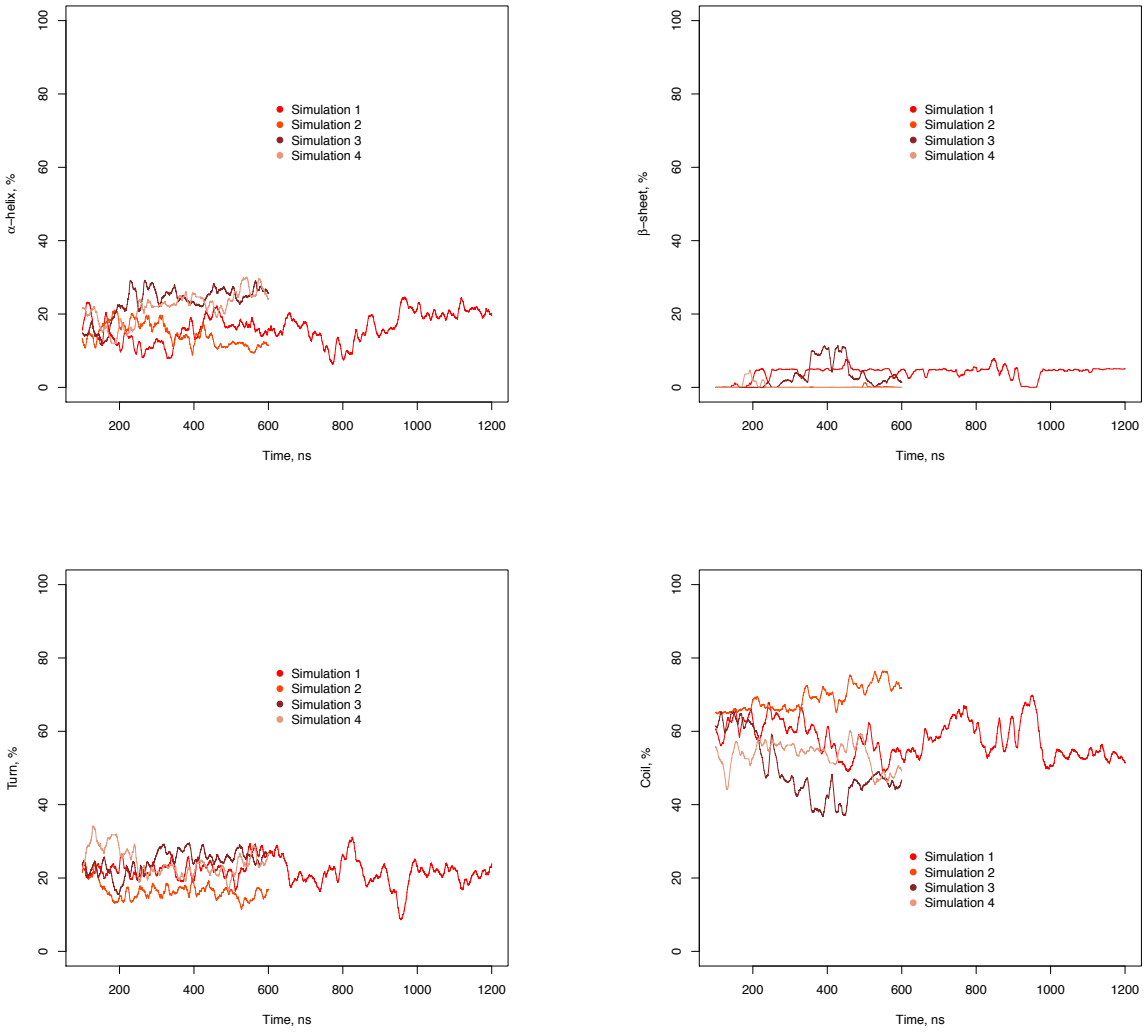


Figure S5. Time evolution of the secondary structure elements for trimer oligomers.

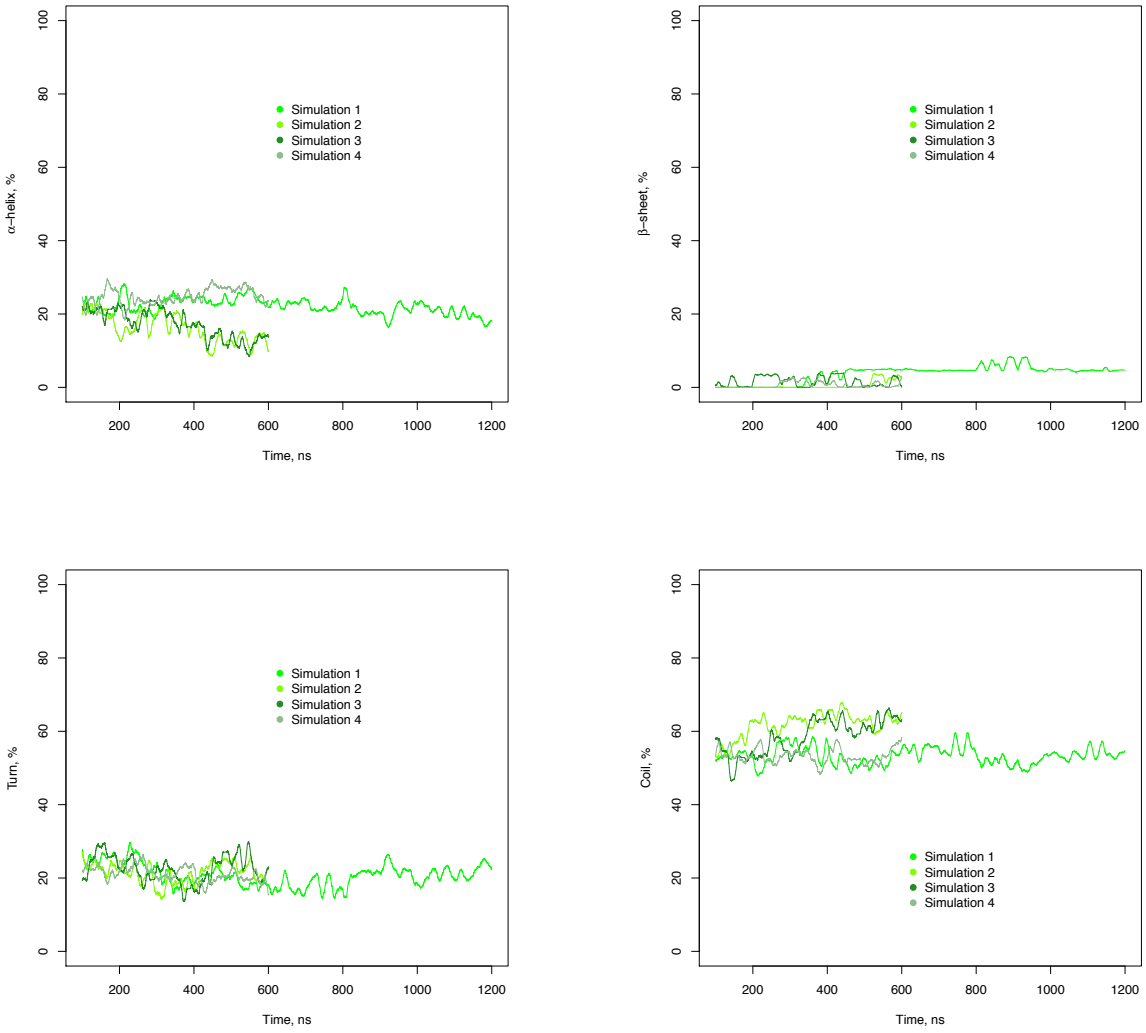


Figure S6. Time evolution of the secondary structure elements for tetramer oligomers.

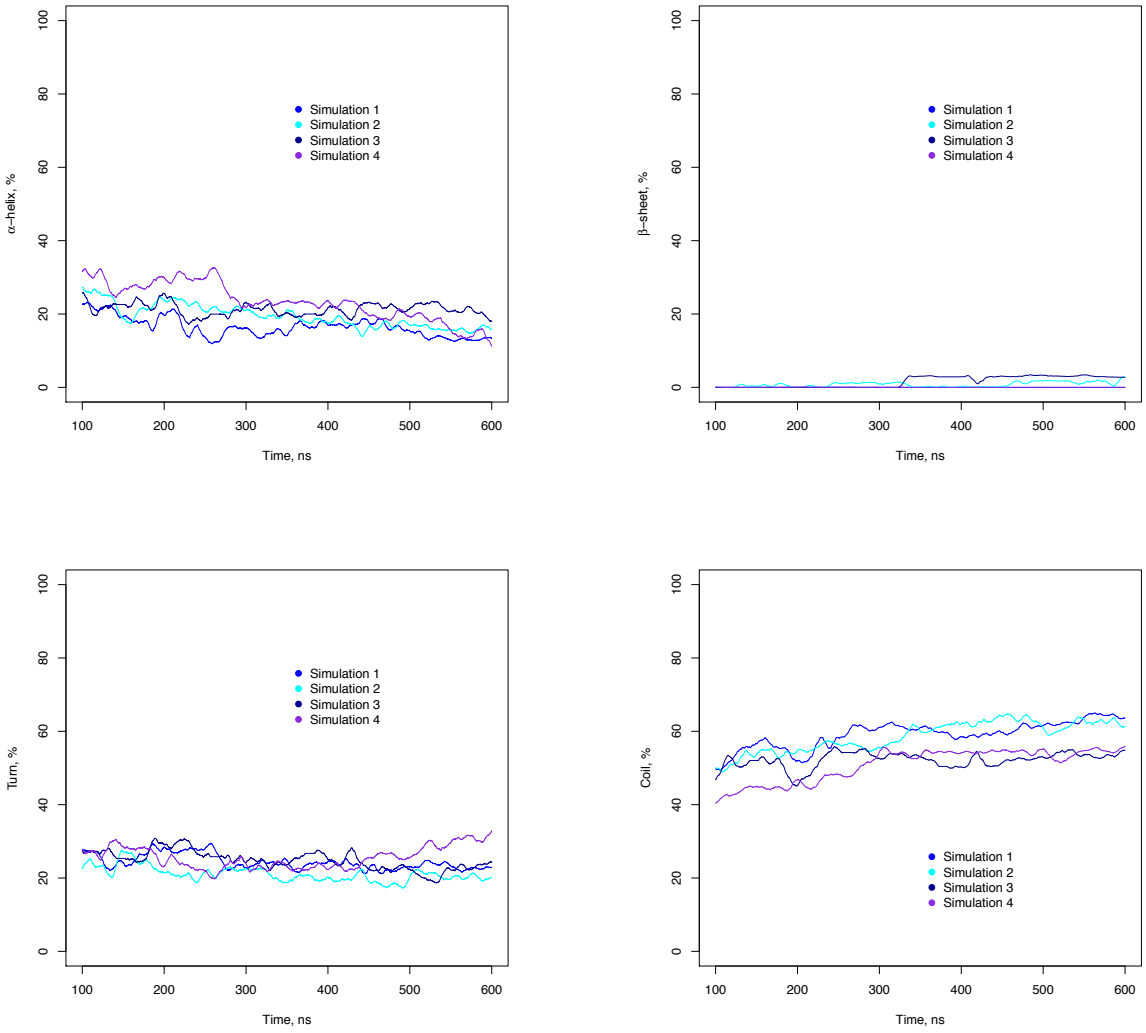


Figure S7. Time evolution of the secondary structure elements for octamer oligomers.

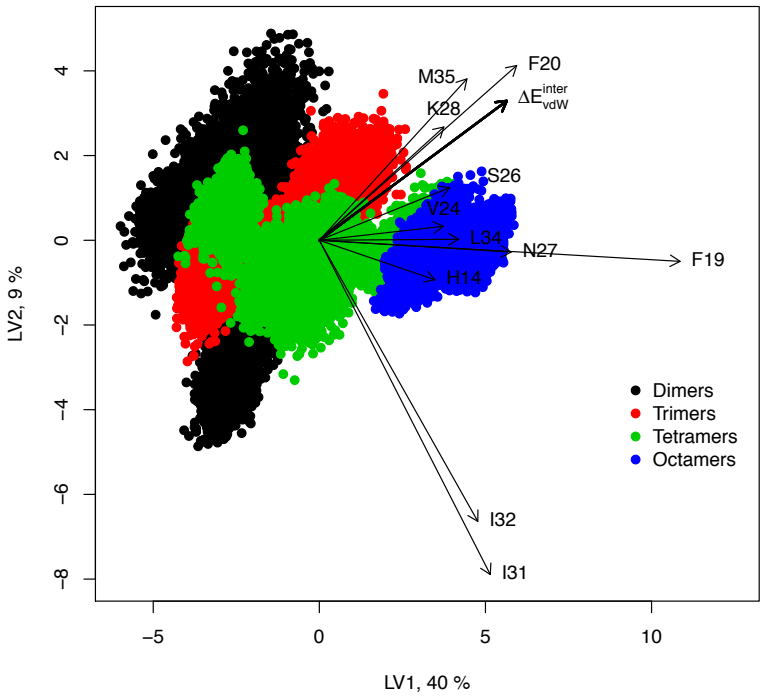


Figure S8. PLS biplot of the residue decomposition of the intermonomeric vdW stability energy, ΔE_{vdW}^{inter}. Only the 10 most important variables are displayed. The plot reveals firstly a distinctive profile between octamers, which are displayed on the right, and dimers, trimers and tetramers (on the left) and secondly the compactness of octamers structures unlike other oligomers. In the plot, the intermonomeric vdW energy points at octamers oligomers, indicating obviously that this oligomer contains the highest energy of this type among all oligomers and that this direction contains the highest variability of the variable. Correlated to this fact appears the energy profile of H14, F19, I32, I31, M35, F20 and L34 in full agreement with the previous findings and corroborating the importance of the NTHR, CHC and CTHR in which these residues take part.