Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

for

Angew. Chem. Int. Ed. Z54114

69451 Weinheim, Germany

Carbopeptoid folding: effects of stereochemistry, chain length, and solvent

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S1 Simulation and Analysis Details

All simulations were carried out using the GROMOS96 suite of programs[1, 2] and the 45A3 united atom force field,[2, 3] supplemented by ester group,[4] chloroform,[5] and DMSO[6] parameters from other work. Periodic boundary conditions were applied with truncated octahedra as unit cells. Non-bonded interactions were truncated at 1.4 nm with a reaction field applied beyond the cutoff to account for the dielectric properties of the solvent (ε_{RF}, chloroform, 5, DMSO, 30). Extended structures of the solute with all backbone dihedral angles in *trans*-configuration were immersed in the solvent (**1**: 1567 [1745], **2**: 2579, **3**: 5479, **4**: 2807, **5**: 6203 chloroform [DMSO] molecules) and subjected to energy minimization to define the initial coordinates. Initial velocities were taken from a Maxwell-Boltzmann distribution at 298 K. Newton's equations of motion were integrated using the leapfrog algorithm with a time step of 2 fs, while keeping bond lengths constrained using the SHAKE algorithm[7] with a relative tolerance of 10^{-4}. The weak coupling algorithm[8] was used with relaxation times of 0.1 ps and 0.5 ps, respectively, to maintain the reference temperature (298 K) and pressure (1 atm). Further details of the simulations are given elsewhere.[9]

Trajectory snapshots of the solute were taken every 0.01 ns and clustered into batches of similar configurations, using backbone atom-positional RMSD values as similarity criterion and a clustering algorithm described previously[10] with cutoffs of 0.13 nm (tetramer), 0.17 nm (hexamers), and 0.28 nm (octamers).

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Table 1. Intramolecular hydrogen bonds.[a]

molecule	H-bond	simulation	model structure	molecule	H-bond	simulation	model structure
cis-tetramer **1**	NH(3) – O(1)	11.1 (1.0)	100	*trans*-octamer **5**	NH(2) – O(4)	1.1	0
	NH(4) – O(2)	6.0 (3.3)	100		NH(2) – O(5)	0.7	0
cis-hexamer **2**	NH(3) – O(1)	11.7	100		NH(2) – O(6)	1.1	0
	NH(4) – O(2)	14.0	0		NH(2) – O(7)	7.8	0
	NH(5) – O(3)	7.6	100		NH(3) – O(5)	0.6	0
	NH(6) – O(4)	9.7	0		NH(3) – O(6)	8.3	0
cis-octamer **3**	NH(3) – O(1)	12.0	100		NH(3) – O(7)	2.9	0
	NH(4) – O(2)	7.6	0		NH(4) – O(6)	3.9	0
	NH(5) – O(3)	13.8	100		NH(4) – O(7)	0.3	0
	NH(6) – O(4)	14.9	100		NH(4) – O(8)	5.7	0
	NH(7) – O(5)	9.2	0		NH(5) – O(7)	1.2	0
	NH(8) – O(6)	6.2	0		NH(5) – O(8)	0.8	0
trans-hexamer **4**	NH(2) – O(4)	1.6	—		NH(7) – O(1)	0.5	0
	NH(2) – O(5)	1.8	—		NH(7) – O(2)	2.9	0
	NH(2) – O(6)	0.5	—		NH(7) – O(3)	3.6	100
	NH(3) – O(5)	0.5	—		NH(7) – O(4)	0.3	0
	NH(3) – O(6)	2.4	—		NH(8) – O(1)	0.5	0
	NH(4) – O(6)	1.1	—		NH(8) – O(2)	1.2	0
	NH(6) – O(1)	0.4	—		NH(8) – O(3)	3.7	0
	NH(6) – O(2)	1.4	—				

[a] Intramolecular backbone NH–CO hydrogen bond occurrences (in %) for the different simulations and model structures of carbopeptoids in chloroform. Residue sequence numbers are given in parentheses (see Figure 1 in the paper for reference). Data for the *cis*-tetramer **1** in DMSO are shown in parentheses. Hydrogen bonds are defined to have a maximum hydrogen-acceptor distance of 0.25 nm and a minimum donor-hydrogen-acceptor angle of 135˚. Only hydrogen bonds occurring for at least 0.3 % of the simulation are shown.