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

Supplementary Information for

Cyclic peptides: Backbone rigidification and capability of mimicking motifs at protein–protein interfaces

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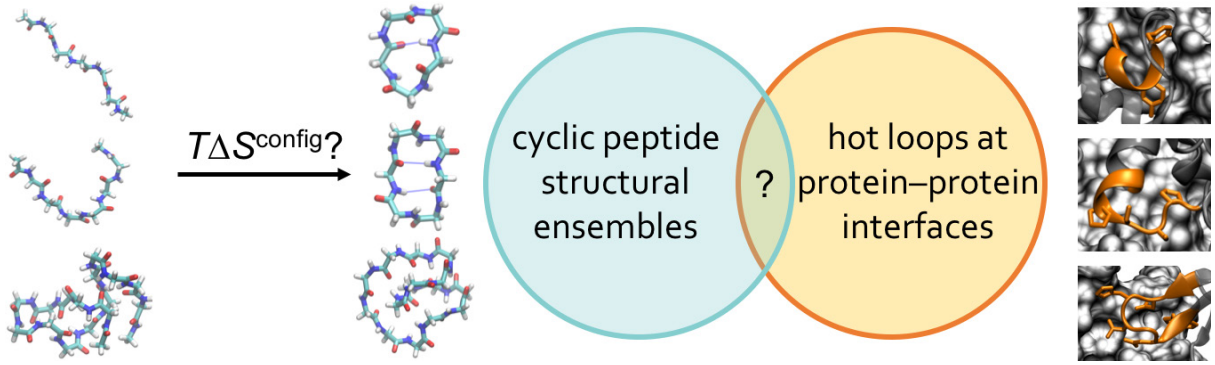

Methods

A. Linear and cyclic peptides of G_5 to G_{15}

Linear and head-to-tail cyclized polyglycine peptides with length varying from 5 to 15 residues, denoted as linear- and cyclo-G_n, with $5 \leq n \leq 15$, were built and simulated. The linear peptides were capped with an acetyl group on the N-terminus and with an *N*-methyl amide group on the C-terminus. The capping prevented creation of charged termini, which could have led to strong Coulombic interaction. It also ensured that linear and cyclic peptides of the same length had the same number of backbone ϕ/ψ dihedrals. For each peptide system, two sets of simulations and analysis, starting from two different initial structures, were performed in parallel to verify the convergence of the simulation results. To generate the two initial structures, a conformation adopting α-helical backbone dihedrals and a fully extended conformation were built. For the linear peptides, the N- and C-terminal capping residues were then added using tLEaP.[1] For the cyclic peptides, head-to-tail cyclization was done in Chimera.[2] However, it was noted that when the end-to-end distance of the peptide was large, the cyclization tended to result in erroneous formation of *cis* peptide bonds. To avoid such artifacts, the rotatable bonds were adjusted to bring the two ends closer before adding a bond to cyclize the peptides in Chimera. The cyclized structures were then energy minimized for 100 steps using the default minimizations in Chimera. If a *cis* peptide bond occurred during the energy minimization, the peptide bond was reformed in the *trans* conformation, followed by further energy minimization. All the peptide bonds in the final prepared structures were in the *trans* conformation.

B. Molecular dynamics simulations

To characterize their thermodynamic and structural properties, all the cyclic and linear peptides were simulated using molecular dynamics (MD) simulation. All the simulations were performed using the GROMACS 4.6.7 suite[3] with the RSFF2 force field and TIP3P water model.[4,5] The RSFF2 force field was parameterized using a coil library and was previously shown to be able to fold well-behaved peptides[6] and recapitulate the crystal structures of cyclic peptides reasonably well.[7]

Each initial structure was first solvated in a cubic box of pre-equilibrated water. The total number of water molecules added for the same peptide system was kept the same for S1 and S2, with the minimum distance of at least 1.0 nm between any atom of the peptide and the walls of the box. The solvated structure was minimized to remove steric clash using the steepest descent algorithm. Equilibrations were then carried out in two stages. In the first stage, all the heavy atoms of the peptide were position-restrained and a 50-ps NVT simulation at 300 K was performed, followed by a 50-ps NPT simulation at 300 K and 1 bar, to equilibrate the solvent molecules. In the second stage, restraints were removed and a 100-ps NVT simulation at 300 K was done, followed by a 100-ps NPT simulation at 300 K and 1 bar, to equilibrate the whole system. A 1.0-μs production run was then performed at 300 K and 1 bar with trajectories output every 1.0 ps for subsequent analysis.

The integration of dynamics used the leapfrog algorithm with a time step of 2.0 fs. A rigid water geometry was maintained using SETTLE. For the peptide, all bonds involving hydrogens were constrained to their equilibrium lengths using the LINCS algorithm. The nonbonded interactions were truncated with a cutoff of 1.0 nm. Long-range electrostatic interactions beyond the cutoff were calculated using the particle mesh Ewald method with a Fourier spacing of 0.12 ns and cubic interpolation. Long-range van der Waals interactions were estimated using analytic dispersion corrections for both energy and pressure. The temperature was regulated using a V-rescale thermostat with a coupling time constant of 0.1 ps. The peptide and solvent molecules were separately coupled to a thermostat to avoid temperature heterogeneity. The pressure was maintained at 1 bar using the Berendsen barostat with a coupling time constant of 2.0 ps and an isothermal compressibility of 4.5×10^{-5} bar^{-1}.

Table S1. Dihedral configurational entropy values for linear-$G_{5–15}$ and cyclo-$G_{5–15}$, as well as the slopes from linear regression fitting and the R^2. The standard deviations calculated from two sets of simulations were given in parentheses.

S[a]	5	6	7	8	9	10	11	12	13	14	15	Slope[b]	R^2	Slope[c]
linear-G_n	26.553	31.993	37.407	42.805	48.218	53.658	59.030	64.538	69.896	75.299	80.715	5.416	1.00000	1.625
S_1	(0.017)	(0.003)	(0.000)	(0.001)	(0.025)	(0.054)	(0.017)	(0.053)	(0.050)	(0.098)	(0.132)			
linear-G_n	24.415	29.206	33.944	38.788	43.494	48.248	52.767	57.473	62.339	66.902	71.487	4.709	0.99996	1.413
S_2^{MIE}	(0.010)	(0.026)	(0.041)	(0.032)	(0.121)	(0.044)	(0.102)	(0.008)	(0.035)	(0.002)	(0.008)			
linear-G_n	24.639	29.572	34.469	39.438	44.321	49.241	54.025	58.973	63.956	68.808	73.682	4.904	0.99999	1.471
S_2^{MIST}	(0.001)	(0.026)	(0.027)	(0.017)	(0.080)	(0.050)	(0.053)	(0.027)	(0.020)	(0.031)	(0.061)			
cyclo-G_n	30.593	34.716	38.510	41.388	47.987	54.830	59.974	65.459	70.918	76.238	81.755	5.266	0.99445	1.619*
S_1	(0.003)	(0.014)	(0.022)	(0.036)	(0.020)	(0.008)	(0.012)	(0.067)	(0.033)	(0.036)	(0.019)			
cyclo-G_n	–6.873	–20.202	26.487	28.002	37.019	43.733	47.942	53.676	58.590	63.006	68.068	4.908	0.99875	1.472*
S_2^{MIE}	(0.177)	(0.033)	(0.024)	(0.070)	(0.108)	(0.107)	(0.063)	(0.051)	(0.280)	(0.328)	(0.018)			
cyclo-G_n	14.847	18.775	30.385	35.026	41.036	47.720	52.168	57.383	62.471	67.353	72.507	4.988	0.99962	1.496*
S_2^{MIST}	(0.011)	(0.012)	(0.003)	(0.002)	(0.084)	(0.004)	(0.057)	(0.074)	(0.154)	(0.018)	(0.061)			

[a] In cal/mol/K
[b] In cal/mol/K/res
[c] Slope×300K; in kcal/mol/res
* For cyclo-G_n, the linear regression fitting was done for only $n \geqslant 10$.

Table S2. Number of frames in cyclo-G$_n$ structural ensembles (the two million conformations sampled in the two sets of 1.0-μs MD simulations) matching the structures of cyclic peptides of equal length from the Cambridge Structural Database (CSD) experimentally characterized by X-ray crystallography. Matching frames were defined as deviation in all backbone dihedral angles < 25°. D_{max} is defined as the highest backbone dihedral deviation observed in the best-matching (lowest maximum deviation) frame.

CSD	SIZE	SEQUENCE	# FRAMES	D_{max} (°)
CGPGAP10	5	GPGaP	1521	7.5
CGPSAQ	5	GPSaP	726	6
FIVSAE	5	GPfGA	16492	7.9
FUDWIK	5	GPfGV	44422	4.1
PAPGAP	5	fPGaP	1509	7.3
AAGAGG10	6	AAGAGG	90418	6.2
AAGGAG10	6	AAGGAG	10479	7.3
BIHXUL10	6	PVFFAG	560	11.2
CAHWEN	6	FlGfLG	597	10.9
CAMVES	6	pPAAAA	6288	9.5
CGLEGL	6	GLGGLG	71602	5.6
CGLPGL	6	GPGGPG	2720	8.1
CINYED	6	PVFFAG	1369	9.7
CLPGDH	6	LFGlfG	16326	7.3
CYBGPP	6	GPfGPf	230	14.5
CYDGPA	6	GPaGPa	1769	9.2
CYHEXG	6	GGGGGG	88026	5.7
DICWET	6	GGsGGS	6340	7.4
DUYTIA	6	PFFpFF	5790	8.7
GAJDUQ	6	FWFpFT	9181	5.8
GAJFAY	6	pFTFWF	7339	7.7
GGAAGG	6	GGaaGG	13809	7.6
GOKZOX	6	pFFPFF	6990	7.2
GUFXOU	6	PFFpAA	208	9.5
JEHMAK	6	GYGPLP	378	11.2
PAPRVA	6	fPVfPV	166	15.6
PHLEGL10	6	FlGFLG	1574	8.1
VAWTAQ	6	GPLTLF	1543	7.9
VEGROO	6	LFGfLG	5258	9.1
VUGMEP	6	pFASFF	10643	7.9
XOPZEH	6	fFfFfF	60	12.5
YEXJIV	6	APGFVS	1295	11.1
ZUKRAY	6	GTFLYV	1697	10.5
KARPIE	7	GSPSWLV	10	20.6
ZORRED	7	GYGPLIL	29	13.2
CACNOJ10	8	aGPFaGPF	1018	11.8
CEWCIQ10	8	aGPFaGPF	1249	11.9
DASXIE	8	aGPfaGPf	42902	9
EVAPUM	8	AAYPPIGV	6	19.7
JINGAO	8	AGPFAGPF	3	15.1
NIWHEH	8	pGaisiyy	2	15.8
UZUKUW	8	PPAGLATF	12	18.9
DEWFEQ	12	$(VPG)_4$	0	60.2
FILPEW	12	$(APGVGV)_2$	0	91.7

Table S3. Number of frames in cyclo-G_n structural ensembles (the two million conformations sampled in the two sets of 1.0-μs MD simulations) matching the structures of cyclic peptides of equal length, experimentally characterized by NMR by Hosseinzadeh *et al.*[8] Matching frames were defined as deviation in all backbone dihedral angles < 25°. D_{max} is defined as the highest backbone dihedral deviation observed in the best-matching (lowest maximum deviation) frame.

PDB	SIZE	SEQUENCE	# FRAMES	D_{max} (°)
6BE9	7	DTnpTkN	2	22.2
6BEW	7	DQSEpHp	0	30.5
6BF3	7	QDPpKtd	2	22.8
6BF5	7	QDPpKtd	3	20.7
6BE7	8	DDPTprQq	0	36.3
6BEN	8	PQrQpqRe	2	23.9
6BEO	9	KDLqpPYhP	0	27.6
6BEQ	10	PEAARvpRlt	0	39.1
6BER	10	EvDPehpNap	0	80.4

Table S4. The minimal cyclic-peptide size needed to mimic the 210 hot loops that satisfied all three hot-loop criteria as reported by Siegert *et al*. Here, a hot loop that "could be mimicked by a cyclic peptide" was defined by having a deviation < 25° for all dihedrals and using the two million conformations sampled in the two sets of 1.0-μs MD simulations of cyclo-G_n. It was noted that three of the 210 hot loops seemed to have additional residues that were not included in the original hot loop library and thus were not included in the analysis. Furthermore, fourteen hot loops had *cis* peptide bonds and were also excluded from the analysis here.

PDB	SIZE	CHAIN	1st RES	SEQUENCE	LAST RES	MIN CP
1dlp	5	F	188	QPNGR	192	6
2jb0	5	A	52	DLIYY	56	9
2rsk	5	D	37	GQWNK	41	>15
2vq5	5	B	132	LDLGV	136	7
3zrl	5	X	199	PHRLL	203	10
4bwy	5	E	77	RDLIG	81	8
4hpo	5	P	173	HALFY	177	10
4jqs	5	A	206	GIKDV	210	8
4ofi	5	A	115	TKDDF	119	9
1dum	6	A	4	KYLHSA	9	>15
1etr	6	L	3	LRPLFE	8	>15
1hao	6	L	3	LRPLFE	8	>15
1hap	6	L	3	LRPLFE	8	>15
1iq6	6	A	26	AALSED	31	9
1jnp	6	B	276	LYPKDR	281	10
1jr0	6	E	31	LAGKRE	36	8
1le8	6	A	95	LNSKEK	100	10
1nfk	6	B	303	VHRQFA	308	13
1nvm	6	A	278	VDRETL	283	13
1pzg	6	B	260	SFLNDE	265	9
1rcu	6	D	145	YLDNRR	150	10
1s5d	6	E	31	LAGKRE	36	8
1xef	6	B	636	LDYESE	641	10
1yfn	6	F	4	PAPHQW	9	10
2afh	6	A	122	DIVFGG	127	11
2ass	6	C	3038	MSESEW	3043	10
2ast	6	C	3038	MSESEW	3043	10
2cvo	6	D	260	ANLYTE	265	8
2fbn	6	B	133	MYFGFL	138	10
2iij	6	B	129	RIRGER	134	>15
2qeu	6	C	117	WGKTGR	122	11
2wam	6	B	90	FKTDHF	95	>15
3ajv	6	A	152	VDRTGL	157	9
3c5x	6	A	243	PHAKKQ	248	9
3dd2	6	L	3	LRPLFE	8	10
3f3f	6	A	333	ATYSNE	338	9
3f9k	6	A	143	YNPQSQ	148	9
3gke	6	A	48	ICPHRF	53	10
3ik5	6	B	72	YNELNL	77	9
3jqy	6	B	150	FDIHSK	155	8
3jrv	6	C	83	SFFSDR	88	8
3mdi	6	B	29	KPLTLE	34	9
3pqr	6	B	344	LKDVGL	349	9
3psm	6	B	35	CRDDFR	40	9
3qht	6	C	77	SYYDLY	82	8
4a0l	6	B	102	QTSILH	107	11
4dih	6	L	3	LRPLFE	8	10
4dii	6	L	3	LRPLFE	8	12
4j2c	6	B	38	KLYYGL	43	10
4mx3	6	B	118	KDYKTM	123	10

4olp	6	C	42	LPVPDL	47	10
1axi	7	B	164	DIQKGWM	170	10
1bxk	7	B	556	PSSPYSA	562	11
1cs1	7	B	15	NDDEQYG	21	10
1hwg	7	B	144	VSLTGIH	150	13
1hx6	7	A	329	RRRIATD	335	10
1krr	7	C	116	PVHHELR	122	>15
1o7d	7	C	570	VPAVGFS	576	12
1wt5	7	B	100	GGPYFFD	106	>15
1xkp	7	A	33	QFRGESV	39	10
2a19	7	B	485	CDTAFET	491	13
2a26	7	B	20	ATRKRVR	26	13
2a2m	7	B	120	YHQTWHL	126	10
2a2m	7	B	121	HQTWHLR	127	10
2aj7	7	A	40	FAAGTPY	46	8
2axi	7	B	21	FEXLDWE	27	>15
2jdi	7	H	20	FASPTQV	26	>15
2ksp	7	B	147	PYNPFEE	153	>15
2ogk	7	C	15	VHSTEDR	21	>15
2ppb	7	E	13	VDSKYRL	19	13
2q4o	7	B	161	AVEEGFI	167	10
2qmh	7	F	204	EIRGLGI	210	12
2vvm	7	B	97	WHQSHVW	103	>15
2xsx	7	A	398	PCRSERL	404	>15
2ylb	7	A	45	LLKNTVS	51	>15
2zih	7	C	200	NFFLFDM	206	10
3co2	7	A	282	VATPNPV	288	13
3hdg	7	B	15	EDDTDAR	21	11
3iaa	7	B	133	SNEHYSF	139	>15
3ijj	7	B	106	VGWNNST	112	11
3j09	7	B	49	VNLATET	55	13
3lm2	7	A	65	VVHNKPL	71	11
3qmn	7	C	111	SDERHYA	117	10
4d9i	7	B	387	EVVWEGK	393	10
4j07	7	E	84	RGDTPHF	90	12
4j07	7	A	105	ALDTSTP	111	14
4jqs	7	C	205	LGIKDVV	211	>15
4k6l	7	E	46	QIDTSPY	52	10
4oig	7	B	227	KSHTLWS	233	15
1b9l	8	B	104	HALRYADS	111	>15
1bii	8	B	355	SFSKDWSF	362	11
1bsu	8	B	23	IISAEGKI	30	12
1egp	8	B	56	YNPGTNVV	63	9
1fth	8	A	1104	SHTDQFVT	1111	10
1fxo	8	C	27	LLPVYDKP	34	>15
1im9	8	A	234	RPAGDGTF	241	>15
1im9	8	F	55	SFSKDWSF	62	11
1jmt	8	A	133	RWFNGQPI	140	11
1ju5	8	C	93	YNHNGEWC	100	11
1kgy	8	F	1321	SPNLWGLE	1328	>15
1kke	8	A	281	INSSGQLT	288	11
1mas	8	B	265	ELTGKLTL	272	>15
1ncp	8	N	2	KCFNCGKE	9	>15
1q4u	8	A	57	RQRWGLVH	64	12
1q5a	8	A	81	VSENGSPV	88	12
1q5b	8	B	80	AVSENGSP	87	>15
1q5b	8	B	81	VSENGSPV	88	12
1qks	8	B	287	MTYDEQEY	294	13
1rve	8	B	23	IISAEGKI	30	>15

1sr4	8	A	120	PGKHREYF	127	12
1ul3	8	B	100	VRIRTGEK	107	10
1vgw	8	B	146	RAESGQIS	153	>15
1wmh	8	A	61	WIDEEGDP	68	11
1xfs	8	A	92	LVKNYRPA	99	11
2ae8	8	B	94	IPXDETLA	101	>15
2bfd	8	B	118	RYRSGDLF	125	12
2czc	8	D	264	RDLHREWN	271	10
2e4m	8	B	97	QDYISRNV	104	10
2fd6	8	A	21	SNKYFSNI	28	13
2fe8	8	A	266	TGNYQCGH	273	10
2hq7	8	B	25	NGENGYPN	32	11
2hzs	8	A	92	VFNGSSTG	99	12
2i9b	8	A	21	SNKYFSNI	28	>15
2j9c	8	B	100	VRVRTKEE	107	10
2jra	8	A	46	IAHGDDRY	53	>15
2jxc	8	B	309	WRATNPFL	316	>15
2kpz	8	A	30	IDHNTKTT	37	>15
2ldx	8	C	293	VLGESGIT	300	11
2ltz	8	A	307	NTATGRVY	314	13
2ns1	8	B	44	ELYRGAEF	51	>15
2nwt	8	A	7	AVYENGVF	14	>15
2o56	8	H	80	LKKTFWGQ	87	>15
2oiz	8	D	147	RPGYEFFL	154	14
2oqb	8	B	92	SRVGRQSF	99	>15
2ovp	8	B	2305	AQTCRYWR	2312	>15
2peh	8	B	375	RYFGGRVV	382	>15
2qnr	8	B	256	RLYPWGVV	263	>15
2qya	8	B	9	HGTGDTVV	16	>15
2x7n	8	D	21	FVRGDSKI	28	>15
2y0n	8	H	573	PVVAFGRP	580	15
2y0n	8	H	574	VVAFGRPL	581	15
2z3h	8	C	46	VYHFTGGP	53	>15
2zih	8	D	199	KNFFLFDM	206	10
2zii	8	A	199	KNFFLFDM	206	>15
2zki	8	C	116	ASTVHGGH	123	>15
3ba3	8	A	20	TAVNNEAD	27	>15
3bdx	8	C	93	SYDSSNHV	100	11
3bt1	8	A	21	SNKYFSNI	28	>15
3bxw	8	A	209	ITPGTDQL	216	>15
3cdx	8	F	31	SRNNSGWG	38	>15
3cea	8	D	275	VFNDQGVV	282	>15
3cfi	8	C	97	KWLGGRDW	104	>15
3chb	8	H	30	SLAGKREM	37	>15
3dem	8	A	139	HNYIGGYY	146	10
3e8m	8	D	21	FYDQTGNE	28	13
3eev	8	C	78	HRSDWIST	85	>15
3euw	8	A	260	KHNAESTE	267	14
3gke	8	B	48	ICPHRFAP	55	>15
3h8v	8	A	285	YNAMQDFF	292	>15
3hi6	8	H	99	SYDFWSNA	106	>15
3hsh	8	B	26	FVAEQEEL	33	>15
3hvd	8	H	221	SSPEKWST	228	>15
3l2h	8	C	138	YRNNGEWN	145	>15
3mmz	8	D	29	LIDSDGRE	36	12
3n6q	8	G	102	MWPGPYGS	109	13
3nvn	8	A	199	GPSSLSSH	206	10
3nvq	8	A	271	GGESSLSV	278	10
3ovg	8	C	135	YNYNGPVV	142	11
3p0g	8	A	134	AITSPFKY	141	>15
3pyi	8	A	150	SKTPISKG	157	>15

3rwr	8	A	99	KNLKDVSF	106	>15
3u28	8	C	82	LGPLNEVF	89	11
3uly	8	B	207	LVDEFGLP	214	11
3vr0	8	A	72	LIRKNSVV	79	11
3vyr	8	A	42	VIVHTGFA	49	>15
3vyr	8	A	43	IVHTGFAI	50	>15
3vyt	8	A	43	IVHTGFAI	50	>15
3zyi	8	B	69	CSHENPYL	76	11
4ani	8	G	370	IETMGGVF	377	>15
4c92	8	C	32	AFDSHCNI	39	11
4c9r	8	B	46	CSKDNGCL	53	12
4cdg	8	C	120	VADYDMGF	127	>15
4ecd	8	A	236	TYVESDRR	243	11
4f88	8	H	30	AFINGVEI	37	>15
4g6u	8	A	244	YALSGREL	251	>15
4ief	8	B	551	VEKYKKDG	558	11
4kng	8	P	64	LERNDIRQ	71	>15
4kng	8	P	65	ERNDIRQV	72	>15
4kt1	8	E	104	ACFSHNFC	111	>15
4m1u	8	F	12	KYNEDDTF	19	11
4mur	8	B	25	APFSDHDV	32	>15
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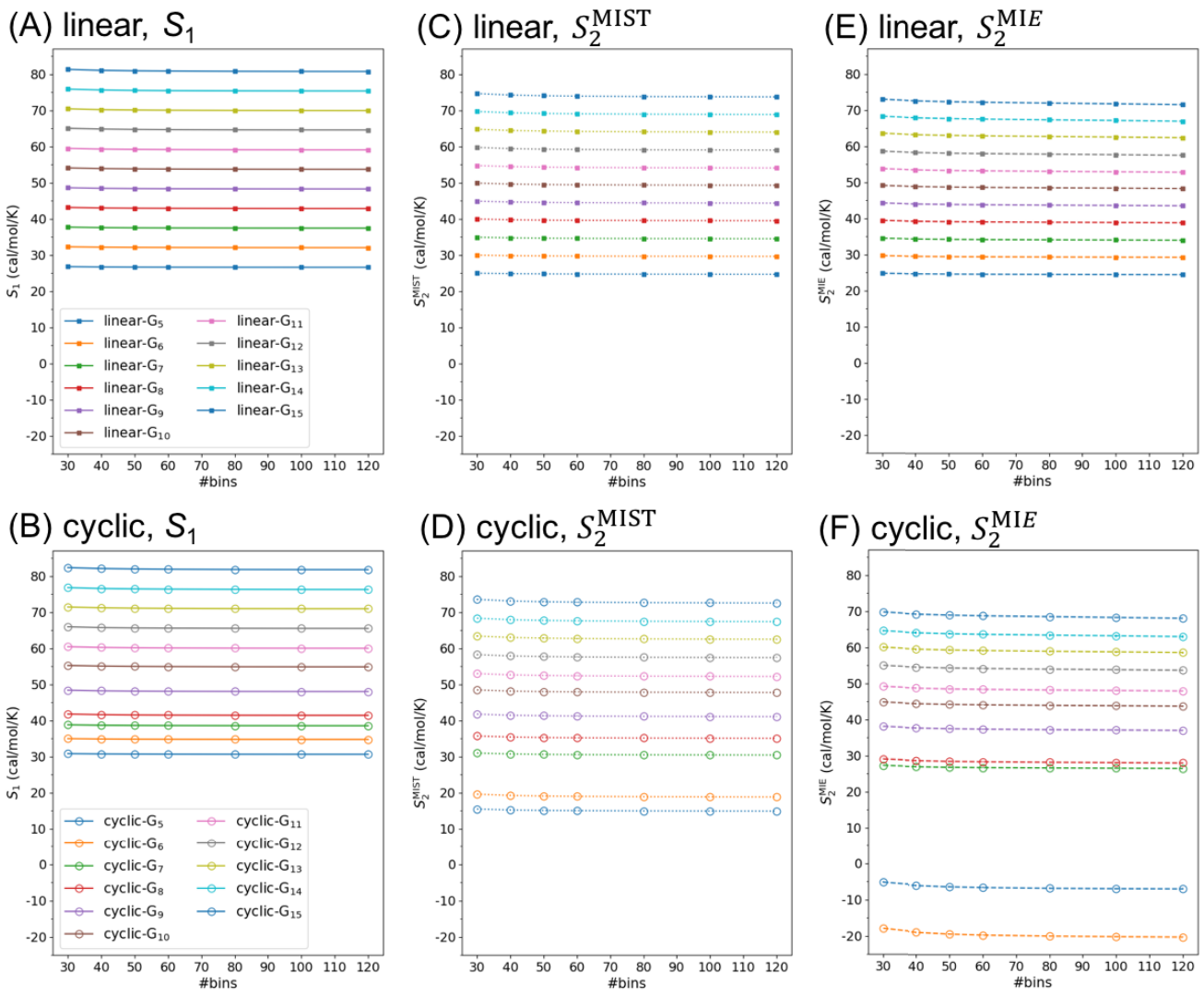

Figure S1. Dependence of the calculated entropies on the number of bins used.

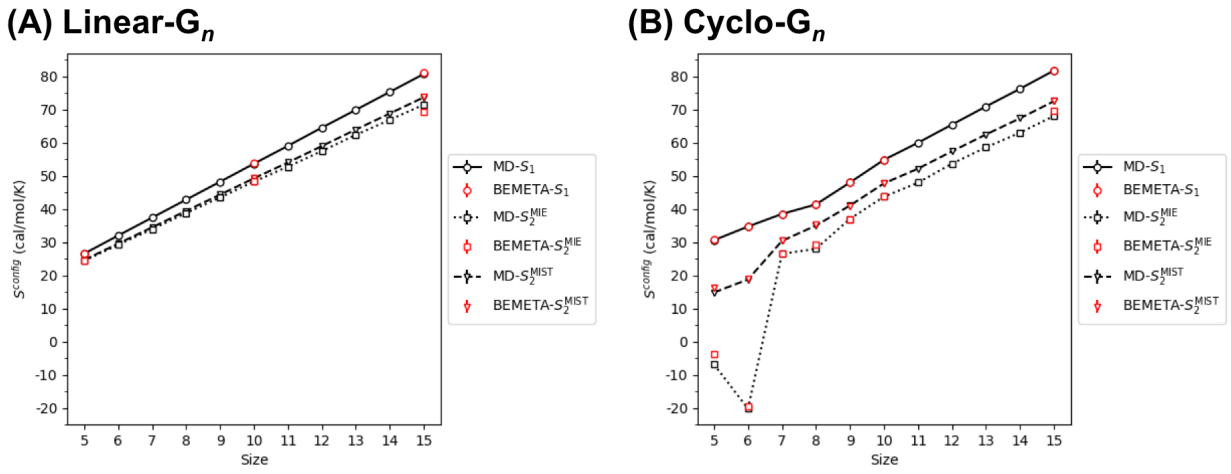

Figure S2. Comparison of entropy calculation results of linear and cyclic G_n from the MD (black) and BE-META (red) simulations. Note that 250-ns BE-META simulations were carried out for selected systems of linear-G_n (n = 5, 10, 15) and cyclo-G_n (n = 5–10, 15); the last 200 ns was used for the entropy calculation so that 200 ns × 5 neutral replicas = 1.0 μs trajectory = one million frames, to be consistent with the number of frames used from the MD simulations.

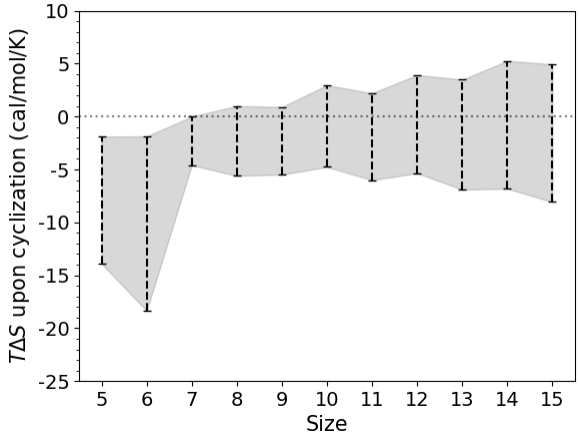

Figure S3. Change in configurational entropy upon cyclization of polyglycines as a function of peptide size at 300 K. The atoms in the in the N- and C-terminal caps of linear-G_n were not included in the entropy calculation, to ensure the same number of atoms as in cyclo-G_n. All degrees of freedom were included in the entropy calculation by the PARENT software.[9]

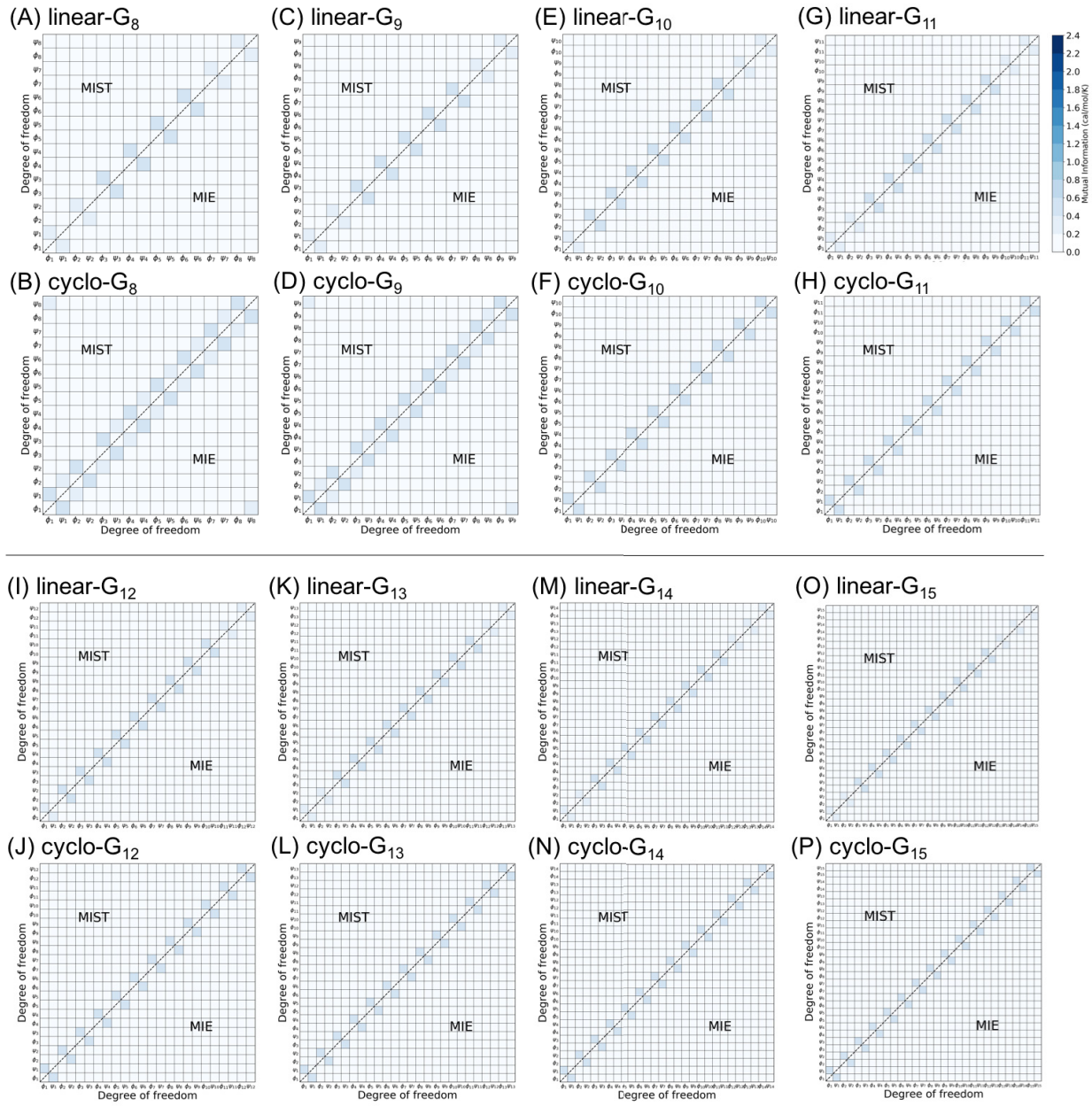

Figure S4. Mutual information for linear- and cyclo-$G_{8–15}$.

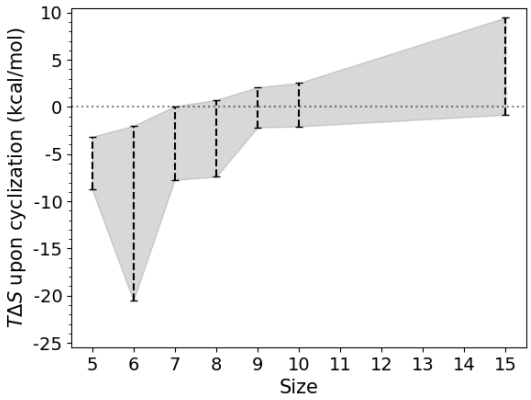

Figure S5. Change in backbone dihedral configurational entropy upon cyclization of polyalanines as a function of peptide size at 300 K. BE-META simulations were carried out for selected systems of linear and cyclic A_n (n = 5–10, 15); the simulation length was 100 ns for linear-A_{15} and 250 ns for all the other systems; the last 50 ns was used for the entropy calculation.

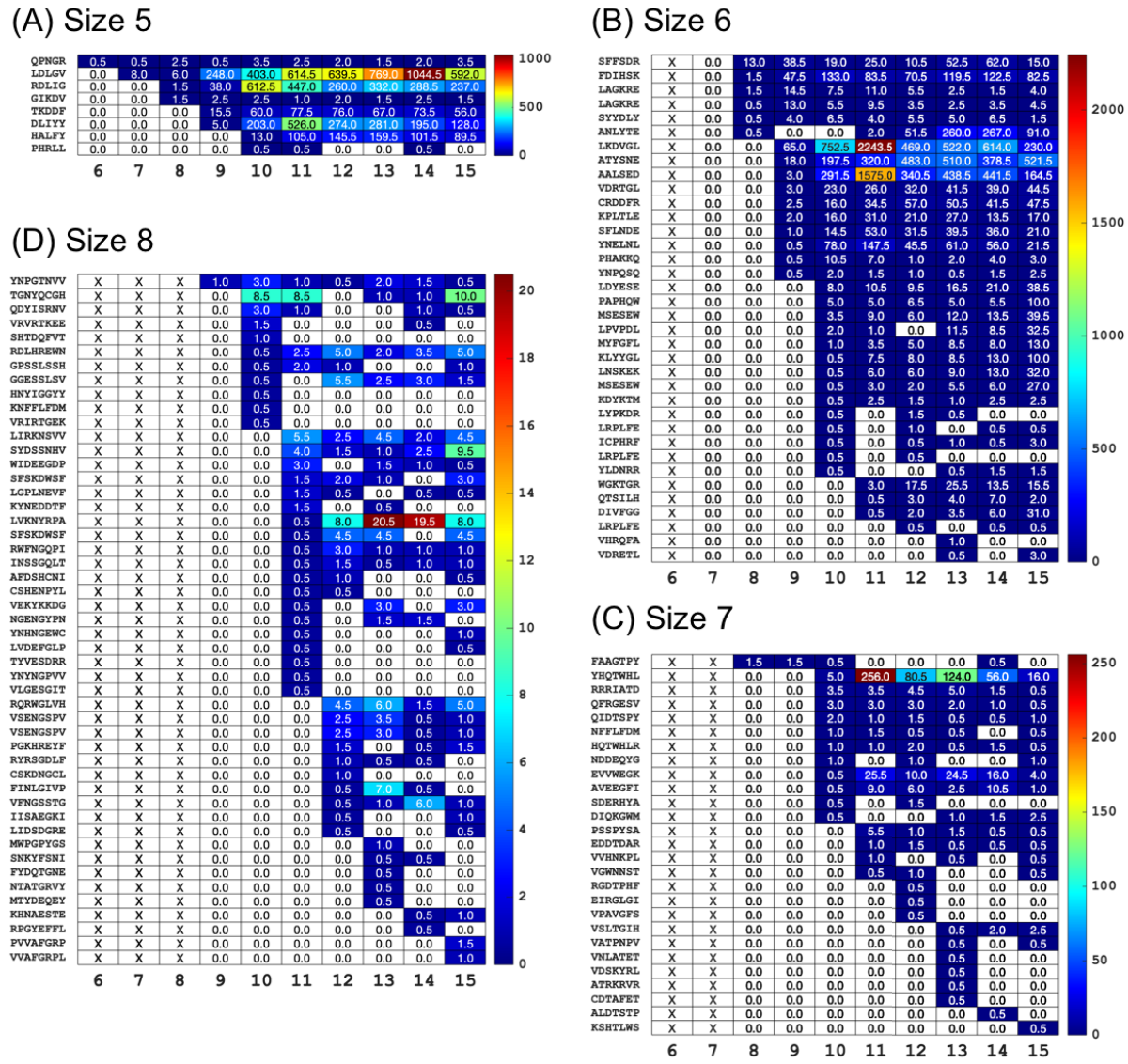

Figure S6. Fraction (in ppm) of the cyclo-G_n structural ensembles mimicking each hot loop. Hot loops whose conformations were never observed in the two sets of 1.0-μs MD simulations of cyclo-G_n were not included in this figure.

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