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Intrinsic folding of the cysteine residue: competition between folded and extended forms mediated by the -SH group

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Supplementary information

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Table S1: Structural and energetic parameters of Z-Cys-NH_2 : effect of the Z-tail rotamerism on the folded and extended forms from the DFT-D (B97-D3/def2-TZVPPD) calculations (same legend as Table 1).

Molecule		Bn-O-CO-Cys-NH_2						
Conformation		#1				#2		
Backbone		Folded				Extended		
Structure		$5^{\gamma}(^{\gamma}6)$-7				5-6^{γ}		
Z-cap		gauche +	gauche-	trans		gauche-	gauche +	trans
Energetics (kJ/mol)								
ΔE (electronic)		0	1.0	4.6		4.9	5.4	9.1
ΔH (0K)		0	1.4	3.7		3.8	4.5	6.6
ΔG (300K)		0	1.8	1.8		1.7	3.2	2.8
Interatomic distance (pm) ($NBO\ \Sigma E_{HB}$) (kcal/mol)								
NH_{Cys} /NH_2 – O		7 : 202 (*6.2*)	203	203		5 : 215 (*1.7*)	215	215
NH_{Cys} /NH_2 – S		5^{γ} : 261 (*2.1*)	261	261		6^{γ} : 249 (*5.5*)	250	248
SH – O		$^{\gamma}6$: 238 (*1.3*)	237	238				

Table S2: Structural, energetic and vibrational parameters of the folded and extended structures of Ac-Cys-NH_2 at the DFT-D (B97-D3/def2-TZVPPD) level of theory, for comparison with Tables 1 and 2 (same legend as Table 1).

Molecule			Ac-Ala-NH_2		
Conformation			#1		#2
Backbone			Folded		Extended
Structure[a]			f-7		5-f
Energetics (kJ/mol)					
ΔE (electronic)			0		6.0
ΔH (0K)			0		3.9
ΔG (300K)			0		1.0
Interatomic distances (pm)					
NH_{Cys}/NH_2– O			7 : 206		5 : 220
Vibrational frequencies (cm^{-1})					
NH stretches sym. NH_2			7 : 3369		
NH_{Ala}					5 : 3442

a) The label f designates a free NH

Table S3: Comparison of the structural, energetic and vibrational parameters of the C5 and C7 structures of Ac-Ala-NH_2 and Ac-Cys-NHMe at the DFT-D (RI-B97-D3(BJ)abc/def2-TZVPPD) level of theory.

Molecule		Ac-Cys-NH_2					Ac-Cys-NH-Me		
Conformation		#1		#2			#1		#2
Backbone		folded		extended			folded		extended
Structure		$5^{\gamma}(^{\gamma}6)$-7		5-6^{γ}			$5^{\gamma}(^{\gamma}6)$-7		5-6^{γ}
Interatomic distances (pm)	NH_{Cys} – O/S	5^{γ} : 257		5 : 214		NH_{Cys} – O/S	5^{γ} : 261		5 : 215
	NH_2 – O/S	7 : 200		6^{γ} : 249		$NH_{C\text{-}term}$ – O/S	7 : 202		6^{γ} : 249
Scaled NH stretch frequencies (cm^{-1})	NH_{Cys} – O/S	5^{γ}: 3408		5 : 3427		NH_{Cys} – O/S	5^{γ} : 3406		5 : 3421
	NH_2 – O/S	7 : 3353		6^{γ} : 3380		$NH_{C\text{-}term}$ – O/S	7 : 3322		6^{γ} : 3379

Table S4: Dependence of the calculated rotational parameters of the lowest energy C5 and C7 conformers of Ac-Ala-NH_2 with the theoretical method and basis set employed.

C7	B3LYP-D3(BJ)/ def2-TZVP	B3LYP-D3(BJ)/ def2-TZVPPD	B97-D3(BJ)/ def2-TZVP	B97-D3(BJ)/ def2-TZVPPD	RI-B97-D3(BJ)-abc/ def2-TZVP	RI-B97-D3(BJ)-abc/ def2-TZVPPD
A	1475	1475	1459	1459	1453	1453
B	833	833	829	828	829	828
C	601	600	597	597	596	596
Dipole moment (Debye)						
Total	2.2	2.2	2.0	2.2	2.0	2.0
a/b/c components	1.7/1.4/0.2	1.7/1.5/0.2	1.6/1.2/0.2	1.7/1.5/0.1	1.5/1.4/0.2	1.5/1.4/0.2
Energetics	0	0	0	0	0	0

C5	B3LYP-D3(BJ)/ def2-TZVP	B3LYP-D3(BJ)/ def2-TZVPPD	B97-D3(BJ)/ def2-TZVP	B97-D3(BJ)/ def2-TZVPPD	RI-B97-D3(BJ)-abc/ def2-TZVP	RI-B97-D3(BJ)-abc/ def2-TZVPPD
A	1432	1431	1423	1423	1421	1423
B	781	781	771	770	770	768
C	538	538	534	534	533	533
Dipole moment (Debye)						
Total	1.5	1.5	1.6	1.6	1.6	1.6
a/b/c components	1.3/0.8/0.3	1.3/0.8/0.3	1.3/0.8/0.3	1.3/0.8/0.4	1.3/0.8/0.3	1.3/0.8/0.4
Energetics (kJ/mol)						
ΔH 0K	**6.3**	**5.8**	**5.8**	**5.2**	**5.6**	**5.0**
ΔG 300K	**3.8**	**3.3**	**3.5**	**2.8**	**2.6**	**1.7**

Table S5 : Dependence of the structural parameters of the lowest energy C5 and C7 conformers of Ac-Ala-NH_2 with the theoretical method and basis set employed. Ramachandran and side chain $\chi 1$ dihedrals are given in degrees, H-bond distances as well as backbone and side chain covalent bonds (two last lines of each sub-table) in pm.

B3LYP-D3(BJ)/def2-TZVP

Parameters	Folded C7	Extended C5
φ	-82	-160
ψ	63	174
χ_1	51	199
NHCys/NH_2---O	200	211
NHCys/NH_2---S	257	249
SH---O	236	
C7 --- CO: 123/122; SH:134; NH_2: 101/101; NH: 101; CC: 151/155/153(SC); CS:183; CN:135/145/135		
C5 --- CO: 122/122; SH:134; NH_2: 101/101; NH: 101; CC: 151/154/154(SC); CS:183; CN:136/144/135		

B3LYP-D3(BJ)/def2-TZVPPD

Parameters	Folded C7	Extended C5
φ	-82	-160
ψ	63	174
χ_1	51	198
NHCys/NH_2---O	199	212
NHCys/NH_2---S	258	250
SH---O	237	
C7 --- CO: 123/122; SH:134; NH_2: 101/101; NH: 101; CC: 151/155/153(SC); CS:183; CN:135/145/135		
C5 --- CO: 122/122; SH:134; NH_2: 101/101; NH: 101; CC: 151/154/154(SC); CS:183; CN:136/144/135		

B97-D3(BJ)-abc/def2-TZVPPD

Parameters	Folded C7	Extended C5
φ	-82	-159
ψ	64	173
χ_1	51	198
NHCys/NH_2---O	199	213
NHCys/NH_2---S	257	249
SH---O	237	
C7 --- CO: 124/123; SH:135; NH_2: 102/101; NH: 101; CC: 152/156/153(SC); CS:183; CN:136/146/135		
C5 --- CO: 123/123; SH:135; NH_2: 101/101; NH: 101; CC: 152/154/155(SC); CS:183; CN:136/144/136		

RI-B97-D3(BJ)-abc/def2-TZVPPD

Parameters	Folded C7	Extended C5
φ	-82	-158
ψ	64	173
χ_1	51	198
NHCys/NH_2---O	200	214
NHCys/NH_2---S	257	249
SH---O	239	
C7 --- CO: 124/123; SH:135; NH_2: 102/101; NH: 101; CC: 152/156/153(SC); CS:183; CN:136/146/135		
C5 --- CO: 123/123; SH:135; NH_2: 101/101; NH: 101; CC: 152/154/155(SC); CS:183; CN:136/144/136		

Figure S1: Structure of the *trans*-Me-CONH-Me···MeSH intermolecular complex at the DFT-D (RI-B97-D3/def2-TZVPPD) level of theory.