The effect of N-methylation of amino acids (Ac-X-OMe) on solubility and conformation: A DFT study

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Table 1S. The effect of N-methylation through the inductive effect of the methyl group on the atomic charges (both NBO and ESP) distributed on Ac-X-OMe (X= Gly).

Atomic number	Natural atomic charges (a.u.)		ESP charges (a.u.)	
	Ac-Gly-OMe	Ac-(Nme)Gly-OMe	Ac-Gly-OMe	Ac-(Nme)Gly-OMe
N_1	-0.675	-0.509	-0.334	-0.011
H_2/C_2	0.446 (H)	-0.474(C)	0.261 (H)	-0.395 (C)
C_3	-0.357	-0.351	-0.608	-0.608
H_4	0.276	0.302	0.216	0.206
H_5	0.276	0.260	0.216	0.194
C_6	0.813	0.811	0.931	0.934
O_7	-0.619	-0.608	-0.544	-0.547
O_8	-0.547	-0.559	-0.401	-0.419
C_9	0.675	0.692	0.745	0.632
C_{10}	-0.337	-0.337	-0.070	-0.045
H_{11}	0.230	0.231	0.086	0.083

H_{12}	0.230	0.226	0.086	0.072
H_{13}	0.236	0.232	0.116	0.108
O_{14}	-0.650	-0.640	-0.547	-0.546
C_{15}	-0.765	-0.772	-0.733	-0.512
H_{16}	0.235	0.250	0.178	0.130
H_{17}	0.267	0.256	0.200	0.147
H_{18}	0.267	0.272	0.200	0.151
H_{19}		0.234		0.151
H_{20}		0.243		0.143
H_{21}		0.241		0.134

Table 2S. Amide bond length (A˚) of Native and N-met analogue of amino acid derivatives, at different conformations.

	Amide Bond length A˚		
	Trans	TS	Cis
X=Gly	1.362	1.454	1.370
X=(NMe)Gly	1.380	1.457	1.382
X=Val	1.375	1.463	1.378
X=(NMe)Val	1.381	1.448	1.382
X=Leu	1.363	1.454	1.372
X=(NMe)Leu	1.380	1.451	1.382
X=Ile	1.375	1.463	1.378
X=(NMe)Ile	1.881	1.449	1.382
X=Phe	1.371	1.464	1.382
X=(NMe)Phe	1.380	1.457	1.383
X=Met	1.371	1.463	1.381
X=(NMe)Met	1.375	1.466	1.382
X=Cys	1.371	1.467	1.382
X=(NMe)Cys	1.376	1.466	1.383
X=Ser	1.368	1.459	1.377
X=(NMe)Ser	1.380	1.458	1.383
X=Asp	1.376	1.464	1.385
X=(NMe)Asp	1.385	1.452	1.388
X=His	1.369	1.445	1.382
X=(NMe)His	1.383	1.449	1.387

In *cis* and *trans* conformation N-methylation leads to an increase of bond length (more single bond character) which ease the amide bond rotation thus facilitate *cis/trans* isomerization.

Table 3S. (Suplimentary) Calculated energies and torsion angles for the conversion of *cis/trans*-amino acids (Ac-X-OMe) and their corresponding N-methylated analogues in gas phase and solvents.

Table 4S. Calculated entropic contribution (ΔS) for the conversion of *cis/trans*-amino acids

		TS1			TS2		
Ac-X-OME	$\Delta H_{cis\text{-}trans}$ /Kcal mol^{-1}	$E_{Acis/trans}$ /Kcal mol^{-1}	$E_{Atrans/cis}$ /Kcal mol^{-1}	Torsion angle/°	$E_{Acis/trans}$ /Kcal mol^{-1}	$E_{Atrans/cis}$ /Kcal mol^{-1}	Torsion angle/°
Gas							
X=Gly	3.77	15.06	18.83	-54	18.83	22.59	108
X=Gly-NMe	1.26	17.57	18.20	-65	20.71	21.96	97
X=Phe	3.77	13.81	16.32	-68	19.45	23.22	111
X=Phe-NMe	1.88	14.43	15.68	-71	18.19	20.08	91
Water							
X=Gly	2.51	16.94	19.45	-54	18.82	21.33	108
X=Gly-NMe	0.00	18.82	18.82	-60	25.10	25.10	120
X=Phe	3.76	14.43	18.19	-50	18.19	23.84	111
X=Phe-NMe	1.88	14.43	16.31	-68	18.82	21.96	111
Hexane							
X=Gly	3.76	16.31	20.08	-54	18.82	22.59	108
X=Gly-NMe	0.00	18.19	18.19	-60	20.70	20.70	102
X=Phe	2.51	14.43	16.94	-68	18.82	23.21	111
X=Phe-NMe	1.88	14.43	16.31	-68	18.82	21.33	111

(Ac-X-OMe) and their corresponding N-methylated analogues using B3LYP/6-311++G(d,p).

Amino acid derivatives	**$\Delta S_{cis\text{-}trans}$ in gas** (Cal/mol.K)
X= Gly	5.405
X =(Nme)Gly	1.361
X =Val	2.342
X =(NMe)Val	1.258
X= Leu	8.456
X= (NMe)Leu	0.509
X = Ile	2.015
X = (NMe)Ile	-3.003
X = Phe	8.300
X = (NMe)Phe	0.168
X = Met	2.047
X = (NMe) Met	1.416
X = Cys	0.102
X = (NMe)Cys	-0.406
X = Ser	3.709
X = (NMe) Ser	1.587
X = Asp	1.554
X =(NMe) Asp	1.352
X = His	0.208
X = (NMe) His	-4.125