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Rationalizing the diversity of amide-amide H-bonding in peptides using the Natural Bond Orbital method

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Supplementary Information

Content

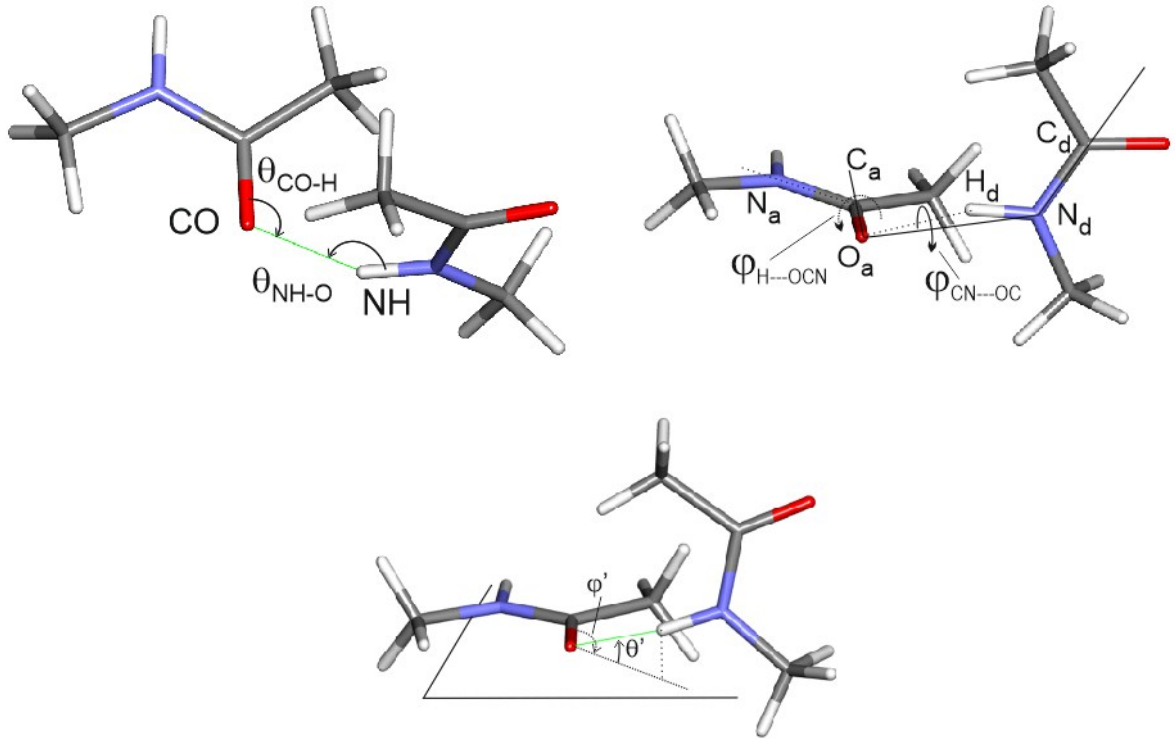

Figure S1 : Description of the geometrical parameters used for the description of H-bonded *trans*-methylacetamide dimers.

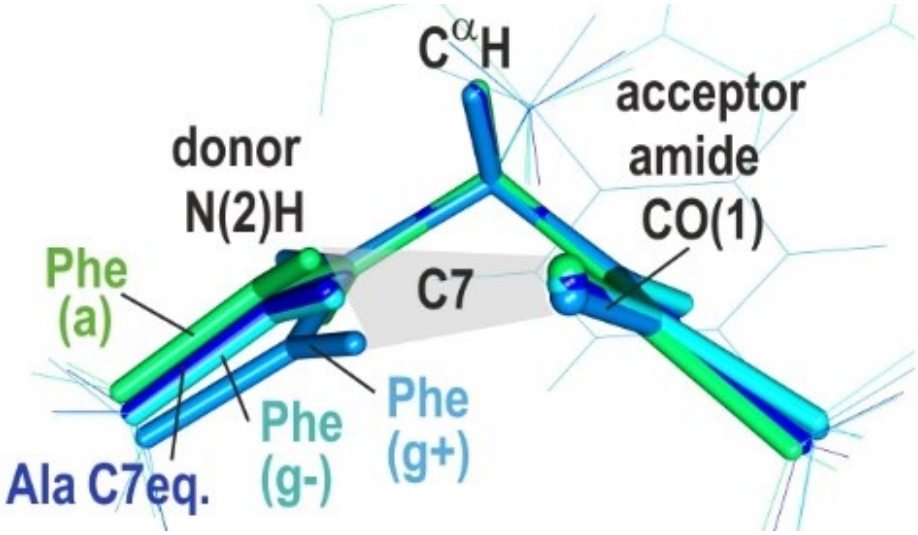

Fig. S2 : Comparison of the C7eq inverse γ-turn of Ala (dark blue) with those of Phe for the three rotamers of the Phe side chain (*gauche +*, in blue; *gauche -* in turquoise and *anti* in green), obtained by overlapping the N(1), C^{α} and C(2) atoms. For the sake of clarity, the side chains are displayed as simple lines. The picture illustrates the slight changes in ψ dihedral and in the HB approach induced by the backbone-side chain interactions.

Table S1 : NBO analysis of the relevant conformations (C7eq, C7ax, C5) of the AcAlaNHMe, AcAibNHMe, AcGlyNHMe and *N*-isopropylacetamide molecules : Stabilisation energy E(2) (kcal/mol) of the relevant donor NBO → acceptor NBO interactions. For C7 structures, the second and third lines indicate the nature of the groups present in equatorial and axial position.

AcAlaNHMe C7eq		**N-isopropyl acetamide**		**AcAlaNHMe C7ax**		**AcAibNHMe C7**			**AcAlaNHMe C5**		**AcGlyNHMe C5**		**AcAibNHMe C5**	
HC0 set														
nN(1) → σ*C$^{\alpha}$C(2)	10.1	nN(1) → σ*C$^{\alpha}$C(2)	9.0	nN(1) → σ*C$^{\alpha}$C(2)	9.6	nN(1) → σ*C$^{\alpha}$C(2)	9.8		**nN(1) → σ*C$^{\alpha}$C(2)**	**1.1**				
nN(1) → σ*C$^{\alpha}$H (ax)	**2.7**	**nN(1) → σ*C$^{\alpha}$H (ax)**	**2.4**	**nN(1) → σ*C$^{\alpha}$H (eq)**	**< 0.5**	**nN(1) → σ*C$^{\alpha}$ C$^{\beta}$ (eq)**	**< 0.5**		**nN(1) → σ*C$^{\alpha}$H**	**5.3**	**nN(1) → σ*C$^{\alpha}$H**	**9.1**	**nN(1) → σ*C$^{\alpha}$C$^{\beta}$**	**7.6**
nN(1) → σ*C$^{\alpha}$C$^{\beta}$(eq)	**1.6**	**nN(1) → σ*C$^{\alpha}$C$^{\beta}$(eq)**	**2.2**	**nN(1) → σ*C$^{\alpha}$C$^{\beta}$(ax)**	**5.8**	**nN(1) → σ*C$^{\alpha}$ C$^{\beta'}$(ax)**	**5.2**		**nN(1) → σ*C$^{\alpha}$C$^{\beta}$**	**9.2**	**nN(1) → σ*C$^{\alpha}$H**	**9.0**	**nN(1) → σ*C$^{\alpha}$C$^{\beta}$**	**7.8**
HC1 set														
σC$^{\alpha}$H (ax) → σ*N(1)H	**3.5**	**σC$^{\alpha}$H (ax)→ σ*N(1)H**	**4.4**	**σC$^{\alpha}$C$^{\beta}$ (ax) → σ*N(1)H**	**1.2**	**σC$^{\alpha}$C$^{\beta}$ (ax)→ σ*N(1)H**	**1.7**		**σC$^{\alpha}$H → σ*N(1)H**	**2.6**	**σC$^{\alpha}$H → σ*N(1)H**	**1.5**	**σ*C$^{\alpha}$C$^{\beta}$ → σ*N(1)H**	**1.2**
									σC$^{\alpha}$C$^{\beta}$ → σ*N(1)H	**0.6**	**σC$^{\alpha}$H' → σ*N(1)H**	**1.5**	**σ*C$^{\alpha}$C$^{\beta}$ → σ*N(1)H**	**1.2**
											σC$^{\alpha}$C(2) → σ*N(1)H	**0.6**	**σ*C$^{\alpha}$C(2) → σ*N(1)H**	**0.7**
σCO(1) → σ*N(1)H	1.7	σCO(1) → σ*N(1)H	1.8	σCO(1) → σ*N(1)H	1.6	σCO(1) → σ*N(1)H	1.7		**σCO(1) → σ*N(1)H**	**1.9**	**σCO(1) → σ*N(1)H**	**1.9**	**σCO(1) → σ*N(1)H**	**1.9**
HC2 set														
σC$^{\alpha}$C$^{\beta}$(eq)→ σ*CN(1)	**3.4**	**σC$^{\alpha}$C$^{\beta}$ (eq)→ σ*CN(1)**	**3.2**	**σC$^{\alpha}$H (eq) → σ*CN(1)**	**6.0**	**σC$^{\alpha}$ C$^{\beta}$(eq) → σ*CN(1)**	**4.7**							
σC$^{\alpha}$C$^{\beta}$ (eq) → σ*CN(2)	**2.6**			**σC$^{\alpha}$H (eq) → σ*CN(2)**	**4.7**	**σC$^{\alpha}$ C$^{\beta}$(eq) → σ*CN(2)**	**3.0**							
σC$^{\alpha}$C$^{\beta}$ (eq)→ σ*N(1)H				σC$^{\alpha}$H (eq) → σ*N(1)H	0.8	σC$^{\alpha}$ C$^{\beta}$(eq) → σ*N(1)H	0.8							
H-bonding									**H-bonding**					
nO(1) → σ*N(2)H	2.49				5.50		9.75		**nO(2) → σ*N(1)H**	**0.15**		**0.21**		**0.69**
n'O(1) → σ*N(2)H	1.27				3.11		3.58		**n'O(2) → σ*N(1)H**	**0.94**		**1.16**		**2.80**
πCO(1) → σ*N(2)H	1.01				1.90		2.17							
Sum of H-bond contributions	*4.8*				*10.5*		*12.0*			***1.1***		***1.4***		***3.5***

Table S2 : Energetic, structural and NBO parameters of the three H-bonded minima of the trans-methylacetamide dimer

	C-side			N-side			N'-side
	Ref. 37	this work		Ref. 37	this work		this work
ΔE kcal/mol	0			0.03			
		0			0.16		0.02
R(H···O) pm	197.1	195.3		197.7	196.6		197.6
θ(NH···O) deg	171	169		175	173		169
θ(CO···H) deg	120	118		142	138		126
φ(H··OCN) deg	−171	-178		−6	-11		+44
φ(CN··OC) deg	−76	-75		−77	-71		-40
E(2) $n_O \rightarrow \sigma^*_{NH}$ + E(2) $n'_O \rightarrow \sigma^*_{NH}$. kcal/mol	13.82			12.56			
ΣE_{HB} kcal/mol		9.90			8.37		7.39
Harmonic NH stretch (cm^{-1}) donor		3406			3442		3437

Table S3 : NBO analysis of the C-side dimer as a function of the HB distance : sum of the stabilization energies related to the HB (ΣE_{HB}), population of the σ^*_{NH} NBOs in the dimer relative to the reference (taken as the separated molecules), and sum of the natural population analysis (NPA) charges of each molecule in the dimer relative to the sum of NPA charges of the isolated monomer. Energies are given in kcal/mol, populations and charges in milli-*e*.

Distances pm	ΣE_{HB} kcal/mol	Pop. σ^*_{NH} / reference[a] m*e*	$\sum q_{NPA}$ m*e*
177.3	20.09 [b]	30.2	±37.3
182.1	16.49	26.1	± 32.8
186.4	13.80	22.8	± 29.2
195.3 equilibrium	**9.90** [b]	**17.2**	**±22.8**
204.3	6.67	12.6	±17.5
210.3	5.23	10.2	±14.8
216.9	3.93 [b]	7.9	±11.7

a) The reference is the population of the σ^*_{NH} of the HB acceptor fragment at the equilibrium geometry of the dimer, 31.3 me.

b) individual E(2) contributions (kcal/mol)

distance (pm)	177.3	min	216.9
$n_{O(1)} \rightarrow \sigma^*_{N(2)H}$	6.58	3.33	1.12
$n'_{O(1)} \rightarrow \sigma^*_{N(2)H}$	13.15	6.58	2.72

Table S4 : NBO analysis of the N'-side dimer as a function of the HB distance : sum of the stabilization energies related to the HB (ΣE_{HB}), population of the σ^*_{NH} NBOs in the dimer relative to the reference (taken as the separated molecules), and sum of the NPA charges of each molecule in the dimer relative to the sum of NPA charges of the isolated monomer. Energies are given in kcal/mol, populations and charges in milli-*e*.

Distances pm	ΣE_{HB} kcal/mol	Pop. σ^*_{NH}/ref[a] me	$\sum q_{NPA}$ m*e*
178.8	16.45	26.1	±32.1
187.3	11.91	18.9	±25.4
197.6 equilibrium	**7.39**	**13.3**	**±18.9**
207.9	4.83	9.0	±14.18

a) The reference is the population of the σ^*_{NH} of the HB acceptor fragment at the equilibrium geometry of the dimer, 31.8 me.

b) individual E(2) contributions (kcal/mol)

distance (pm)	178.8	187.3	**197.6 equilibrium**	207.9
$n_{O(1)} \rightarrow \sigma^*_{N(2)H}$	8.04	5.75	3.58	2.13
$n'_{O(1)} \rightarrow \sigma^*_{N(2)H}$	5.62	4.10	2.73	1.81
$\pi co \rightarrow \sigma^*_{N(2)H}$	2.18	1.68	1.08	0.76

Table S5 : H-bonds analyzed using the NBO methodology, sorted according to the sequence, the molecular conformation and the caps, with short notation, HB distance, NBO stabilization energies ΣE_{HB}, population of the σ^*_{NH} NBO and harmonic NH stretch frequency at the B97D3-BJ-abc/def2-

Residue/Sequence Conformation	N-terminal cap	C-terminal cap	Abbreviation	NH - OC Distance (pm)	ΣE_{HB} (kcal/mol)	Pop. (m*e*) σ*NH NBO	Harm. NH stretch freq. (cm^{-1})
C-side t-MAA dimer			C-side	195.3	9.90	48.51	3406
N-side t-MAA dimer			N-side	196.6	8.37	44.79	3442
N'-side t-MAA dimer			N'-side	197.6	7.39	45.10	3437
Ala C7eq	Ac-	-NHMe	Ala 7eq	206.3	4.77	42.60	3442
Ala C7ax	Ac-	-NHMe	Ala 7ax	189.3	10.51	51.85	3385
Aib C7	Ac-	-NHMe	Aib C7	185.8	12.50	55.60	3359
Gly C7	Ac-	-NHMe	Gly C7	203.7	5.38	36.95	3529
Phe(g+) C7eq	Ac-	-NHMe	Phe(g+) C7eq	195.5	7.98	48.10	3400
Phe(g-) C7eq	Ac-	-NHMe	Phe(g-) C7eq	201.2	6.36	45.51	3415
Phe(a) C7eq	Ac-	-NHMe	Phe(a) C7eq	218.8	2.52	38.67	3483
Ala C5	Ac-	-NHMe	Ala C5	222.0	1.09	36.43	3531
Aib C5	Ac-	-NHMe	Aib C5	203.4	3.49	42.03	3490
Gly C5	Ac-	-NHMe	Gly C5	219.7	1.37	36.95	3529
Phe(a) C5	Ac-	-NHMe	Phe C5	222.8	1.05	36.85	3531
β^3hPhe C6	Ac-	-NHMe	β^3hPhe C6	211.8	3.34	39.95	3502
Gly-Phe β-turn typeI	Ac-	$-NH_2$	GF C10 I	208.6	4.18	42.34	3498
Gly-Phe β-turn typeII'	Ac-	$-NH_2$	GF C10 II'	207.5	4.14	41.71	3492
Ala-Ala-Ala 3_{10} N-term HB	Ac-	-NHMe	310 AAA N-term	214.0	3.46	43.55	3477
Ala-Ala-Ala 3_{10} C-term HB	Ac-	-NHMe	310 AAA C-term	217.3	2.55	39.77	3529
Aib-Aib-Aib 3_{10} N-term HB	Ac-	-NHMe	310 $(Aib)_3$ N-term	215.2	3.42	42.51	3481
Aib-Aib-Aib 3_{10} C-term HB	Ac-	-NHMe	310 $(Aib)_3$ C-term	207.9	3.49	41.96	3507
Ala-Phe-Ala 3_{10} N-term HB	Ac-	-NHMe	310 AAA N-term	205.1	5.25	47.39	3455
Ala-Phe-Ala 3_{10} C-term HB	Ac-	-NHMe	310 AAA C-term	220.9	2.27	43.32	3495
ACHC C9 Ref. 31	Ac-	-NHBn	ACHC C9	187.9	13.05	56.49	3353
ACHC C9	Ac-	-NHMe	ACHC Me Me C9	192.1	9.49	50.35	3404
t-ACBC t-1 Ref. 30	tBuO-CO-	-NHBn	tACBC C8	195.8	9.64	50.87	3390
t-ACBC t-1	Ac-	-NHMe	tACBC Me Me C8	191.7	11.09	51.29	3394
c-ACBC c-1 Ref. 30	tBuO-CO-	-NHBn	cACBC C8	225.5	2.16	37.73	3497
Aza z-1 Ref. 30	tBuO-CO-	-NHBn	Aza C8+C5	208.4	6.10	46.77	3416

TZVPPD level of theory.