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Communication

Conformational properties of N',N'-dimethylamides of N-acetyldehydroalanine and N-acetyl-(Z)-dehydrophenyl - alanine[★][✪]

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Conformational preferences of Ac-ΔAla-NMe$_2$ and Ac-(Z)-ΔPhe-NMe$_2$ were studied and compared with those of their monomethyl counterparts as well as with those of their saturated analogues. X-Ray data and energy calculations revealed a highly conservative conformation of the dehydro dimethylamides, which is located in a high-energy region of the Ramachandran map.

An essential point in peptide-targeted molecular design is introducing a specialised amino acid into an elaborated molecule, which confers local constraints on the backbone main chain and the side chain moiety. The specialised amino acids are, e.g., α,β-dehydroamino acids. Among these, ΔAla occurs most often and (*Z*)-ΔPhe is the most commonly used modifier. On the other hand, numerous modifications of peptides and peptide mimetics are based on the tertiary amide bond. The latter can be modelled by the N',N'-dimethylamide group. Within the Ac-ΔAla-NMe$_2$ and Ac-(*Z*)-ΔPhe-NMe$_2$ molecules, we combined the C$^{\alpha}$ =

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Abbreviation: Δ, dehydro.

C^{β} double bond and the N',N'-dimethylamide group, and investigated conformations of these compounds in the solid state and in the gas phase. Ac-ΔAla-NHMe and Ac-L-Ala-NMe$_2$ as well as Ac-(*Z*)-ΔPhe-NHMe and Ac-L-Phe-NMe$_2$ were taken for comparison.

MATERIALS AND METHODS

Ac-ΔAla-NMe$_2$, Ac-L-Ala-NMe$_2$, Ac-(*Z*)-ΔPhe-NMe$_2$ and Ac-L-Phe-NMe$_2$ were synthesised using standard methods. Their structures were solved by X-ray analysis. X-Ray data for Ac-ΔAla-NHMe were taken from [1] and those for Ac-(*Z*)-ΔPhe-NHMe from [2]. The AM1 and DFT/B3LYP/6-31G** methods were used for theoretical calculations in the gas phase.

RESULTS AND DISCUSSION

Figure 1 A–F presents the molecular crystal conformations of Ac-ΔAla-NMe$_2$, Ac-ΔAla-NHMe, Ac-L-Ala-NMe$_2$, Ac-(Z)-ΔPhe-NMe$_2$, Ac-(Z)-ΔPhe-NHMe and Ac-L-Phe-NMe$_2$. Figure 2 A–F gives their AM1 energy maps, in the ϕ,ψ torsion space *in vacuo,* together with the DFT/B3LYP/6-31G** re-optimised minima. Table 1 lists some selected conformational parameters of these sample molecules in the solid state and those of all their low-energy conformers in the gas phase.

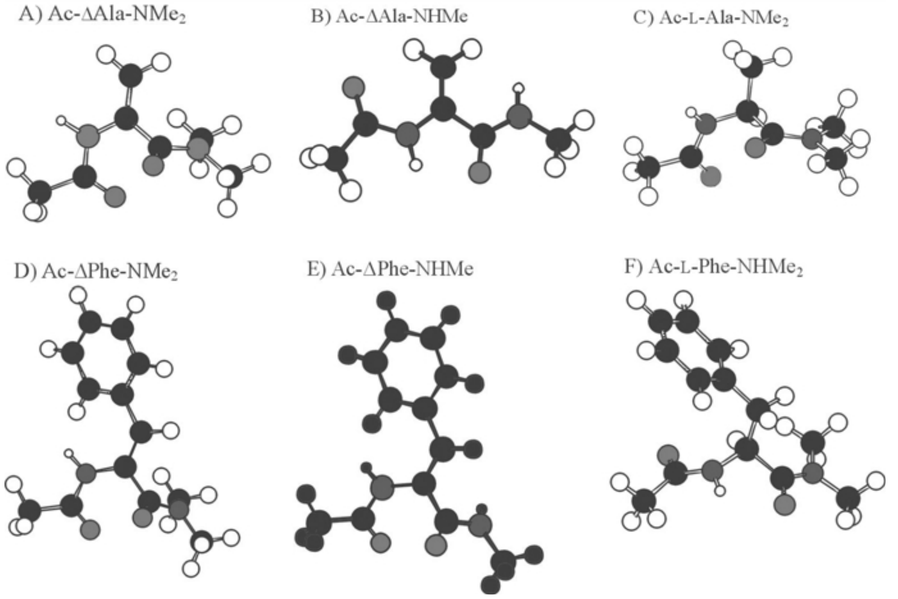

Figure 1. The molecular conformations of the studied molecules in the solid state.

In crystal, Ac-ΔAla-NMe$_2$ adopts ϕ,ψ = –43°, 127° and Ac-L-Ala-NMe$_2$ adopts ϕ,ψ = –82°, 157°. Two independent molecules with ϕ,ψ = –172°, 154° and 163°, –169° were found for Ac-ΔAla-NHMe [1]. As can be seen, the conformations of these three compounds differ significantly from each other, and that of Ac-ΔAla-NMe$_2$ is located in the high-energy region (region H [3]) of the Ramachandran diagram. Moreover, the out-of-plane parameters, χ_N and χ_C, and the twisting parameter τ [4], of the C-terminal amide bond of Ac-ΔAla- NMe$_2$ indicate a considerably high degree of non-planarity, whereas this moiety both in Ac-L-Ala-NMe$_2$ and Ac-ΔAla-NHMe is rather flat.

The conformational map of Ac-ΔAla-NMe$_2$ (Fig. 2A) has two minima and their mirror image. The energy difference and the magnitude of the separation between them amount to 4.2 and 6.3 kcal mol^{-1}, respectively. The lower energy minimum (ϕ,ψ = 179°, 154°) is positioned in the region of extended conformations. The other (ϕ,ψ = –37°, 124°) is located in a narrow and relatively highly separated area in region

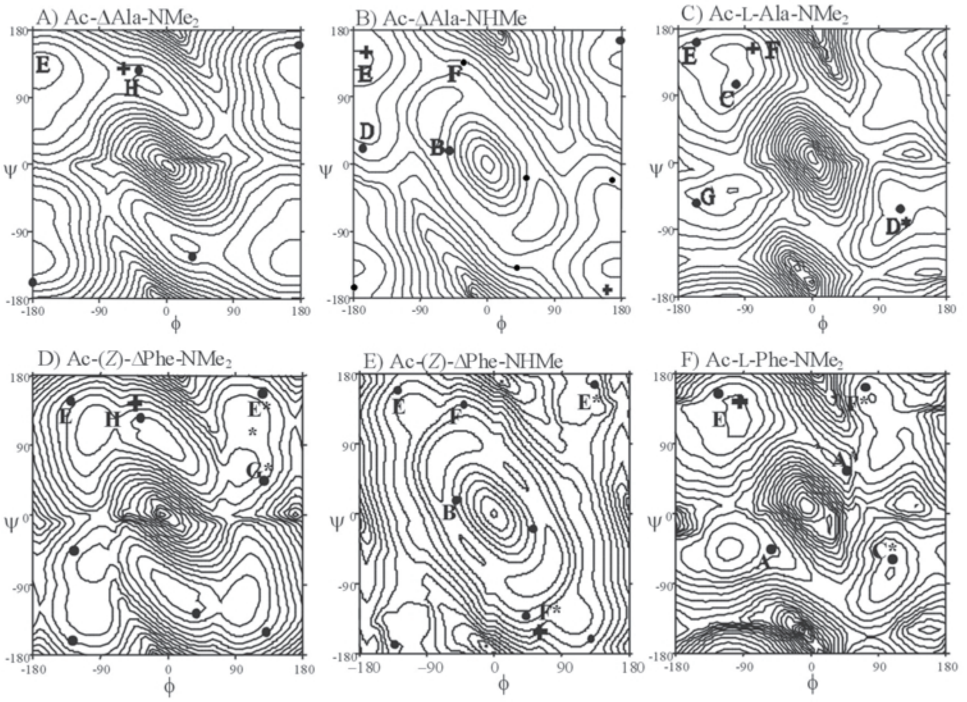

Figure 2. Energy maps in the ϕ–ψ torsion space *in vacuo* computed by the AM1 method on a grid with 10° spacing.

The isopotential lines are drawn every 1 kcal mol^{-1}. +, Crystal structures; •, DFT/B3LYP/6-31G** minima.

H of the Ramachandran diagram. The crystal conformer (ϕ,ψ = –42°, 127°) corresponds exactly to the second minimum. All these data taken together indicate some limited conformational freedom of the Ac-ΔAla-NMe$_2$ molecule. Both the conformation of Ac-ΔAla-NMe$_2$ in crystal and those calculated display a significant deformation of the tertiary amide bond, which means that this non-planarity is an intrinsic feature of the Ac-ΔAla-NMe$_2$ molecule.

The conformational map of Ac-ΔAla-NHMe (Fig. 2B) has four minima (and their mirror image). The global minimum (ϕ,ψ = –179°, 166°), located in region E, is populated in the crystal structure. The remainder, one conformer in the moderate energy bridge region (region B) (ϕ,ψ = –52°, 20°) and the others in region D (ϕ,ψ = –168°, 22°) and F (ϕ,ψ = –42°, 138°) have much higher energies (ΔE = 5.1, 5.8, and 7.3 kcal mol^{-1}, respectively). As is the case for Ac-ΔAla-NMe$_2$, the C-terminal amide bond reveals some deformation, in all the conformers. The deformation, however, is smaller, particularly that characterised by the out-of-plane parameter χ_C and the twisting parameter τ.

The Ac-L-Ala-NMe$_2$ molecule in the gas phase (Fig. 2C) has four minima, which in the order of increasing energy are as follows: in region E (ϕ,ψ = –157°, 161°), in region C (ϕ,ψ = –101°, 109°), in region G (ϕ,ψ = –160°, –47°), and in region D* (ϕ,ψ = 114°, –59°). The energy difference and the barrier between the two former minima equal to only 1.0 kcal mol^{-1} and 1.6 kcal mol^{-1}, respectively. The conformation found in the crystal structure lies on this flat potential energy surface. So, the molecule has a high degree of conformational freedom. The out-of-plane parameters of the tertiary amide in all the conformers except conformer G point to a fairly planar system.

In the solid state, Ac-(*Z*)-ΔPhe-NMe$_2$ adopts ϕ,ψ = –50°, 133° whereas Ac-(Z)-ΔPhe-NHMe

Table 1. Selected conformational parameters of six sample molecules in the solid state and of all their low-energy conformers in gas phase.

The conformers are labelled according to the name of the Ramachandran map regions [3].

Compound	Conformer	Energy difference kcal mol^{-1}	ϕ	ψ	χ^2	χ_C	χ_N	τ
Ac-ΔAla-NMe$_2$	(H)[a]		-43.1	127.9	-	-5.5	-11.0	171.6
	E	0.0	179.0	153.9	-	-2.1	-16.7	164.0
	H	4.2	-37.3	123.8	-	-6.6	-26.2	168.0
Ac-ΔAla-NHMe	(E)[a,b]		-172.2	154.1	-	-1.0	-2.0	-179.1
	(E*)[a,b]		162.6	-169.4	-	1.4	0.2	-178.6
	E	0.0	178.9	166.4	-	0.2	-11.4	175.0
	B	5.1	-52.3	19.8	-	1.2	21.3	-172.3
	D	5.8	-167.8	22.4	-	1.1	30.1	-171.0
	F	7.3	-42.0	138.0	-	-4.9	-22.3	174.1
Ac-L-Ala-NMe$_2$	(F)[a]		-81.8	157.4	-	-3.3	-1.4	178.7
	E	0.0	-156.6	161.0	-	-6.7	-3.9	177.0
	C	1.0	-101.2	109.3	-	0.5	0.0	175.3
	G	7.5	-160.0	-47.5	-	-1.5	-20.5	170.8
	D*	8.2	113.9	-59.5	-	-0.3	-1.7	178.0
Ac-ΔPhe-NMe$_2$	(F)[a]		-49.5	132.6	26.4	-3.2	-7.9	170.7
	H	0.00	-37.1	126.4	-29.7	-6.4	-26.2	167.6
	E	1.05	-130.4	148.0	16.5	-2.5	-17,8	163.8
	E*	3.11	126.4	157.0	-19.6	-1.3	-22.3	160.3
	G*	6.97	128.4	45.7	-17.7	3.0	31.2	-160.0
Ac-ΔPhe-NHMe	(F*)[a,c]		56.8	-148.7	39.8	1.9	6.8	-174.6
	B	0.00	-51.0	19.1	-31.5	1.3	22.5	-172.0
	E	2.12	-129.8	160.6	18.5	-1.2	-19.5	172.5
	E*	2.31	133.1	168.2	-19.6	-1.4	19.6	172.7
	F	2.79	-41.7	140.5	-27.2	-4.5	-24.8	173.4
Ac-L-Phe-NMe$_2$	(F)[a]		-99.5	148.5	-85.6	-3.5	3.6	179.9
	E	0.00	-125.6	154.4	-85.9	-3.1	-0.3	177.3
	A*	4.84	47.1	56.2	-79.0	-5.4	-8.1	-176.3
	A	5.37	-53.4	-44.1	-72.8	6.9	9.4	179.3
	F*	6.04	71.4	163.2	-87.1	-0.3	-2.9	174.2
	C*	6.31	109.1	-59.7	-75.1	0.6	-3.2	176.9

[a] Crystal data values; [b] Ref. [1]; [c] Ref. [2]

and Ac-L-Phe-NMe$_2$ assume ϕ,ψ = 57°, −149° and ϕ,ψ = −100°, 149°, respectively. As can be seen, the conformations of the dehydro compounds are similar and that of the saturated dimethylamide is quite different. Out of plane parameters point to the most non-planar tertiary amide bond in the Ac-(*Z*)-ΔPhe-NMe$_2$ molecule and the almost planar tertiary amide bond in Ac-L-Phe-NMe$_2$.

The conformational map of Ac-(*Z*)-ΔPhe-NMe$_2$ (Fig. 2D) has four minima and their mirror image. The global minimum (ϕ,ψ = −37°, 126°) is located in an area of a clearly distinct topology, in region H of the Ramachandran diagram. The conformation found in the crystal (ϕ,ψ = −50°, 132°) corresponds quite well to this minimum. The second-lowest minimum (ϕ,ψ = − 130°, 148°), of energy difference 1.1 kcal mol^{-1}, is located in the region of C$_5$ conformations (region E). The remaining two minima occur in the upper-right quarter of the map and have much higher energies (ΔE = 3.1 and 7.0 kcal mol^{-1}). The Ac-(*Z*)-ΔPhe-NMe$_2$ molecule in crystal as well as in all the calculated conformers displays a significant non-planarity of the tertiary amide bond, which means that this non-planarity is its intrinsic feature. In all four theoretical conformers as well as in the crystal conformation, the angle χ^2 is relatively small and does not exceed ±30°. This indicates a π-coupling tendency between the phenyl ring and the C^α=C^β double bond, which provides a strong steric constraint on the backbone torsion ϕ angle and prevents the molecule from assuming the fully extended conformation.

The conformational map of Ac-(*Z*)-ΔPhe-NHMe (Fig. 2E) also has four minima (and their mirror image). The lowest (ϕ,ψ = −51°, 19°) is located in bridge region B. The remainder, in region E (ϕ,ψ = −130°, 161°), in region E* (ϕ,ψ = 133°, 168°), and in region F (ϕ,ψ = −42°, 141°) (ΔE = 2.1, 2.3, and 2.8 kcal mol^{-1}, respectively). In contrast to Ac-(*Z*)-ΔPhe-NMe_2, the conformation of Ac-(*Z*)-ΔPhe-NHMe found in the crystal (ϕ,ψ = 57°,−149°) corresponds to the highest energy minimum, which is placed in the mirror image region F*. As is the case for Ac-(*Z*)-ΔPhe-NMe_2, the C-terminal amide bond of all four conformers reveals some deformation, although — particularly for the out-of-plane parameter χ_C and the twisting parameter τ — smaller. The value of the angle χ^2 in all the calculated conformers and that in the crystal (about ±30° on average) indicates a π-coupling tendency between the phenyl ring and the C^α=C^β double bond.

Energy calculations show that the Ac-L-Phe-NMe_2 molecule represents an entirely different conformational pattern. The conformational map (Fig. 2F) has five minima, which in the order of increasing energy are as follows: in region E (ϕ,ψ = −126°, 154°), in region A* (ϕ,ψ = 47°, 56°), in region A (ϕ,ψ = −53°, −44°), in region F* (ϕ,ψ = 71°, 163°) and in region C* (ϕ,ψ = 109°, −60°). The conformation found in the crystal structure (ϕ,ψ = −100°, 149°) lies in the broad and flat area surrounding the minimum E. The out-of-plane parameters of the tertiary amide in all conformers point to a rather planar system. The angle χ^2 is close to −90° and allows the molecule to assume the fully extended conformation. All this indicates that the compound has a high degree of conformational freedom.

CONCLUSION

X-Ray analysis of Ac-ΔAla-NMe_2 and Ac-(Z)-ΔPhe-NMe_2 reveals a highly conservative conformation of these compounds. Both adopt a structure with the torsion angles ϕ, ψ = ∼−45°, ∼130° and show some non-planarity of its C-terminal amide. This conformation is located in the high-energy region (region H) of Ramachandran diagram, which is not readily accessible to their saturated analogues. Theoretical calculations on isolated Ac-ΔAla-NMe_2 and Ac-(*Z*)-ΔPhe-NMe_2 molecules corroborate these findings. A comparison of all respective conformational data indicates that Ac-ΔAla-NMe_2 and Ac-(*Z*)-ΔPhe-NMe_2 share more conformational features with their monomethyl rather than saturated analogues.

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