



Conformational Properties of N-Formyl-L-Cys-NH₂ in Its γ_D -Backbone Conformations as Computed by Semi-Empirical and *Ab Initio* Methods

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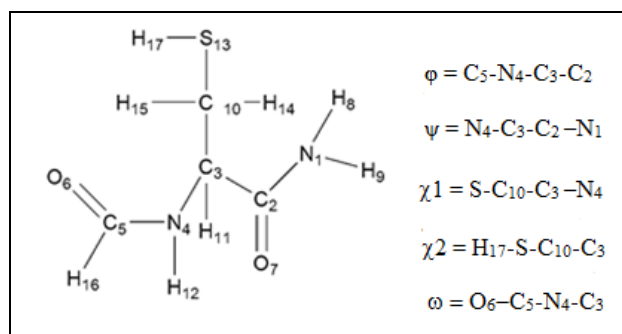
ABSTRACT

A conformational study on the preferred minima γ_D (C_7^{ax}) of N-For-L-Cys-NH₂ in isolated state was carried out using multi niche crowding genetic algorithm coupled with semi empirical-method AM1 (AM1/GA-MNC). All conformations located were subjected to geometry optimization at the HF/3-21G and the HF/6-31G++ (d, p) levels of theory. Six of the nine side-chain conformers were located and are $\gamma_D[g-, g+]$, $\gamma_D[g-, g-]$, $\gamma_D[g-, a]$, $\gamma_D[a, g-]$, $\gamma_D[a, g+]$ and $\gamma_D[g+, g-]$, no conformational migrations were observed. All these structures are stabilized by the hydrogen bond associated with the seven-member ring of the γ backbone conformation C=O...H-N. Two conformers had side chain-backbone intramolecular hydrogen bonding S-H...O=C at AM1/GA-MNC and HF/3-21G.

Keywords: Genetic algorithm; Semi-empirical; *Ab initio*; Cysteine; Conformational space

INTRODUCTION

Characteristics of Ramachandran map of trans N-For-L-Ser-amide have already been studied extensively [1-5], while the informations about conformational analysis of potential energy surface of L-Cysteine diamides are limited [6-8]. A preliminary work has already analyzed the potential energy surface (PES) of neutral and protonated glycine using the AM1/GA-MNC method [9]. In the present study, we wish to explore the whole conformational space of N-For-L-Cys-NH₂ in isolated state and carried out all γ_D conformations using our computing calculation technique, AM1/AG-MNC. The equilibrium structures obtained had been re-optimized by ab initio calculation (HF/3-21G, HF/6-31G++(d, p)). In scheme 1, are represented the numbering system and the torsional angles definition adopted in this study.



Scheme1: The atomic numbering adopted in this study

Computational method

we carried out a conformational study of potential energy surface $E(\phi, \psi, \chi_1, \chi_2)$ of N-For-L-Cys-NH₂ using multi niche crowding genetic algorithm coupled with semi empirical-method AM1 (AM1/GA-MNC) [9]. The

six side chain conformers located were subjected to geometry optimization at two levels of theory: HF/3-21G and the HF/6-31G++ (d, p), using the Gaussian 09 [10]. Torsional angles were specified within -180° and 180° for both backbone (ϕ, ψ) and side-chain (χ_1, χ_2) conformations. All the relative energies are given in kcal/mol using the conversion factor 1 hartree = 627.5 kcal/mol. Three stable orientations can be found for χ_1 and χ_2 ; gauche + (g+), anti (a) and gauche - (g-).

RESULTS AND DISCUSSION

Limiting our considerations only to trans-peptide bonds, $\omega = \text{O}_6\text{-C}_5\text{-N}_4\text{-C}_3 \approx 0^\circ$. The potential energy surface is a function of four independent variables ϕ, ψ, χ_1 and χ_2 as defined in scheme 1. The Ramachandran map $E = E(\phi, \psi)$ obtained using AM1/GA-MNC is represented in figure 1.

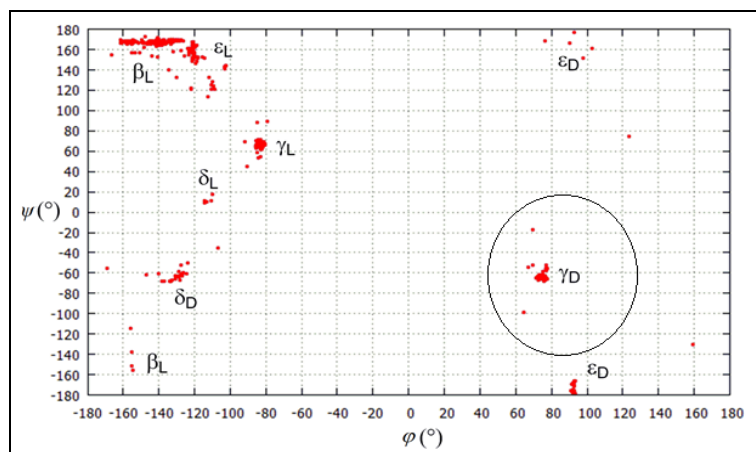


Figure 1: Representation of the Ramachandran map $E(\phi, \psi)$ for N-For-Cys-NH₂ obtained from AM1/GA-MNC calculation

Figure 1 shows all backbone conformers found for trans N-For-Cys-NH₂ in isolated state. The backbone conformation γ_D mentioned in figure 1 occupies 14% of the population of the last generation. The torsional angles $\phi \approx 73.8^\circ$ and $\psi \approx -61.5^\circ$ at AM1/GA-MNC calculation.

By associating the γ_D backbone conformation with the $-\text{CH}_2\text{-SH}$ side-chain conformation, six side-chain conformers were located on the side-chain PES, $E_{\gamma_D}(\chi_1, \chi_2)$ as shown in figure 2.

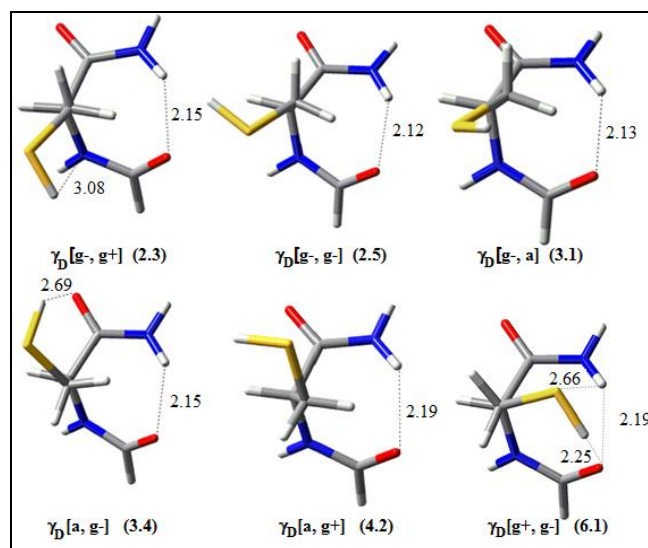


Figure 2: The optimized geometries of side-chain conformers found for γ_D conformations located at AM1/AG-MNC calculation. In brackets the relative energies calculated compared to the global minimum $\gamma_L [g+, g+]$ conformation having $\Delta H_f = -81.3$ kcal/mol

The γ_D backbone conformation is stabilized by intramolecular H-bonding $\text{C}=\text{O} \dots \text{H}-\text{N}$, which is characteristic to this specific backbone structure [11]. Thus, the relative stabilities of these various conformers were analyzed in terms of side-chain-backbone interactions (hydrogen bonds and steric effect).

The optimized torsional angles, relative energies and intramolecular interactions for γ_D conformation of N-For-L-Cys-NH₂ are summarized in table 1 and table 2, respectively.

Table 1: Relative energies, bonds angles for γ_D conformations of N-For-L-Cys-NH₂ optimized at AM1/GA-MNC, HF/3-21G and HF/6-31G++(d, p) levels of theory

	Conformation	$\Delta\Delta H_f$ (kcal/mol)	ϕ (°)	ψ (°)	χ_1 (°)	χ_2 (°)
AM1/GA-MNC ^a	Semiempirical method					
	[g-, g+]	2.3	71.9	-65.3	-71.4	78.6
	[g-, g-]	2.5	75.8	-63.8	-69.3	-72.8
	[g-, a]	3.1	76.9	-66.6	-73.3	161.3
	[a, g-]	3.4	76.3	-53	-155.2	-52
	[a, g+]	4.2	74.1	-64.9	179.8	53.7
HF/3-21G ^b	<i>ab initio</i>					
	[g-, g+]	5.6	74.4	-57.8	-62.2	87.9
	[g-, g-]	5.5	74.7	-57	-61.9	-74.3
	[g-, a]	6.02	74.6	-56.9	-59.2	-166.6
	[a, g-]	7.6	73.1	-52.2	-162.5	-46.8
	[a, g+]	8.01	74	-62.8	-179.6	63.4
HF/6-31G++(d,p) ^c	<i>ab initio</i>					
	[g-, g+]	3.8	75.4	-53.7	-61.2	82.1
	[g-, g-]	4	76	-52.3	-61.7	-73.3
	[g-, a]	5.1	76	-53.9	-59.5	-172.9
	[a, g-]	5.2	73.7	-75	-168.5	-72.2
	[a, g+]	5.8	75	-70.7	-174.6	62.5
	[g+, g-]	8.6	70.1	-31.5	91	-64.6

Relative energies were calculated compared to the global minimum γ_L [g+, g+] conformation having: ^a $\Delta H_f = -81.3$ kcal/mol; ^b $\Delta H_f = -808.03285866$ hartrees; ^c $\Delta H_f = -812.33016178$ hartrees

Table 2: Summary of intramolecular interactions (in Å) in γ_D conformations of N-For-L-Cys-NH₂ calculated at HF/3-21G and HF/6-31G++(d, p) levels of theory

	Conformation	O ₇ ...H ₁₇ S	O ₆ ...H ₉ (C7)	O ₆ ...H ₁₇ S	S...H ₉	N ₄ ...H ₁₇ S
HF/3-21G	[g-, g+]		1.93			3.12
	[g-, g-]		1.9			
	[g-, a]		1.9			
	[a, g-]	2.55	1.89			
	[a, g+]		1.95			
	[g+, g-]		1.93	2.2		
HF/6-31G++(d,p)	[g-, g+]		2.08			
	[g-, g-]		2.04			
	[g-, a]		2.05			
	[a, g-]		2.13			
	[a, g+]		2.15			
	[g+, g-]		2.14	2.31		

From the data presented in tables 1 and 2, two of the six conformers (γ_D [a, g-] and γ_D [g+, g]) are stabilized by SH...OCNH interaction, using the AM1/GA-MNC and the HF/3-21G calculation. While at the HF/6-31G++(d, p), one conformation (γ_D [g+, g-]) exhibit this interaction.

The energy gap between γ_D [g-, g+] and γ_D [g-, g-] (≈ 0.2 kcal/mol) is in relationship with the weak interaction SH...NH, which is established in γ_D [g-, g+].

The geometrical form adopted by γ_D [g-, a] is similar to that of γ_D [g-, g-] with one exception. The position of the acid hydrogen of sulfur as shown by the angle values χ_1 in table 1. Thus, in γ_D [g-, a] the side chain -CH₂-SH becomes more close to the C7 which increases the steric effect in this conformation. Therefore, its heat of formation has increased by 0.6 kcal/mol.

The least stable minimum is γ_D [g+, g-]. According to AM1/GA-MNC results, both S...HNH and SH...OC side chain-backbone interactions are favored for this conformation. While, only SH...OC is favored at HF/3-21G and HF/6-31G++(d, p) levels of theory. In addition, this conformation is more compact than the five others.

For CH₃CO-Cys-NHCH₃ [8] and For-L-Ser-NH₂ [5], all nine side chain conformers were located at the HF/3-21G as shown in table 3.

Table 3: Relative energies and torsional angles of γ_D side-chain conformers found for For-L-Ser-NH₂ [5] and CH₃CO-Cys-NHCH₃ [8] at the HF/3-21G

Conformation	$\Delta\Delta H_f$ (kcal/mol)	ϕ (°)	ψ (°)	χ_1 (°)	χ_2 (°)
For-L-Ser-NH ₂ [5]					
[g-, g+]	12.5	72.2	-57.5	-61.1	79.1
[g-, g-]	12.9	74.7	-55.2	-57.6	-78.2
[g-, a]	12	75.4	-56.1	-58.6	176
[a, g-]	10.6	67.5	-31.2	-163.8	-39.9
[a, g+]	12	71.3	-52.2	170.8	49
[g+, g-]	9.4	78	-45.2	81.9	-62.2
[g+, g+]	14	62.9	-40.3	41.7	48.7
[g+, a]	17.1	51.9	-28.7	65.8	173.3
[a, a]	12.7	74	-65	-177.5	-158
CH ₃ CO-Cys-NHCH ₃ [8]					
[g-, g+]	5.7	75.7	-58.5	-60.8	88.9
[g-, g-]	5.54	76.3	-57.3	-60.6	-73.2
[g-, a]	6.04	76	-57.2	-58	-167.3
[a, g-]	7.55	73.6	-69.3	-174.1	-74.7
[a, g+]	8.26	74.7	-63.9	-178.8	62.5
[g+, g-]	11.7	66.8	-37.2	89	-57.6
[g+, g+]	12.45	47.2	-25.9	58.3	55.6
[g+, a]	13.66	55.6	-28.4	70.6	162.9
[a, a]	9.53	74.9	-62.1	-171.4	-176.6

For the two diamides models (For-L-Ser-NH₂ and CH₃CO-Cys-NHCH₃), all nine side-chain conformers have been found at the HF/3-21 level of theory. As can be seen from this table, three conformers (γ_D [g+, g+], γ_D [g+, a] and γ_D [a, a]) are not located in our study using AM1/GA-MNC. Furthermore, the size difference between sulfur and oxygen could play an important role in kinds of intramolecular interactions established and the energy quantities noticed.

At HF/3-21G, the relative energies and torsional angles values of side chain conformers γ_D [g-, g+], γ_D [g-, g-], γ_D [g-, a], γ_D [a, g-], γ_D [a, g+] and γ_D [g+, g-] obtained for CH₃CO-Cys-NHCH₃ [8] and For-Cys-NH₂ (this study) are equal as can be seen from tables 1 and 3. Therefore, the AM1/GA-MNC provides optimized geometries that can be used as starting structures for ab initio calculation.

CONCLUSION

We carried out a conformational study on the preferred minima γ_D (C₇^{ax}) of trans N-For-L-Cys-NH₂ in isolated state by AM1/GA-MNC calculation. All conformations located were subjected to geometry optimization at the HF/3-21G and the HF/6-31G++ (d, p) levels of theory. Six of the nine side-chain conformers were located γ_D [g-, g+], γ_D [g-, g-], γ_D [g-, a], γ_D [a, g-], γ_D [a, g+] and γ_D [g+, g-].

The three levels of theory reported here (AM1/GA-MNC, HF/3-21G and HF/6-31G++(d,p)), Provide the same results. No conformational migrations were observed.

According to our calculations, the AM1/GA-MNC provides optimized geometries that can be used as starting structures for ab initio calculation. It can be a reliable technique for the study of conformational spaces of molecules with large sizes like proteins.

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