



## Research Article

ISSN : 0975-7384  
 CODEN(USA) : JCPRC5

## Conformational Properties of N-Formyl-L-Cys-NH<sub>2</sub> in Its $\gamma_D$ -Backbone Conformations as Computed by Semi-Empirical and *Ab Initio* Methods

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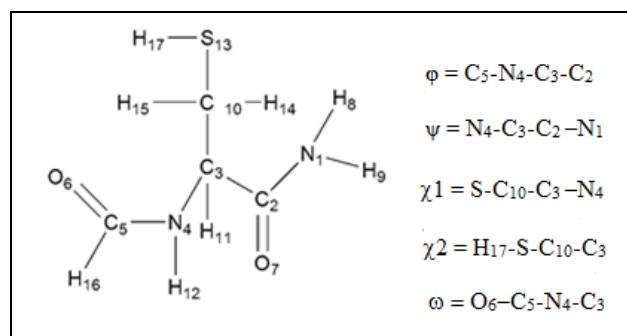
### ABSTRACT

A conformational study on the preferred minima  $\gamma_D$  ( $C_7^{ax}$ ) of N-For-L-Cys-NH<sub>2</sub> 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  $\gamma$  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-NH<sub>2</sub> in isolated state and carried out all  $\gamma_D$  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

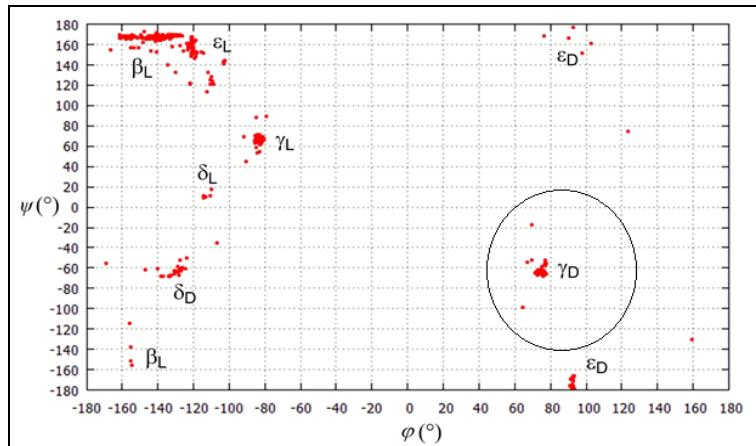
### Computational method

we carried out a conformational study of potential energy surface E ( $\phi$ ,  $\psi$ ,  $\chi_1$ ,  $\chi_2$ ) of N-For-L-Cys-NH<sub>2</sub> 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 ( $\phi, \psi$ ) and side-chain ( $\chi_1, \chi_2$ ) 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  $\chi_1$  and  $\chi_2$ ; gauche + (g+), anti (a) and gauche -(g-).

## RESULTS AND DISCUSSION

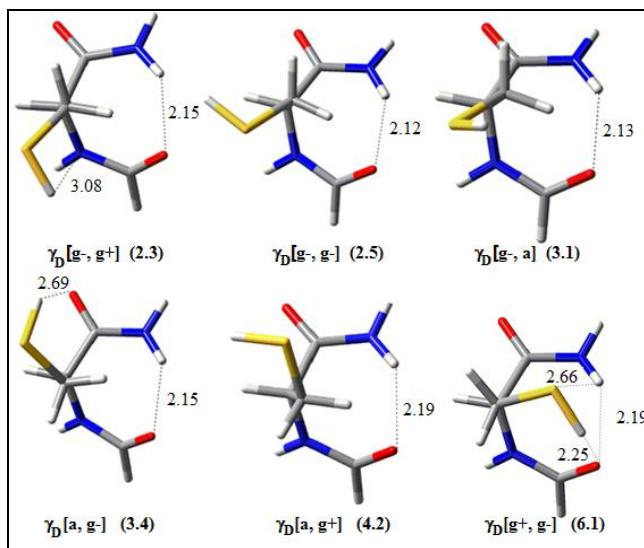
Limiting our considerations only to trans-peptide bonds,  $\omega = O_6-C_5-N_4-C_3 \approx 0^\circ$ . The potential energy surface is a function of four independent variables  $\phi, \psi, \chi_1$  and  $\chi_2$  as defined in scheme 1. The Ramachandran map  $E = E(\phi, \psi)$  obtained using AM1/GA-MNC is represented in figure 1.



**Figure 1:** Representation of the Ramachandran map  $E(\phi, \psi)$  for N-For-Cys-NH<sub>2</sub> obtained from AM1/GA-MNC calculation

Figure 1 shows all backbone conformers found for trans N-For-Cys-NH<sub>2</sub> in isolated state. The backbone conformation  $\gamma_D$  mentioned in figure 1 occupies 14% of the population of the last generation. The torsional angles  $\phi \approx 73.8$  and  $\psi \approx -61.5^\circ$  at AM1/GA-MNC calculation.

By associating the  $\gamma_D$  backbone conformation with the -CH<sub>2</sub>-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  $\gamma_D$  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  $\gamma_D$  backbone conformation is stabilized by intramolecular H-bonding C=O...H-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  $\gamma_D$  conformation of N-For-L-Cys-NH<sub>2</sub> are summarized in table 1 and table 2, respectively.

**Table 1: Relative energies, bonds angles for  $\gamma_D$  conformations of N-For-L-Cys-NH<sub>2</sub> optimized at AM1/GA-MNC, HF/3-21G and HF/6-31G++(d, p) levels of theory**

	Conformation	$\Delta\Delta H_f$ (kcal/mol)	$\phi(^{\circ})$	$\psi(^{\circ})$	$\chi_1(^{\circ})$	$\chi_2(^{\circ})$
Semiempirical method						
AM1/GA-MNC <sup>a</sup>	[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
	[g+, g-]	6.1	67.7	-55.6	87.6	-71.9
<i>ab initio</i>						
HF/3-21G <sup>b</sup>	[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
	[g+, g-]	11.5	65.1	-36.2	87.3	-57.2
HF/6-31G++(d,p) <sup>c</sup>						
	[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  $\gamma_L$  [g+, g+] conformation having: <sup>a</sup>  $\Delta H_f = -81.3$  kcal/mol; <sup>b</sup>  $\Delta H_f = -808.03285866$  hartrees; <sup>c</sup>  $\Delta H_f = -812.33016178$  hartrees

**Table 2: Summary of intramolecular interactions (in Å) in  $\gamma_D$  conformations of N-For-L-Cys-NH<sub>2</sub> 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 ( $\gamma_D$  [a, g-] and  $\gamma_D$  [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 ( $\gamma_D$  [g+, g-]) exhibit this interaction.

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

The geometrical form adopted by  $\gamma_D$  [g-, a] is similar to that of  $\gamma_D$  [g-, g-] with one exception. The position of the acid hydrogen of sulfur as shown by the angle values  $\chi_1$  in table 1. Thus, in  $\gamma_D$  [g-, a] the side chain  $-CH_2-SH$  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  $\gamma_D$  [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 CH<sub>3</sub>CO-Cys-NHCH<sub>3</sub> [8] and For-L-Ser-NH<sub>2</sub> [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  $\gamma_D$  side-chain conformers found for For-L-Ser-NH<sub>2</sub> [5] and CH<sub>3</sub>CO-Cys-NHCH<sub>3</sub> [8] at the HF/3-21G

Conformation	$\Delta\Delta H_f$ (kcal/mol)	$\phi(^{\circ})$	$\psi(^{\circ})$	$\chi_1(^{\circ})$	$\chi_2(^{\circ})$
For-L-Ser-NH <sub>2</sub> [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 <sub>3</sub> CO-Cys-NHCH <sub>3</sub> [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-NH<sub>2</sub> and CH<sub>3</sub>CO-Cys-NHCH<sub>3</sub>), 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 ( $\gamma_D$  [g+, g+],  $\gamma_D$  [g+, a] and  $\gamma_D$  [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  $\gamma_D$ [g-, g+],  $\gamma_D$ [g-, g-],  $\gamma_D$ [g-, a],  $\gamma_D$ [a, g-],  $\gamma_D$ [a, g+] and  $\gamma_D$ [g+, g-] obtained for CH<sub>3</sub>CO-Cys-NHCH<sub>3</sub> [8] and For-Cys-NH<sub>2</sub> (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  $\gamma_D$  ( $C_7^{ax}$ ) of trans N-For-L-Cys-NH<sub>2</sub> 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  $\gamma_D$ [g-, g+],  $\gamma_D$ [g-, g-],  $\gamma_D$ [g-, a],  $\gamma_D$ [a, g-],  $\gamma_D$ [a, g+] and  $\gamma_D$ [g+, g-].

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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