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Theoretical study of the conformational energy hypersurface of cyclotrisarcosyl

Research Article

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Abstract: The multidimensional Conformational Potential Energy Hypersurface (PEHS) of cyclotrisarcosyl was comprehensively investigated at the DFT (B3LYP/6-31G(d), B3LYP/6-31G(d,p) and B3LYP/6-311++G(d,p)), levels of theory. The equilibrium structures, their relative stability, and the Transition State (TS) structures involved in the conformational interconversion pathways were analyzed. Aug-cc-pVTZ//B3LYP/6-311++G(d,p) and MP2/6-31G(d)//B3LYP/6-311++G(d,p) single point calculations predict a symmetric *cis-cis-cis* crown conformation as the energetically preferred form for this compound, which is in agreement with the experimental data. The conformational interconversion between the global minimum and the twist form requires 20.88 kcal mol^{-1} at the MP2/6-31G(d)//B3LYP/6-311++G(d,p) level of theory. Our results allow us to form a concise idea about the internal intricacies of the PEHSs of this cyclic tripeptide, describing the conformations as well as the conformational interconversion processes in this hypersurface. In addition, a comparative analysis between the conformational behaviors of cyclotrisarcosyl with that previously reported for cyclotriglycine was carried out.

Keywords: *Cyclic tripeptides • Potential energy hypersurface • Conformational study • DFT calculations • Cyclotrisarcosyl*

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1. Introduction

There is currently great interest in cyclic peptides and cyclic pseudopeptides due to the different biological activities reported for many compounds possessing this structural characteristic [1,2]. There are several reasons for such interest, but probably the most important are the following: first, in contrast to linear peptides, cyclic peptides are not susceptible to attack by exopeptidases (amino- and carboxy-peptidases); second, their constrained nature reduces the entropic penalty and offers the potential for improved binding and often improved selectivity toward a given biological receptor. However, information about the conformational behavior of medium or large cyclic peptides is scarce. This is logical - after all, why expect a full understanding of the conformational behavior of a complex cyclic structure when many conformational aspects of very simple cyclic compounds remain unknown?

Small cyclic peptides form an interesting class of compounds for study by conformational analysis by virtue of their particular conformational features and potential biological properties. However, exploration of conformational space is a difficult problem, which is especially acute for cyclic molecules due to the interdependence of torsional angles [3]. We have previously reported a comprehensive conformational study of the PEHS of cyclononane using *ab initio* and DFT calculations [4]. Our results showed that the PEHS of this apparently simple molecule in fact is very complex. In addition we reported the PEHS of two cyclic compounds possessing nine carbon atoms: *cic-cis-cis-*

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1,4,7–cyclononatriene and tribenzocyclononatriene [5]. More recently we reported a detailed conformational study for cyclic triglycine [6]. These results indicated that the conformational interconversion process in small-size cyclic peptides is very complex and somewhat different than those of cyclic polyenes [5].

In order to extend the conformational study of cyclic compounds possessing nine carbon atoms we performed a comprehensive conformational study on the PEHS of cyclotrisarcosyl. Interestingly, cyclic peptides of sarcosine are suitable for the study of the conformational interconversion mechanism; these compounds displayed a more restricted conformational flexibility with respect to the cyclic peptides containing glycine residues. Amide bonds of NMe-type can equally well be *cis* as *trans*, and the site exchange for the aminoacid residues in homodetic rings, and quite generally the interconversion of different conformers, must therefore involve *cis-trans* isomerization which in open chains is found to have a barrier of around 19 kcal mol^{-1} [7-13]. Our own DFT calculation results indicate a range between 17 and 21 kcal mol^{-1} depending on the molecular system [14]. Cyclic tripeptides which contain nine member rings are in general strained systems. Not many cyclic tripeptides are known. Those on which crystal structure information is available are cyclotrisarcosyl [15] and others containing Prolyl and N-BzlGlycyl residues. One common feature in all these is the occurrence of *cis* peptide units which are a geometric feature required for the formation of cyclic tripeptides. N-methylated cyclic triglycine has a C_3 symmetry conformation (crown form) elucidated by NMR [16,17] and X-ray crystallography studies [15]. Cyclotrisarcosyl [18] is the only example of a cyclic tripeptide which can undergo a conformational interconversion process. Since in its single observable conformation all three amide groups are *cis*, only the exchange of the inner with the outer hydrogen within each of the three CH_2 groups can be observed. This process gives a calculated free energy of activation of 20.1 kcal mol^{-1} [17]. This barrier is higher than the normal barrier for *cis - trans* isomerization of amides, so that a multi-step interconversion path through less stable conformers having one or two *trans* amide groups cannot *a priori* be excluded.

There have been very few theoretical calculations performed on cyclic tripeptides, and the ones that are available have generally been carried out using low levels of theory. A conformational study performed for cyclic triglycine was reported by Ramakrishan *et al*. [19] using MM calculations. However, it must be pointed out that the complete PEHS of this compound was not evaluated in the aforementioned study. The PEHS of cyclic triglycine was recently reported by our group [5]. To the best of our knowledge, the PEHS of trisarcosyl has not been reported yet. In the present paper we performed a systematic and comprehensive analysis of the different conformational interconversion processes for this cyclic tripeptide. Thus, we report here an exhaustive conformational analysis of cyclotrisarcosyl using Density Functional Theory (DFT) computations. Aside from the populations of the conformers, it is of great interest to know the nature of the interconversions between the conformers and which of them occur most readily. The equilibrium structures, their relative stability, and the Transition State (TS) structures involved in the conformational interconversion pathways were analyzed. In addition, a comparative analysis between the conformational behaviors of cyclotrisarcosyl with that previously reported for cyclotriglycine [5] was carried out.

2. Calculation details

All the calculations reported here were performed using the GAUSSIAN 03 program [20]. Critical points (low-energy conformations and Transition State structures) were optimized at the DFT level of theory. An extensive search to localize the critical points on the PEHSs was carried out first by using starting geometries suggested by the GASCOS algorithm [21-24]. These input files were used to obtain the low-energy conformations and TS structures using B3LYP/6-31G(d), B3LYP/6-31G(d,p) and B3LYP/6-311++G(d,p) calculations. Vibrational frequencies for the optimized structures were computed to evaluate the zero-point energies (ZPE) as well as to confirm the nature of the singular points along the potential energy surface. The stationary points have been identified as minima with no imaginary frequencies, or as first-order transition states characterized by the existence of only one imaginary frequency in the normal mode coordinate analysis. Transition state structures were searched until the Hessian matrix had only one imaginary eigenvalue, and the transition states were also confirmed by visualizing the negative eigenvectors with a visualization program and internal reaction coordinate (IRC) calculations [25,26]. B3LYP/6-31G(d) IRC calculations were performed on the transition state structures to check that the TS structures lead to the initial conformer and to the final conformation (forward and reverse directions of the conformational interconversion path). IRC calculations were carried out along the conformational path in 6 steps in the relevant Cartesian coordinates in the forward direction and 6 steps in the reverse direction, with each step having a size of 0.3 $amu^{1/2}$ bohr.

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After obtaining the optimized structures from B3LYP/6-311++G(d,p) computations, single point calculations using the most reliable and flexible basis sets, (aug-cc-pVTZ and MP2/6-31G(d,p)) were carried out in order to evaluate the energies of the preferred conformers.

3. Results and discussion

3.1. Computation and analysis of critical points on the PEHS of trisarcosyl

3.1.1. Low-energy conformations

Eleven different conformations were found in the GASCOS-B3LYP/6-31G(d) search (Table 1). All the conformations obtained in the GASCOS-B3LYP/6-31G(d) search were further analysed by B3LYP/6-31G(d,p) and B3LYP/6-311++G(d,p) optimizations. Next a series of single point energy calculations using Aug-cc-pVTZ//B3LYP/6-311++G(d,p) and MP2/6-31G(d)//B3LYP/6-311++G(d,p) calculations were carried out for the low-energy conformations, in order to investigate the effects of a more extended basis set. Once obtained the different conformations of cyclotrisarcosyl we performed a comparative analysis between the PEHS obtained for cyclotrisarcosyl with that previously reported for cyclotriglycine [6]. These results are summarized in Table 1. Only conformation **6** previously obtained for cyclotriglicyne is missing in the PEHS of cyclotrisarcosyl. It should be noted that this conformer is absent due to the steric hindrance of the two methyl groups located in the same plane. From these results it appears that the PEHS of both cyclic peptides cyclotrisarcosyl and cylcotriglycine are related; it is clear however that the global minimum and the energy gaps obtained among the conformers are very different.

All the levels of theory employed here indicate that the highly preferred conformation of cyclotrisarcosyl is the symmetric *cis,cis,cis* crown conformation (Fig. 1; conformation **2** in Table 1). This is an important difference with respect to the PEHS reported for cyclotriglycine where the preferred form was the *trans-cis-cis* conformation **1**. The second low-energy conformation obtained for cyclotrisarcosyl is the somewhat distorted form and so-called twist conformation **3** displaying an energy gap of 2.92 kcal mol^{-1} over the global minimum at the MP2/6-31G(d)//B3LYP/6-311++G(d,p) level. In turn, the *trans-cis-cis* conformation **1**, which is the global minimum for cyclotriglycine, possesses an energy gap of 3.95 kcal mol^{-1} above the crown form in cyclotrisarcosyl, indicating that conformation **1** is thermodynamically irrelevant for this compound. Titlestad [17] has previously reported that cyclotrisarcosyl displayed one N-methyl signal and one methylene quartet, with an intensity of 9.6, and that the quartet coalesces to a single line at 135°C. This clearly shows that only one conformer was present in solution and that this contained only one type of amide bond. The author pointed out, "they must all be *cis* since they cannot all be *trans*". Our theoretical calculations confirm this assumption, indicating that the highly preferred conformation for trycyclosarcosyl is the *cis-cis-cis* crown conformation. The different conformational interconversion processes for this conformation are discussed in details in the next section.

The reliability of B3LYP/6-311++G(d,p) geometries can be investigated here since we have experimental results from X-ray analysis [15]. It is worthwhile, at this point, to make a comparison. Our results indicate that B3LYP/6-311++G(d,p) optimizations produce only moderate changes in the geometries obtained from

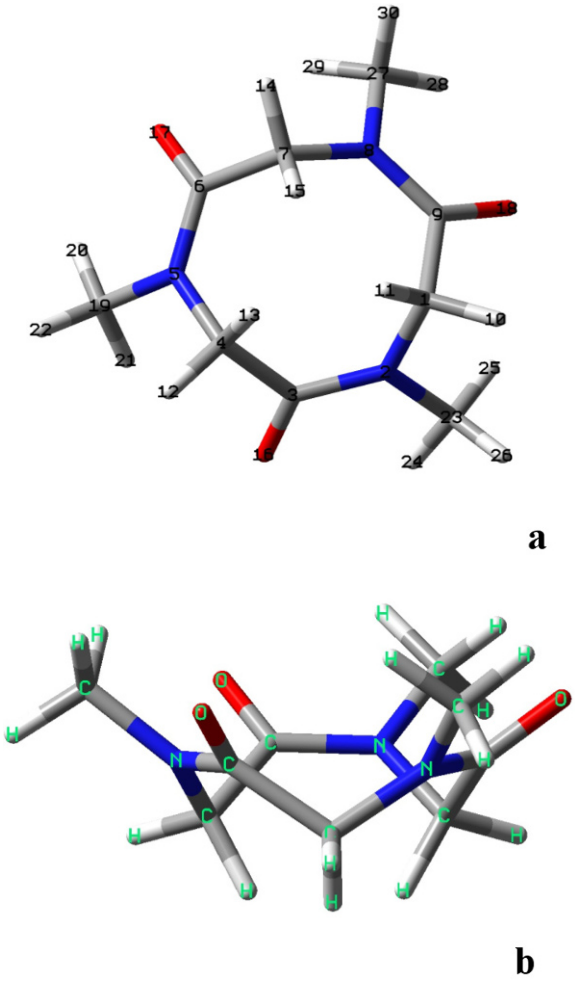

Figure 1. Spatial view of the energetically preferred cis-cis-cis crown conformation (conformer **2**) obtained for cyclotrisarcosyl. The numbering of atoms is shown in this figure: a) frontal view, b) lateral view.

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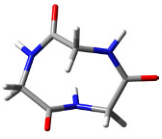
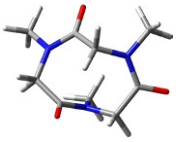
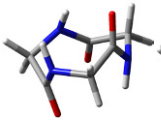
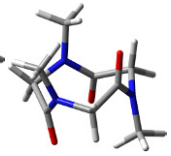
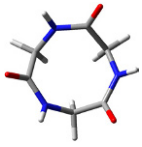
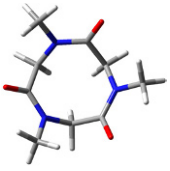
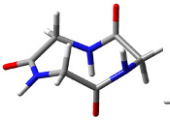
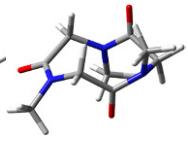
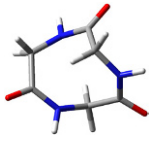
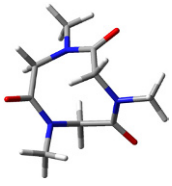
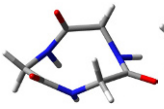
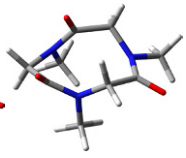
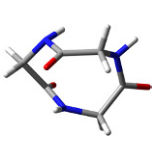
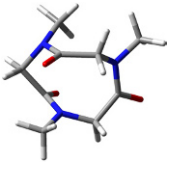
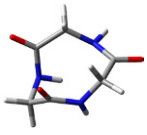
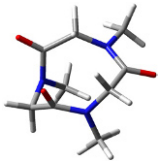
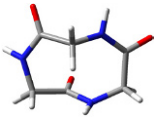
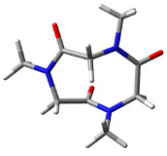
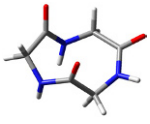
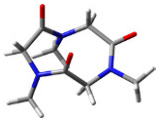
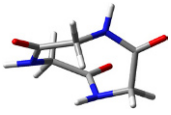
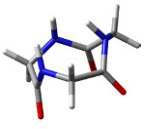
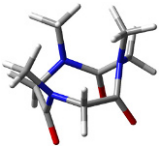
Table 1. The different conformers obtained for CTG and CTS. The corresponding isomer and topology type are also shown.

Conf.	Isomer Topology	CTG	CTS	Conf.	Isomer Topology	CTG	CTS
1*	trans-cis-cis tCOdown-up-up			7	trans-trans-trans tCOup-tCOdown-tCOdown		
2**	cis-cis-cis up-up-up (crown)			8	trans-trans-cis tCOup-tCOdown-up		
3	cis-cis-cis down-up-up (twist)			9	trans-trans-cis tCOdown-tCOdown-up		
4	trans-trans-cis tCOdown-tCOup-up			10	trans-trans-cis tCOdown-tCOdown-up		
5	trans-cis-cis tCOup-up-up			11	trans-trans-cis tCOdown-tCOdown-down		
6	trans-cis-cis tCOup-down-up			12	trans-trans-trans tCOdown-tCOdown-tCOdown		

* *global minimum of CTG*
** *global minimum of CTS*

X-ray studies (Table 2) indicating an excellent agreement between the theoretical and experimental results. The accuracy of the key torsion angles (in the present case the C–C torsion angles) is of great importance. A significant correlation was found between the torsional angles optimized and those obtained from experimental techniques (Fig. 2). Thus, only minute deviations were found between the torsional angle values found at the B3LYP/6-311++G(d,p) level when compared to those found from X-ray. When correlating the torsional angles optimized with B3LYP/6-311++G(d,p) against the experimental data, a strong correlation that has a least square value of r = 0.9947 was found (Fig. 2a). When correlating the bond distances optimized with B3LYP/6-311++G(d,p), another strong correlation with a least square value of r = 0.9964 was found (Fig. 2b). Although the trend observed for the bond angles was slightly less significant, r = 0.9735 (Fig. 2c), the correlation was clearly strong and unquestionable. The difference observed between the experimental and theoretical data for the bond angles is a consequence of a slight distortion in one of the N-methyl groups of the X-ray values.

3.1.2. First-order Transition States (TS)

The GASCOS algorithm suggested 24 starting geometries (data not shown) which were in turn maximised using B3LYP/6-31G(d) calculations following the proper routine implemented in the Gaussian 03 program. Thus, we obtained 13 B3LYP/6-31G(d)/TS structures, which were further analysed using B3LYP/6-31G(d,p) and B3LYP/6-311++G(d,p) calculations. It is interesting to note that the theoretical total number of

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Table 2. Interatomic distances, bond angles and torsional angles obtained from MP2/6-31G(d.p)//B3LYP/6-311++G(d.p) calculations and X- ray experimental data [15]. The absolute differences for each parameter are also shown. The numbering of the atoms is shown in Fig. 1.

Interatomic Distances (Å)				Bond Angles (º)				Torsional Angles (º)			
	[1]Exp	[2]Calc	[3]Dif		[1]Exp	[2]Calc	[3]Dif		[1]Exp	[2]Calc	[3]Dif
O18-C9	1.233	1.224	0.009	**O18-C9-C1**	118.6	118.2	0.4	**N2-C1-C9-N8**	91.0	95.3	4.3
O16-C3	1.232	1.224	0.008	**O16-C3-C4**	118.6	118.2	0.4	**C1-C9-N8-C7**	7.3	2.4	4.9
N8-C27	1.466	1.468	0.002	**O17-C6-N5**	122.3	122.6	0.3	**C9-N8-C7-C6**	-102.8	-98.7	4.1
N2-C1	1.466	1.465	0.001	**C1-C9-N8**	119.1	119.1	0.0	**N8-C7-C6-N5**	99.7	96.2	3.5
N5-C4	1.448	1.465	0.017	**C4-C3-N2**	119.6	119.2	0.4	**C7-C6-N5-C4**	-9.9	0.4	10.3
N8-C9	1.358	1.369	0.011	**C27-N8-C7**	115.0	115.5	0.5	**C6-N5-C4-C3**	-86.8	-97.0	10.2
C1-C9	1.518	1.541	0.023	**C23-N2-C3**	117.4	118.9	1.5	**N5-C4-C3-N2**	107.8	96.6	11.2
C4-C3	1.516	1.541	0.025	**C19-N5-C6**	116.8	118.9	2.1	**C4-C3-N2-C1**	-11.9	0.7	12.6
O17-C6	1.232	1.224	0.008	**C9-N8-C7**	125.9	125.6	0.3	**C3-N2-C1-C9**	-91.7	-97.8	6.1
N2-C23	1.465	1.468	0.003	**N2-C1-C9**	109.3	111.6	2.3				
N5-C19	1.476	1.468	0.008	**N5-C4-C3**	110.3	111.8	1.5				
N8-C7	1.462	1.465	0.003	**O17-C6-C7**	118.5	118.1	0.4				
N2-C3	1.357	1.369	0.012	**O18-C9-N8**	122.3	122.6	0.3				
N5-C6	1.352	1.369	0.017	**O16-C3-N2**	122.0	122.6	0.6				
C7-C6	1.533	1.541	0.008	**C7-C6-N5**	119.2	119.2	0.0				
				C23-N2-C1	115.8	115.5	0.3				
				C19-N5-C4	117.9	115.5	2.4				
				C27-N8-C9	119.0	118.8	0.2				
				C3-N2-C1	125.7	125.6	0.1				
				C6-N5-C4	124.4	125.6	1.2				
				N8-C7-C6	111.7	111.8	0.1				

1: Experimental; 2: Calculated; 3: Absolute differences

saddle points for cyclotrisarcosyl is unknown. All that can be said is that our results do not violate the so-called Morse inequalities [27]. In principle, one would expect that there is at least one saddle point associated with each pair of minima, *i.e.*, (X(X-1)/2) saddle points, where X is the number of minima. However, this is not likely to be the case for cyclic molecules where certain conformational interconversions would require passing infinite energy barriers, *e.g.* by breaking a bond.

Considering that the basic units of the network of conformational interconversions are the directly interconnected minimum-transition states-minimum triads (M/TS/M triads), the different M/TS/M triads obtained for cyclotrisarcosyl are shown in Fig. 3. It should be noted that each M/TS/M triad represents a single conformational interconversion. Single-point calculations using a more accurate and extended basis set were carried out on the 13 TS structures obtained from the B3LYP/6-311++G(d,p) optimizations.

Considering that conformer **2** is the highly preferred form of cyclotrisarcosyl, we focused our attention on the possible conformational interconversions for this conformation. Thus, we found three different conformational interconversion paths for the global minimum **2**. These are the conformational interconversions between conformer **2** with conformers **1**, **3** and **5,** throughout TS_{1-2}, TS_{2-3} and TS_{2-5}, respectively (Fig. 4). The transition structure TS_{2-3} is mainly governed by the movement of one of the alpha carbons, allowing the simultaneous up-down inversion of two peptide planes. It should be noted that the environment of the alpha carbon for this structure is not symmetric and consequently the overall structure of this TS is not symmetric. This is a striking difference with respect to the equivalent TS structures previously reported for 1,4,7-cyclononatriene and tribenzocyclononatriene (TBCN) [5]. On the other hand, this conformational interconversion process is also different from that previously reported for cyclotriglycine [6]. It should be noted that for cycloctriglicyne, this movement is mainly determined by one of the peptide bond components, in general by the NH group [5,6]. The conformational interconversion between conformers **1** and **2** involves the TS_{1-2} and in this case the movement is mainly determined by the carbonyl group, whereas the adjacent groups are helping to obtain this spatial reordering.

Conformer **12** represents a particularly noteworthy case. The conformational interconversions for this conformer involve conformers **7** and **9** whose transition state structures (TS_{7-12} and TS_{9-12}) require very high energies and therefore they were not considered in this study. There is no conformational interconversion between conformers **9** and **12** for cyclictrisarcosyl because such interconversion is highly hindered. This is a clear difference with respect to cyclotriglycine, where the TS_{9-12} energy is only 19.96 kcal mol^{-1} [6],

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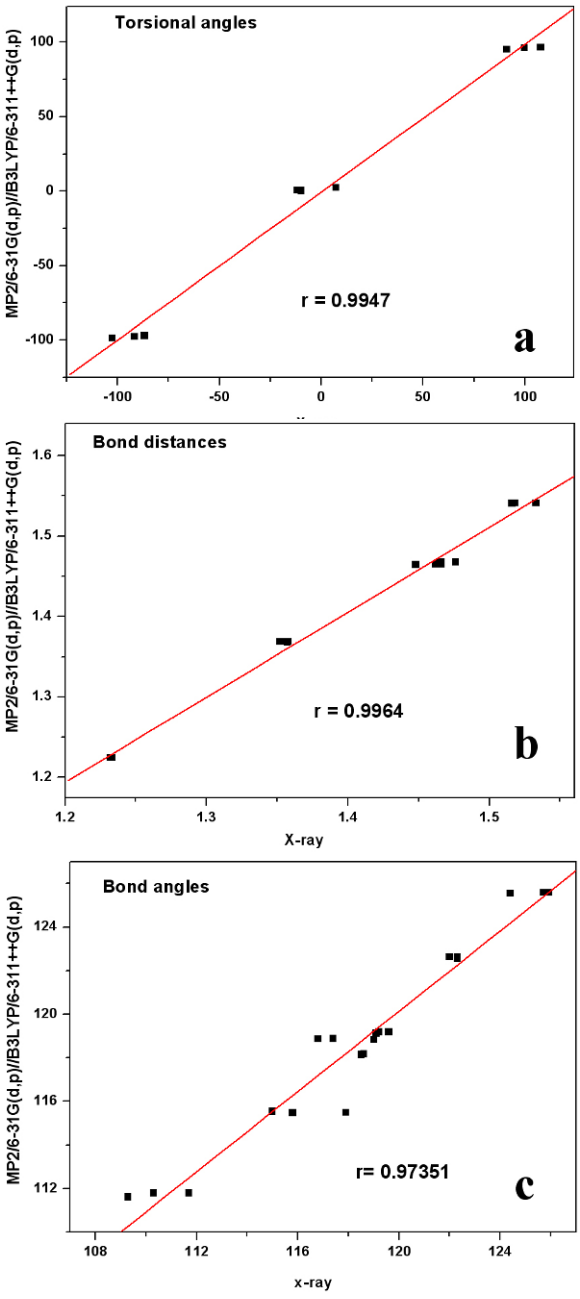

Figure 2. A graph showing the correlation between theoretical calculations obtained from MP2/6-31G(d,p)//B3LYP/6-311++G(d,p) calculations *versus* experimental data (X-ray, [15]). a) bond distances; b) bond angles and c) dihedral angles.

indicating that this interconversion does not possess a significant steric hindrance in cyclotriglycine. A similar situation might be observed for $TS_{7\text{-}12}$ which connects conformer **7** with **12**. Whereas $TS_{7\text{-}12}$ requires 126 kcal mol^{-1} for cyclotrisarcosil, for cyclictriglycine it requires only 45 kcal mol^{-1} (see Fig. 3).

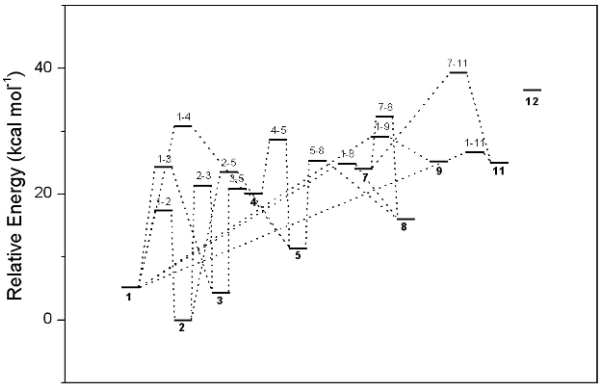

Figure 3. The energy profiles in kcal mol^{-1} obtained from MP2/6-31G(d,p)//B3LYP/6-311++G(d,p) calculations for the different conformational interconversions of trisarcosyl.

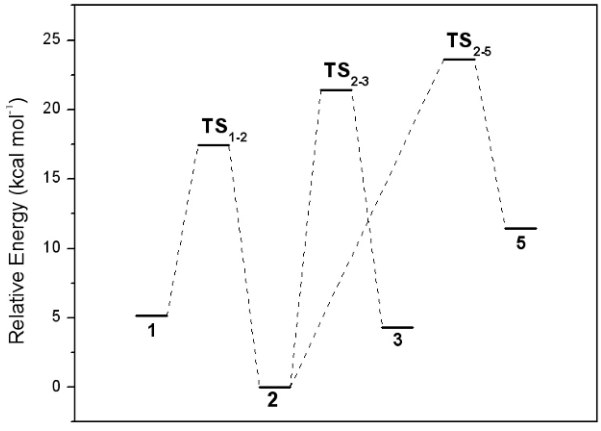

Figure 4. Energy profiles for the different conformational interconversions obtained for conformer 2.

Once cyclotrisarcosyl adapts conformation **3**, the interconversion process from **3** to its specular image **3***can be easily explained by the simultaneous movement of two adjacent methylene groups (alpha carbons). To avoid misleading terminology, the symbol * will be used for specular images. The complete ring inversion process from conformer **2** to **2***might be well appreciated in Fig. 5. MP2/6-31G(d)//B3LYP/6-311++G(d,p) calculations predict that this process requires 20.88 kcal mol^{-1}. Schaug previously reported that the activation energy for the ring inversion is 17.7 kcal mol^{-1}; however, he pointed out that the quality of the spectra does not permit any further conclusion due to undesirablerandom errors in the computations [18]. Dale and Titlestad suggested from experimental data [17] that this interconversion process requires 20.1 kcal mol^{-1}. It is clear that our theoretical calculations offer additional support for such suggestions.

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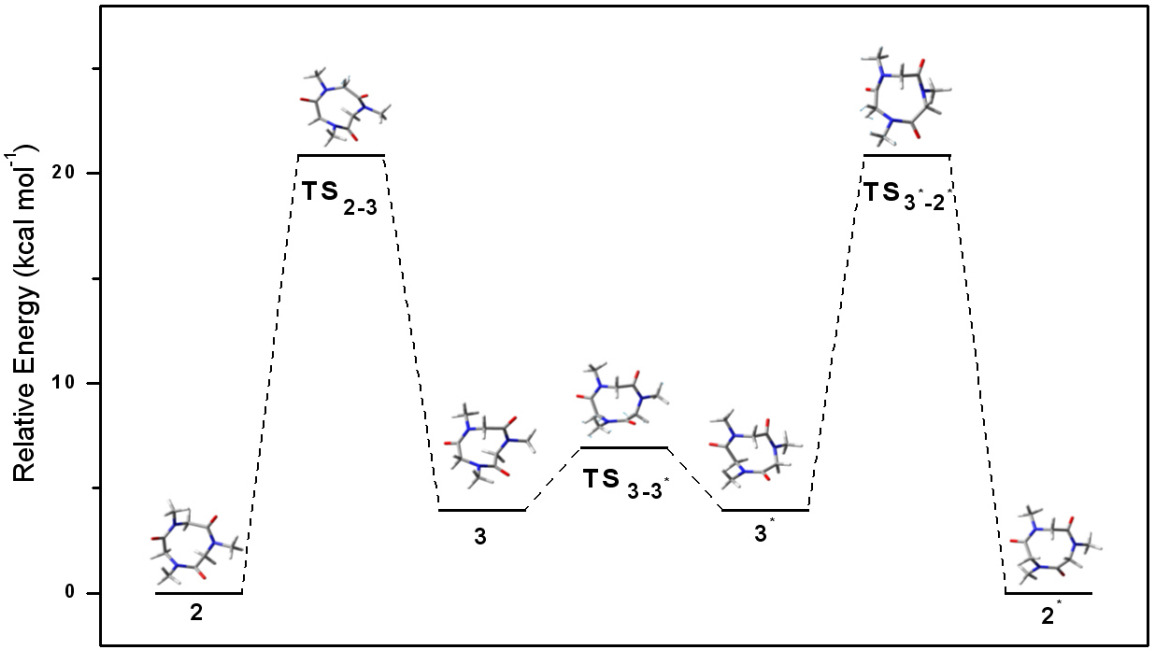

Figure 5. The energy profiles in kcal mol^{-1} obtained from MP2/6-31G(d,p)//B3LYP/6-311++G(d,p) calculations for the enantiomeric 2-2* interconversion. Spatial views of the minima and TSs involved in these interconversion are also shown here.

4. Conclusions

The PEHS of cyclotrisarcosyl was investigated using theoretical calculations. *Ab initio* and DFT computations provide a clear picture for the conformational PEHS of this molecule from both structural and energetic points of view.

The exploration of a conformational energy hypersurface by methods that ignore all features other than local energy minima do not always give a satisfactory picture of the problem. It is very desirable to at least determine the lowest energy transition states linking all pairs of conformations. The elementary steps in conformational interconversion paths for cyclotrisarcosyl were discussed in detail. Thus, the different conformational interconversions have been properly analyzed, giving a better idea of the conformational intricacies of the PEHSs of this compound. Altogether, 24 geometries (11 minima and 13 transition states) were found to be important for a description of the conformational features of cyclotrisarcosyl. Our results confirm that the *cis-cis-cis* "crown" form is the highly preferred conformation of cyclotisarcosyl in agreement with the experimental data. MP2/6-31G(d)//B3LYP/6-311++G(d,p) calculations predict that the conformational interconversion between the crown and twist forms requires 20.88 kcal mol^{-1}, which is in perfect agreement with the experimental data. The possible conformational intreconversion paths for the energetically preferred crown form have been described in this study.

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