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An ab initio conformational study on captopril

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Abstract

Captopril can interact regio- and stereo-specifically with various functional groups present at the active site of angiotensin converting enzyme (ACE). Since no X-ray structure of ACE is available, Captopril, as an ACE inhibitor may be used as a 'molecular caliper', to estimate upper and lower bound values for separation *d*, where the mercaptidic terminal group of the molecule is linked to the enzyme Zn^{2+} cofactor, while the carboxylate links via an hydrogen bond to the guanidine moiety of an arginine side chain. As the results of this Ab Initio study, the conformations of the dianionic form of the full captopril molecule are reported here.
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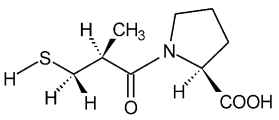
Keywords: Captopril; Antihypertensive drug; Role of Zn^{2+} cofactor; Molecular caliper; Organic sulphur

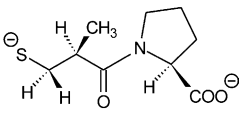
1. Introduction

1.1. Biomedical background

Captopril, 1-(D-3-mercapto-2-methylpropionyl)L-proline, an effective anti-hypertensive drug, is a relatively small molecule [1], which may be in a neutral [**1a**] or biologically active dianion form [**1b**].



[1a]



[1b]

It has several functional groups, and the molecule may assume numerous stable conformations. Consequently, captopril [**1**] can interact regio- and stereo-specifically with various functional groups present at the active site of angiotensin converting enzyme (ACE) [2], as illustrated schematically by Scheme 1.

Since no X-ray structure of ACE is available, one does not know the stereochemical separations of the various sites of the enzyme involved in the reaction mechanism. As an ACE inhibitor, captopril may be

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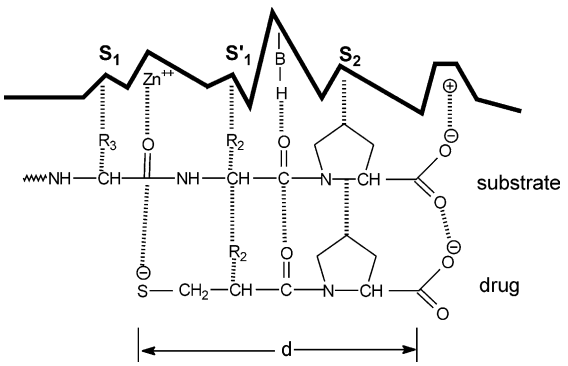
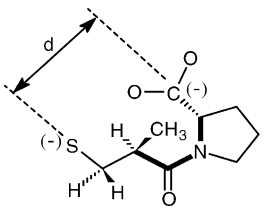


Scheme 1. Schematic illustration of the natural substrate and captopril docking to angitensin converting enzyme (ACE).

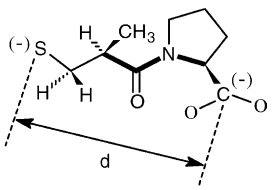
used as a 'molecular caliper' to estimate the upper and lower bound values for the internuclear separation (*d*) where the mercaptidic terminal group of the molecule is linked to the enzyme Zn^{2+} cofactor, while the carboxylate links via an hydrogen bond to the guanidine moiety of an arginine side chain.

Obviously, the internuclear separation between sulfur (S) and the carboxylate (C) cannot exceed a certain limit. In addition to regular conformational change, captopril can go through a *cis-trans* isomerization process [**2**]:



cis

[2a]



trans

[2b]

It is very important to study in considerable detail the conformations of both the *cis* and *trans* isomers to obtain an upper and lower value of *d*. Such detailed conformational study is necessary to make an estimate of the enzyme active site geometry.

1.2. Computational background

Captopril has been studied [3] by a 'classical potential energy' force field type method as early as 1985. Subsequently, Hillier et al. [4] carried out AM1 computations on Captopril in 1991. This was followed by Luke [5] in 1994. Luke also reported [6] AM1 calculations on the demethylated analogue of Captopril in 1995. To the best of our knowledge no ab initio computation has been reported as yet on captopril.

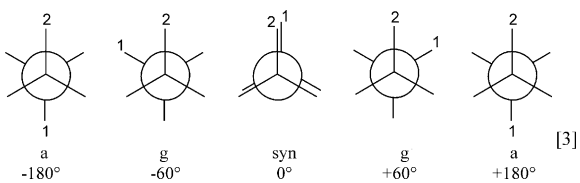
Captopril poses a non-trivial multidimensional conformational problem. For this reason, it seemed prudent to study some fragments of captopril first [**1**], or preferably the fragments of its biologically active dianionic form [**1b**].

In the present paper, our examination of the *N*-acetyl prolinate fragment and the results of an exploratory study on the conformations of the dianionic form of the full captopril molecule [**1**] will be reported here.

1.3. Conformational analysis of captopril fragments

1.3.1. One-dimensional conformational analysis

Rotation about a single bond that joins two tetrahedral (sp^3) atoms, leads to clockwise *gauche* or *gauche* $^+(g^+)$, *anti*(*a*) and counter clockwise *gauche* or *gauche* $^-(g^-)$ conformers [**3**]. Note that the same anti conformation may be reached by both clockwise and counter clockwise rotations.



[3]

This conformational pattern is frequently exemplified by *n*-butane. Here rotations about the $HS-CH_2$ bond and about the $H_2C-CHMe$ bond of captopril are governed by such conformational characteristics.

Rotation about a single bond that joins a tetrahedral (sp^3) and a trigonal planar (sp^2) atoms is not so obvious. Minimum energy conformations may involve perpendicular arrangement or they may occur at an eclipsed/staggered arrangement.

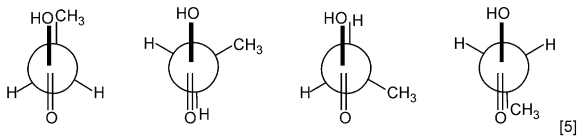
[4]

perpendicular
90°

eclipsed / staggered
0° / 180°

This conformational pattern may be exemplified by ethyl benzene [7], where 1 = CH_3 and the heavy line is the benzene ring. In that case, the perpendicular structure turned out to be the global minimum while eclipsed staggered turned out to be the local minimum. In the case of the propionate ion [8], where 1 = CH_3 and the heavy line is COO(−), the 90° is the high TS and 0° (as well as 180°) is almost the global minimum. As a slight variation, the 0 and 180° are low energy local maximal (0.015 kcal/mol) and the actual global minima (0.00 kcal/mol) is displaced by ±15°. Thus, the potential energy curve for Et–COO(−) is the mirror image of Et–Ph.

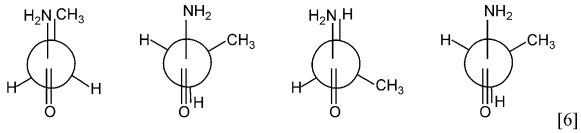
The situation is different in the case of propionic acid [8] since only eclipsed/perpendicular structures turned out to be critical point.



[5]

0° TS | 60° local min | 120° TS | 180° global min

Propionic acidamide [9] is completely analogous to propionic acid.

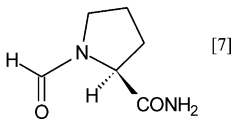


[6]

0° TS | 60° local min | 120° TS | 180° global min

The potential energy curves for the four molecular systems are shown in Figs. 7 and 8 of Ref. [9].

The rotation of the $-CONH_2$ functionality in *N*-formyl-L-prolinamide [**7**] can be compared to [**6**].

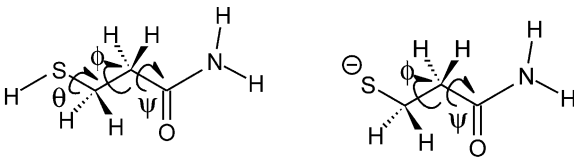


[7]

Since the $-CONH_2$ in [**7**] is attached to a stereo centre (the α-carbon of proline) the potential energy curves obtained for the *cis* and *trans* peptide bond (HCO–N <) in [**7**] is heavily distorted [10] as shown in Fig. 1.

1.3.2. Multi-dimensional conformational analysis

Beyond the proline residue, the other conformational variations of captopril are residing in the flexible open chain which may be represented, at least in a preliminary fashion, as 3-mercapto propanamide [**8a**] or its *S*-deprotonated conjugate base [**8b**].



[8a] [8b]

In these structures, the five member ring is omitted with respect to captopril and hydrogen atoms are attached to the amide nitrogen.

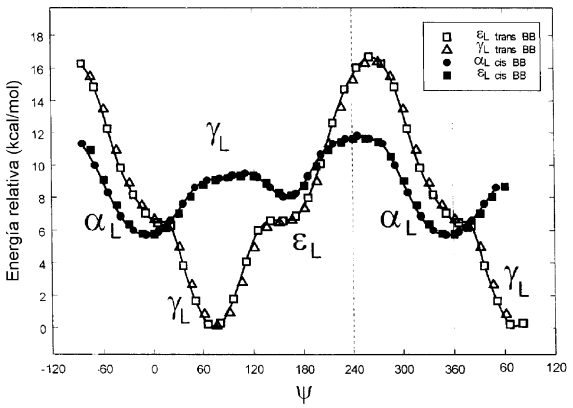
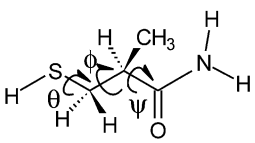
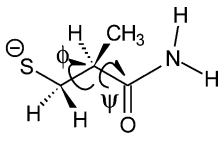


Fig. 1. Conformational potential energy curve, $E = E(\psi)$ for *N*-formyl-L-prolinamide containing either *trans*- and *cis*- peptide bond. The scan for the *trans*- isomer was started at both the ϵ_L and γ_L conformations while the scan for the cis isomer was started at both the α_L and the ϵ_L conformations.

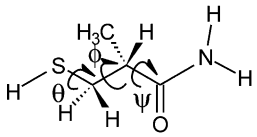
Of course compounds [**8a**] and [**8b**] are missing the methyl group at the α-carbon (i.e. at C^2) which is present in captopril. If that methyl group is included then two enantiomers may be generated (*S*)-2-methyl-3-mercapto-propanamid [**9a**] and its conjugate base [**9b**] as well as (*R*)-2-methyl-3-mercapto-propanamid [**10a**] and its conjugate base [**10b**].



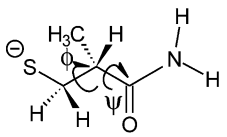
[9a]-*S*



[9b]-*S*



[10a]-*R*



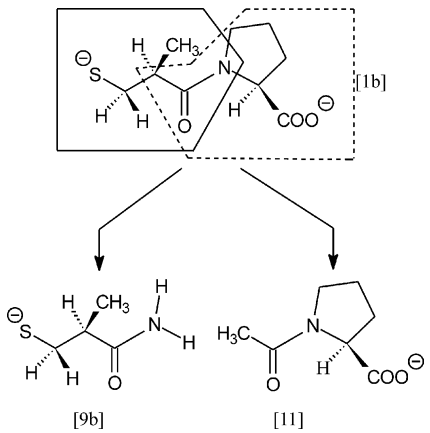
[10b]-*R*

The *S*-deprotonated conjugate bases, i.e. [**8b**], [**9b**] and [**10b**], represent a simple conformational problem than their neutral counterparts, i.e. [**8a**], [**9a**] and [**10a**], because there are one fewer torsional angles in the conjugate bases than in the corresponding neutral compounds.

Clearly, in any study the conjugate bases (*b*-series) should be given the first attention before the neutral counterparts (*a*-series) are discussed. Such an approach is prudent because only two torsional (ϕ and ψ) are to be studied in the *b*-series while three torsional angles (θ, ϕ and ψ) need to be studied in the *a*-series. The acidamide moiety is always planar. Consequently, ω may be ignored, as a variable, in both series. The value of ω, however, may be recorded as an optimized value being in the vicinity of 180 or 0° depending on which hydrogen atom of the $-NH_2$ moiety is considered. The results reported earlier [11] are summarized in Fig. 2.

2. Scope

One of the conformational intricacies is associated with the five member ring on the proline moiety. The $-CO-N<$ moiety may be of *cis* or *trans* configurations. Also, the five-member ring may be in a number of non-planar conformation. Finally, the –COOH moiety of [**1a**] could assume three conformations (g^+, *a*, g^-) leading to γ_L, ϵ_L and α_L peptide folding. Consequently, it seemed prudent to study the fragments of captopril or preferably the fragments of its biologically active dianionic form [**1b**].



[1b] [9b] [11]

The conformational intricacies of compounds [**8a**], [**9a**] and [**10a**] as well as their conjugate bases [**8b**], [**9b**] and [**10b**] have been reported previously [11]. Clearly, the *R* and *S* isomeric forms represent crucial spatial requirement for docking of the two enantiomers. We also wish to report our finding on the *N*-acetyl prolinate fragment [**11**] and its stereochemical similarities and/or differences to the previously studied formylproliamide [**7**]. Also, as the results of this exploratory study, the conformations of the dianionic form of the full captopril molecule will be reported here.

3. Methods

3.1. Molecular computations

Using the GAUSSIAN 98 program system [12], ab initio computations have been carried out at the HF/3-21G level of theory, with full geometry optimization. HF/6-31 + G(d) and HF/6-311++G(d) calculations were carried out for the minimal energy structures obtained with the minor base set.

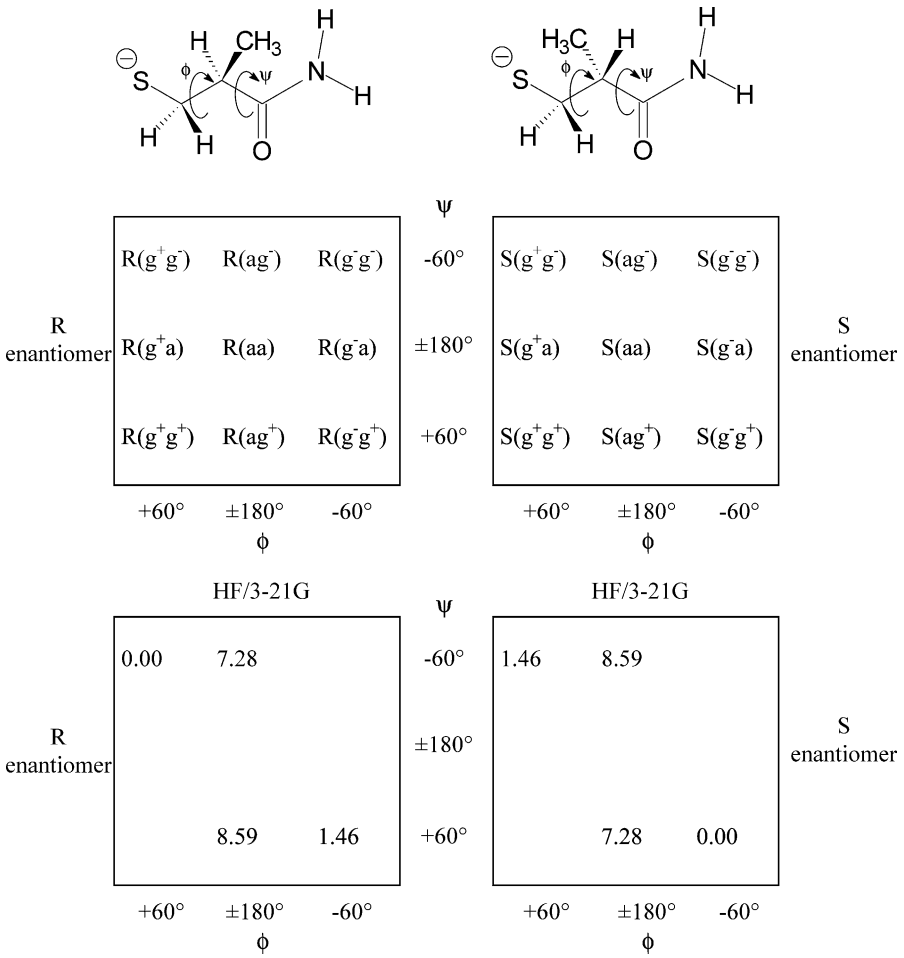
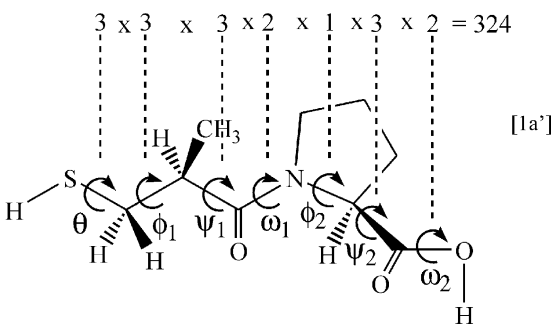


Fig. 2. Optimized (HF/3-21G) conformers (top) and computed relative energies (bottom) of *R*- and *S*-enantiomers of S-deprotonated 2-methyl-3-mercapto-propanamide.

Potential energy curves were plotted using the AXUM 5.0 software.

3.2. Internal co-ordinates

Considering all torsional angles, a complete conformational study on captopril essentially means that the geometric optimization of 324 structures for *R*-Captopril is required, and as many for *S*-Captopril. The predicted 324 structures are the result of the assumed topological periodicities of the seven torsional angles shown below [**1a**′]. Half of the structures (i.e. 162) are for the *trans* and the other half are for the *cis* isomers.



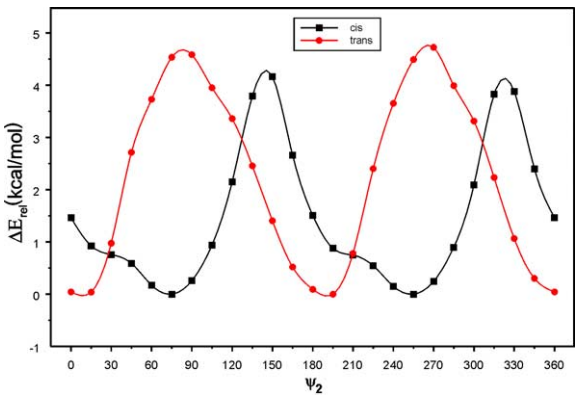


Fig. 3. Conformational potential energy curves (HF/3-21G), $E = E(\psi_2)$ for **N**-acetyl prolinate fragment [**11**] for molecule with *cis* and *trans* peptidic bond.

Similarly, for the double anions, the number of structures to be studied may be estimated from the topological periodicities of the five torsional angles involved. The number (54) includes 27 *cis* and 27 *trans* isomers as shown in [**1b**′].

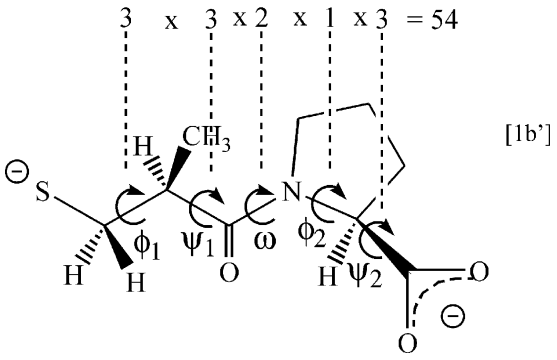


Table 1
Conformations of *trans*-captopril dianion optimized at the HF/3-21G level of theory

Conformations	φ_1	ψ_1	ω	φ_2	ψ_2	d1-12	E (hartree)	ΔE (kcal/mol)
$\alpha_L(g^+g^+)$	No found							
$\alpha_L(g^+a)$	No found							
$\alpha_L(g^+g^-)$	No found							
$\alpha_L(ag^+)$	No found							
$\alpha_L(aa)$	179.565	158.415	−6.011	−109.125	−15.493	6.537	−1019.462417	0.00
$\alpha_L(ag^-)$	No found							
$\alpha_L(g^-g^+)$	No found							
$\alpha_L(g^-a)$	No found							
$\alpha_L(g^-g^-)$	No found							
$\epsilon_L(g^+g^+)$	85.490	78.807	12.856	−129.771	169.819	5.871	−1019.4456347	10.53
$\epsilon_L(g^+a)$	No found							
$\epsilon_L(g^+g^-)$	No found							
$\epsilon_L(ag^+)$	No found							
$\epsilon_L(aa)$	−179.571	158.418	−5.994	−109.138	171.136	6.537	−1019.462417	0.00
$\epsilon_L(ag^-)$	−157.342	−65.316	−5.897	−99.473	124.315	6.233	−1019.4603437	1.30
$\epsilon_L(g^-g^+)$	No found							
$\epsilon_L(g^-a)$	No found							
$\epsilon_L(g^-g^-)$	No found							
$\gamma_L(g^+g^+)$	No found							
$\gamma_L(g^+a)$	No found							
$\gamma_L(g^+g^-)$	No found							
$\gamma_L(ag^+)$	No found							
$\gamma_L(aa)$	174.134	160.675	−4.561	−89.527	68.110	6.200	−1019.460301	1.32
$\gamma_L(ag^-)$	No found							
$\gamma_L(g^-g^+)$	No found							
$\gamma_L(g^-a)$	No found							
$\gamma_L(g^-g^-)$	−49.449	−58.267	10.128	−108.936	75.115	5.528	−1019.4525700	6.18

Table 2
Conformations of *cis*-captopril dianion optimized at the HF/3-21G level of theory

Conformations	φ_1	ψ_1	ω	φ_2	ψ_2	d1-12	E (hartree)	ΔE (kcal/mol)
$\alpha_L(g^+g^+)$	81.096	75.018	176.288	−96.610	−14.378	6.957	−1019.4532255	9.43
$\alpha_L(g^+a)$	No found							
$\alpha_L(g^+g^-)$	No found							
$\alpha_L(ag^+)$	−171.826	87.795	−178.862	−102.625	−15.986	7.393	−1019.4682589	0.00
$\alpha_L(aa)$	No found							
$\alpha_L(ag^-)$	−166.996	−56.039	−172.119	−107.206	−16.944	7.182	−1019.4559158	7.74
$\alpha_L(g^-g^+)$	−83.658	115.111	175.485	−107.551	−15.221	6.520	−1019.4602905	5.00
$\alpha_L(g^-a)$	No found							
$\alpha_L(g^-g^-)$	No found							
	No found							
$\epsilon_L(g^+g^+)$	No found							
$\epsilon_L(g^+a)$	No found							
$\epsilon_L(g^+g^-)$	No found							
$\epsilon_L(ag^+)$	−171.832	87.877	182.004	−102.864	170.242	7.394	−1019.468258	0.00
$\epsilon_L(aa)$	No found							
$\epsilon_L(ag^-)$	No found							
$\epsilon_L(g^-g^+)$	No found							
$\epsilon_L(g^-a)$	No found							
$\epsilon_L(g^-g^-)$	No found							
$\gamma_L(g^+g^+)$	No found							
$\gamma_L(g^+a)$	No found							
$\gamma_L(g^+g^-)$	No found							
$\gamma_L(ag^+)$	No found							
$\gamma_L(aa)$	No found							
$\gamma_L(ag^-)$	No found							
$\gamma_L(g^-g^+)$	No found							
$\gamma_L(g^-a)$	No found							
$\gamma_L(g^-g^-)$	No found							

In the present study, we have investigated structure [**1b′**] in which the following torsional angles were considered: ϕ_1, ψ_1, ω, ϕ_2 and ψ_2. All $3N-6 = 3\times 27-6 = 75$ geometrical parameters were optimized for the 116 electron-containing species.

4. Results and discussion

The conformational intricacies of compound [**9b**] have been reported previously [11] and are shown in Fig. 2. Clearly, the *R* and *S* isomeric forms contain crucial spatial requirements for docking of the two enantiomers.

Results obtained on the *N*-acetyl prolinate fragment [**11**] are pictorially represented in the potential energy curve $E = E(\psi_2)$ shown in Fig. 3 for molecule with *cis* and *trans* peptidic bond.

Tables 1 and 2 display the geometrical parameters and energies obtained for *cis*- and *trans*- dianionic captopril, respectively. As it can be seem in Fig. 4, only four α_L conformers were found for *trans*-dianionic captopril, while for *cis*- dianionic captopril most and the better structures were found and ϵ_L conformers are prevailing. In Fig. 5, the PEC [$E = E(\psi_2)$] for the *cis*- and *trans*- conformers can be compared. As the PEC obtained for the *N*-acetyl prolinate fragment, it shows the conformer with *cis*-peptide bond as the most stable, but the corresponding ΔE are much minor indicating that all *cis* structures are possible to be found.

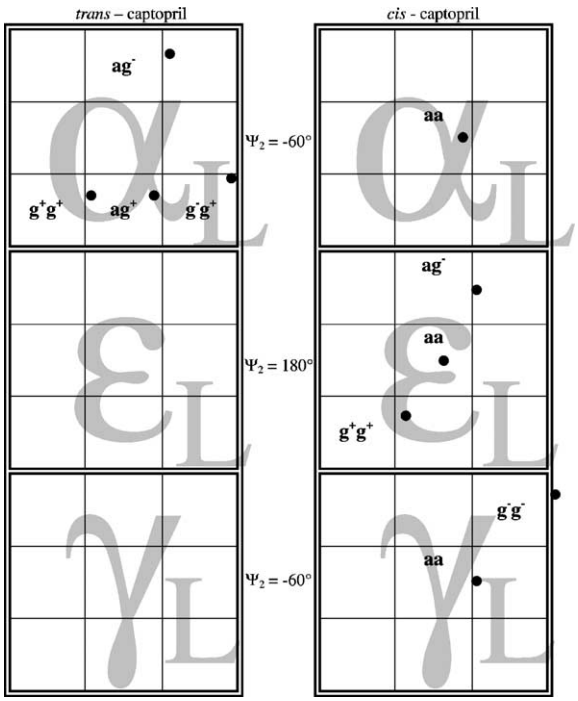


Fig. 4. Topological representation of the HF/3-21G optimized conformers of the *S* and *O* deprotonated Captopril double conjugate base containing either a *trans*- or a *cis*- peptide bond.

The conformational potential energy surfaces (at HF/3-21G level of theory), $E = E(\varphi_1, \psi_1)$ for Captopril in its dianionic form containing either a *trans*- or a *cis*- peptide bond are shown in Figs. 6 and 7, respectively.

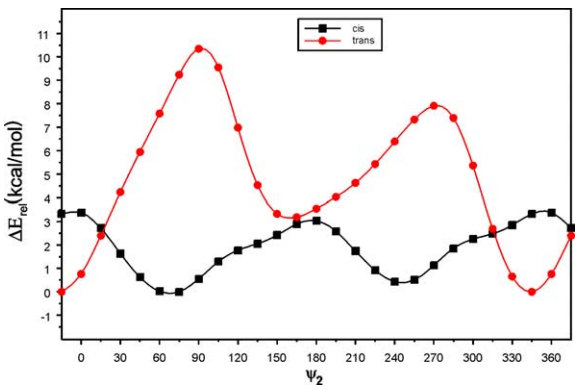


Fig. 5. Conformational potential energy curves (HF/3-21G), $E = E(\psi_2)$ for Captopril in its dianionic form containing either a *trans*- or a *cis*- peptide bond.

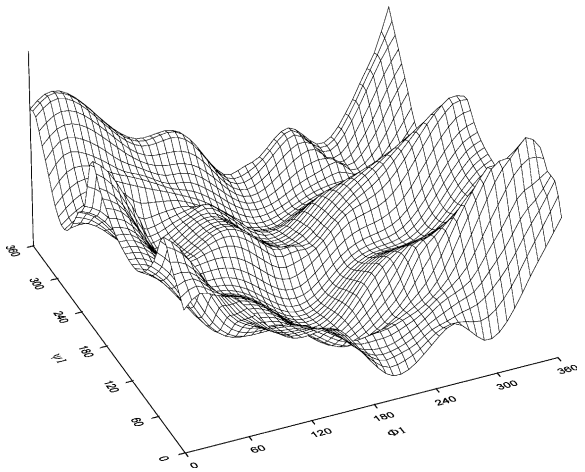


Fig. 6. Conformational potential energy surface (HF/3-21G), $E = E(\varphi_1, \psi_1)$ for Captopril in its dianionic form with *cis*- peptide bond.

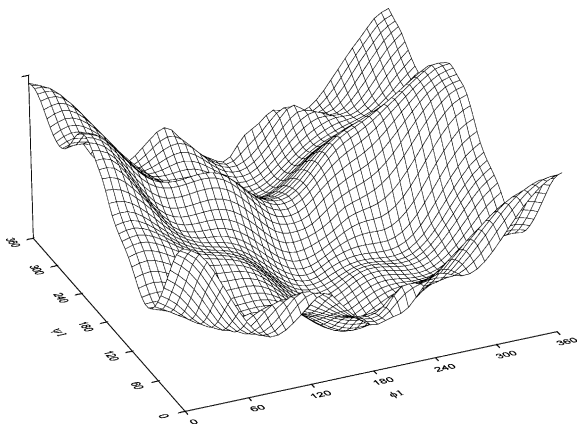


Fig. 7. Conformational potential energy surface (HF/3-21G), $E = E(\varphi_1, \psi_1)$ for Captopril in its dianionic form with *trans*- peptide bond.

5. Conclusion

It is believed [13,14], that the *trans* structure is the active form of captopril. In Tables 3 and 4 the geometrical parameters and energies for the best structures of *cis*- and *trans*- captopril at three levels of theory: HF/3-21G, HF/6-31 + G(d) and HF/6-11++G(d) are shown. The ΔE at the highest level of theory is 4.43 kcal/mol suggesting that

Table 3
Geometrical parameters and energies for the best structures of *cis*-captopril at three levels of theory (HF/3-21G, HF/6-31 + G(d) and HF/6-311++G(d))

Method	Φ_1	Ψ_1	ω	Φ_2	Ψ_2	d	Energy
HF/3-21G	179.565	158.415	−6.011	−109.125	−15.493	6.536762	−1019.462417
HF/6-31G*	181.762	152.069	−2.437	−101.872	170.220	6.248863	−1024.946834
HF/6-311++G*	−178.014	151.817	−1.947	−102.848	−12.352	6.252749	−1025.1175346

Table 4
Geometrical parameters and energies for the best structures of *trans*- captopril at three levels of theory (HF/3-21G, HF/6-31 + G(d) and HF/6-311++G(d))

Method	Φ_1	Ψ_1	ω	Φ_2	Ψ_2	d	Energy
HF/3-21G	188.171	87.756	181.939	−102.549	−16.003	7.392116	−1019.4682589
HF/6-31G*	192.788	92.793	183.177	−96.660	−15.262	7.389190	−1024.9539993
HF/6-311++G*	192.973	92.690	183.396	−97.004	−14.158	7.387116	−1025.1245956

both, the *cis* and *trans* forms may contribute to the activity.

In (Fig. 8), the minima energy structures obtained at the higher level of theory are represented, d_{trans} being more than 1 Å longer that d_{cis}, where d is the separation between the negative charges or docking points in the biologically active captopril molecule.

So far, it can be assumed that distance between the two positive points in the active site of ACE (d_{ACE}), which is the distance between the Zn^{2+} cofactor and the guanidine moiety of an arginine side chain, must obey the relationship:

$$d_{trans} < d_{ACE} < d_{cis} \Rightarrow 7.38\ \text{Å} < d_{ACE} < 6.25\ \text{Å}$$

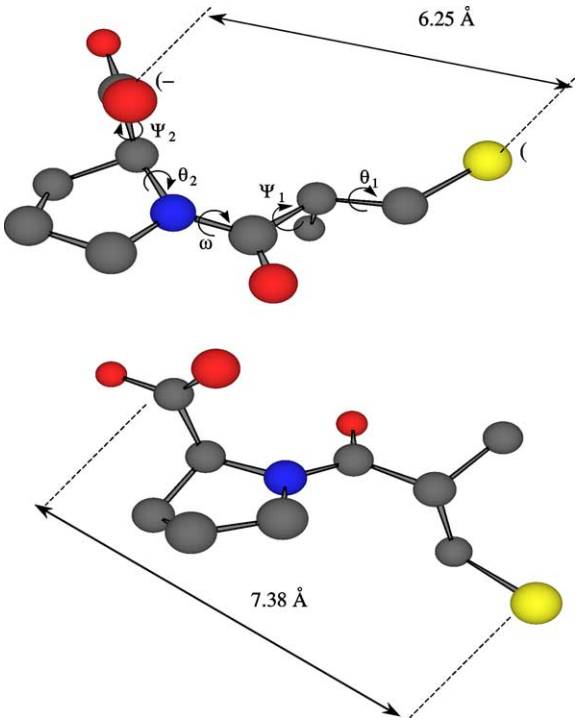


Fig. 8. Lowest energy conformers of *trans*- and *cis*-captopril double anion at HF/6-311G(d,p) level of theory.

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