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An exploratory conformational analysis of 3-mercapto-propanamide and 2-methyl-3-mercapto-propanamide as well as their *S*-deprotonated conjugate basis: an ab initio study

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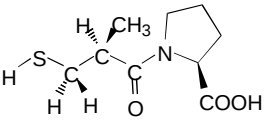
Abstract

Ab initio conformational analysis has been carried out on 3-mercapto-propanamide, (*R*)- and (*S*)-2-methyl-3-mercapto-propanamide as well as their **S**-deprotonated conjugate basis. They were carried out at the HF/3-21G level of theory. The topology of the conformational potential energy surfaces and hypersurfaces have been analysed.

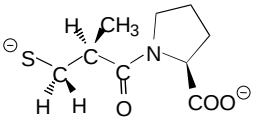
Keywords: 3-Mercapto-propanamide; (*R*)- and (*S*)-2-methyl-3-mercapto-propanamide; *S*-deprotonated conjugate basis

1. Introduction

Captopril [**1**] an effective antihypertensive drug [1–4] is a relatively small molecule which may be in its biologically active dianion [**1b**] or neutral form [**1a**]. It has several functional groups and the molecule may assume numerous stable conformations. Consequently, captopril [**1**] can interact regio and stereospecifically with various functional groups present at the active site of the angiotensin converting enzyme (ACE) [1–4] as illustrated schematically, by Fig. 1.



[1a]



[1b]

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 action mechanism. Captopril as an ACE-inhibitor may be used as a "molecular calliper" to estimate the upper and lower bound values for the separation **d** shown in Fig. 1.

Captopril has been studied [5] by a "classical potential energy" force field type method as early as 1985.

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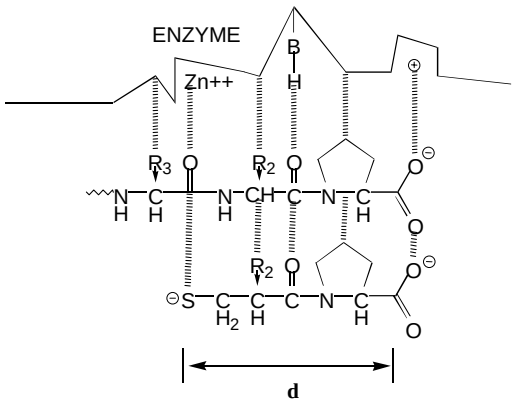


Fig. 1. Docking model for ACE with substrate peptide (top) and captopril (bottom).

Subsequently Hillier et al. [6] carried out AM1 computations on this molecule in 1991. This was followed by Luke in 1994. Luke [7] also reported [8] AM1 calculations on the demethylated analogue of captopril in 1995. As far as it can be ascertained no ab initio calculations have been reported as yet on captopril.

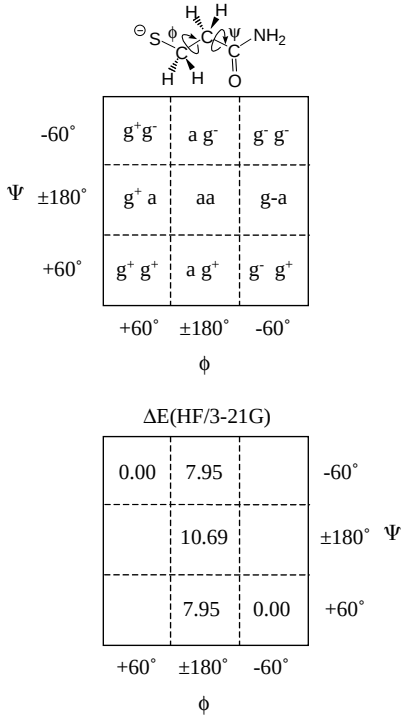


Fig. 2. Expected conformations (top) and computed relative energies, Δ*E* (kcal/mol)(bottom) of *S*-deprotonated 3-mercapto-propanamide structures.

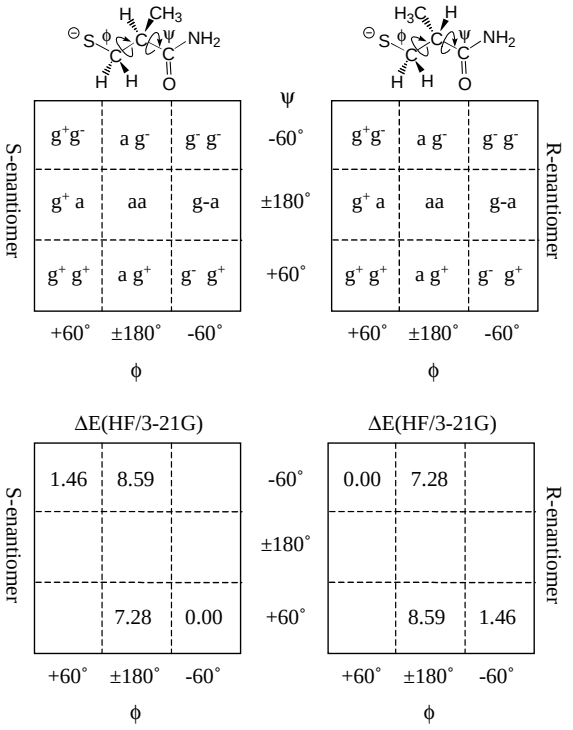


Fig. 3. Expected conformations (top) and computed relative energies, Δ*E* (kcal/mol) (bottom) of *R* and *S* enantiomers of **S**-deprotonated 2-methyl-3-mercapto-propanamide structures.

2. Method

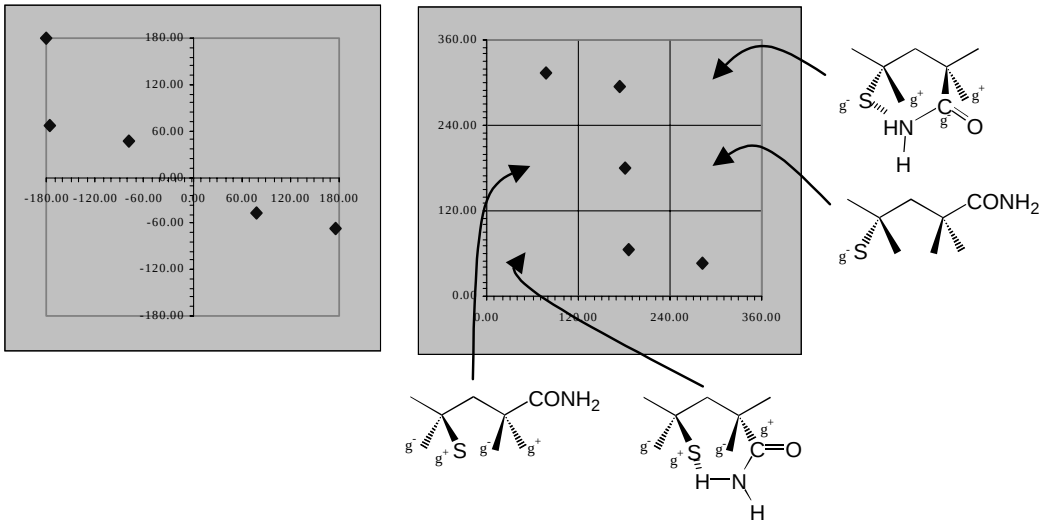
Ab initio computations have been carried out at the HF/3-21G level of theory, using the GAUSSIAN 94 software [9].

3. Results and discussion

Captopril poses a non-trivial multidimensional conformational problem. One of the conformational intricacies is associated with the five-member ring of the proline moiety. The –CO–NH< moiety may be of *cis* or *trans* configurations. The five-member ring may be in a number of non-planar conformations. Finally the –COOH moiety of [**1a**] could assume three

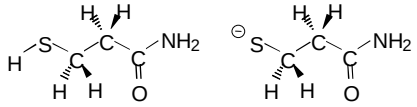
Table 1
Computed conformational characteristics of **S**-deprotonated 3-mercapto-propanamide optimised at the HF/3-21G level of theory

	ϕ	ψ	ω	E_{total}	ΔE
g^+g^+	Not found				
g^+a	Not found				
g^+g^-	78.79	−46.17	−177.29	−640.6483579	0.00
ag^+	−175.19	66.76	175.02	−640.6356826	7.95
aa	−180.00	179.98	−179.98	−640.6313114	10.70
ag^-	175.19	−66.75	−175.02	−640.6356825	7.95
g^-g^+	−78.76	46.21	177.22	−640.6483579	0.00
g^-a	Not found				
g^-g^-	Not found				



conformations (g^+, a, g^-) leading to γ_L, ϵ_L, and α_L peptide foldings.

The other conformational variations of captopril [**1**] are residing in the flexible open chain which may be represented as 3-mercapto propanamide or its neutral form [**2a**] or *S*-deprotonated conjugate base [**2b**].



[2a] [2b]

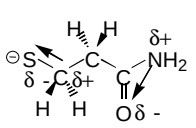
In these structures, the five member ring is omitted with respect to [**1**] and the hydrogen atoms are attached to the amide nitrogen.

Compounds [**2a**] and [**2b**] are also missing the methyl group at the α-carbon (i.e. at C^2) with respect to [**1**]. If that methyl group is included then two enantiomers may be generated, (*S*)-2-methyl-3-mercapto-propanamide [**3a**] and its conjugate base [**3b**] as well as (*R*)-2-methyl-3-mercapto-propanamide [**4a**] and its conjugate base [**4b**].

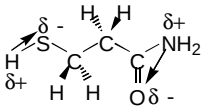
Consequently, it seemed prudent to study the fragments [**3b**] and [**5**] of captopril [**1**] preferably related to its biologically active dianionic form [**1b**]. A derivative of [**5**], *N*-formyl-L-prolinamide [**6**] has already been studied [10] in a preliminary fashion.

The *S*-deprotonated forms of 3-mercapto-propanamide [**2b**] and (*S*)-2-methyl-3-mercapto-propanamide [**3b**] as well as and (*R*)-2-methyl-3-mercapto-propanamide [**4b**] have been studied by the ab initio method at the HF/3-21G levels of theory. The results

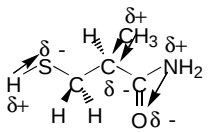
for [**2b**] are shown in Fig. 2 and Table 1. It is interesting to note that the four annihilated minima (g^+g^+, g^+a, g^-a, g^-g^-) correspond to the same four conformers annihilated in *N*-formyl-glycin-amide. In peptides (c.f. [**7**]) such an annihilation is traditionally rationalised [11] in terms of dipole/dipole repulsion.



[8]



[10]



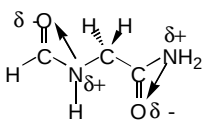
[11]

The orientation at the bond moments in [**7**] and [**8**] seem to be analogous if not quite identical.

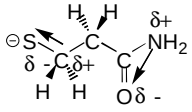
The introduction of methyl group at the α-carbon upsets the previous dipole/dipole repulsion [**8**] to such an extent [**9**] that another minimum (*a*, *a*) was annihilated. The results are shown in Fig. 3 and Table 2, for both the *S*- and *R*-enantiomers of [**3b**] and [**4b**], respectively.

In the case of the 2-methylated compound [**11**] the introduction of the Me-group does not make any difference for the *anti*-oriented S–H conformation [$\theta = 180°$] as may be seen in Fig. 5. However, it allows more minima for the $\theta = g^+$ and $\theta = g^-$ conformation as shown in Fig. 5 and in Tables 4 and 5.

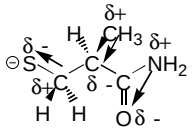
The other fragment of captopril contains a proline residue. As discussed before such a residue could be



[7]

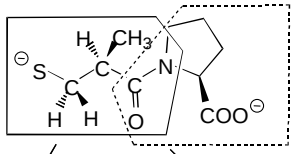


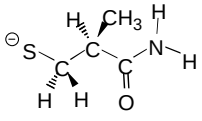
[8]



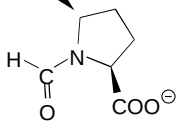
[9]

[1b]

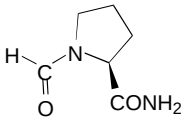




[2b]



[5]



[6]

Considering the neutral forms of 3-mercapto-propanamide and the *R*- and *S*-enantiomers of 2-methyl-3-mercapto-propanamide one may anticipate some change due to the fact that the H–S bond moment will dominate over the C–S bond moment. These may be seen by comparing [**8**], [**10**] and [**11**].

Since in [**10**] the H–S bond moment is further out than the C–S bond moment in [**8**], less repulsion is anticipated. Indeed, this is the case as shown in Fig. 4 and summarised in Table 3.

studied in the form of **N**-formyl-prolinate [**5**]. So far we have investigated the conformational behaviour of **N**-formyl-prolinamide [**6**]. As it has to be emphasised that the five-member ring in the proline residue [**12**] allows the variable ϕ to be in the vicinity of g^- and

Table 2
Computed conformational characteristics of the *R*- and *S*-enantiomers of *S*-deprotonated 2-methyl-3-mercapto-propanamide optimised at HF/3-21G level of theory

	ϕ	ψ	ω	χ	E_{total}	$\Delta\Delta E$
R-enantiomer						
g^+g^+	Not found					
g^+a	Not found					
g^+g^-	79.39	−49.48	−174.38	65.92	−679.4712174	0.00
ag^+	170.75	51.27	174.45	61.01	−679.4575281	8.59
aa	Not found					
ag^-	165.45	−73.57	−175.37	54.73	−679.459622	7.28
g^-g^+	−73.78	46.38	174.67	69.36	−679.468885	1.46
g^-a	Not found					
g^-g^-	Not found					
S-enantiomer						
g^+g^+	Not found					
g^+a	Not found					
g^+g^-	73.78	−46.45	−174.58	−69.34	−679.4688851	1.46
ag^+	−165.43	73.57	175.31	−54.69	−679.4596221	7.28
aa	Not found					
ag^-	−170.81	−51.50	−174.41	−61.16	−679.4575282	8.59
g^-g^+	−79.39	49.53	174.43	−65.90	−679.4712174	0.00
g^-a	Not found					
g^-g^-	Not found					

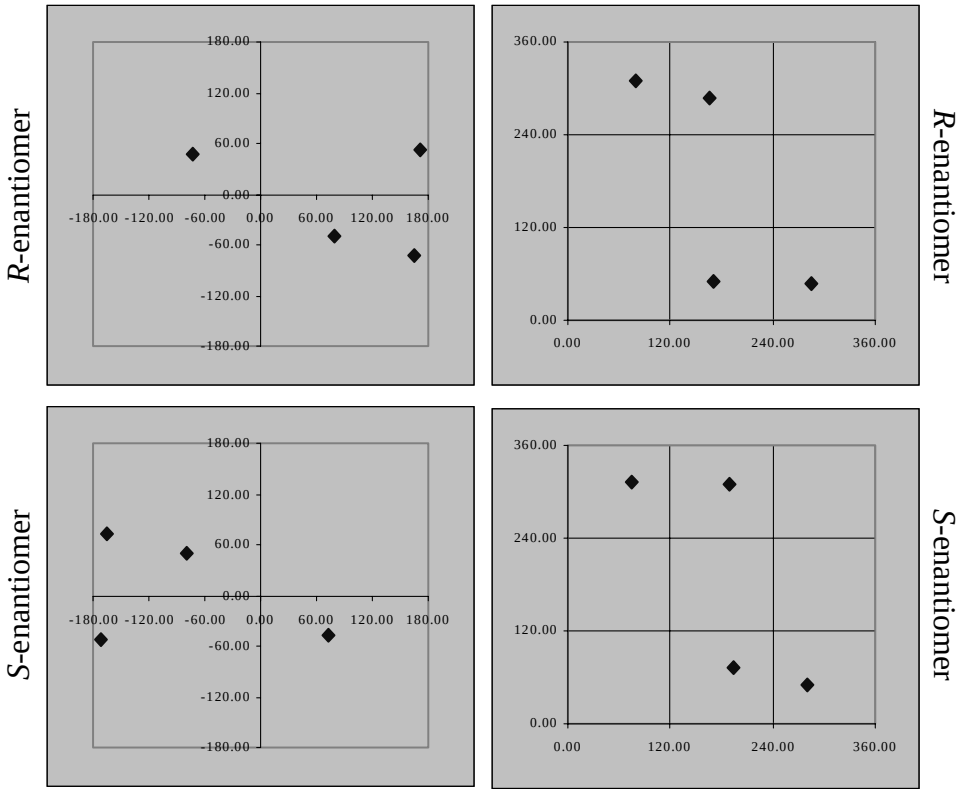


Table 3
Computed conformational characteristics of the 3-mercapto-propanamide optimised at HF/3-21G level of theory

	θ	ϕ	ψ	ω	χ	E_{total}	ΔE	$\Delta\Delta E$
$g^+g^+g^+$	59.62	54.85	56.78	179.12	64.63	−680.0077715	3.71	4.96
g^+g^+a	75.46	70.88	−144.73	−175.96	59.04	−680.0124754	0.76	2.01
$g^+g^+g^-$	71.24	81.89	−64.46	−177.07	62.42	−680.0118538	1.15	2.40
g^+ag^+	81.75	169.72	66.10	−178.03	68.19	−680.0074814	3.89	5.15
g^+aa	86.80	175.44	−159.35	−177.50	61.92	−680.0118794	1.13	2.39
g^+ag^-	81.05	170.72	−82.77	176.21	56.72	−680.0113095	1.49	2.74
$g^+g^-g^+$	Not found							
g^+g^-a	70.57	−70.11	−173.72	−177.63	61.04	−680.0136855	0.00	1.25
$g^+g^-g^-$	43.64	−68.84	−89.11	178.25	53.86	−680.0107768	1.83	3.08
ag^+g^+	179.46	61.49	57.67	179.87	65.42	−680.0056264	3.69	6.31
ag^+a	Not found							
ag^+g^-	Not found							
aag^+	−167.67	172.23	65.53	−177.61	67.04	−680.0071222	2.75	5.37
aaa	−175.46	172.88	−164.66	−177.59	59.84	−680.0115057	0.00	2.62
aag^-	178.94	178.94	−82.57	176.34	53.19	−680.0103653	0.72	3.34
ag^-g^+	158.71	−83.27	47.96	−178.89	62.74	−680.0074613	2.54	5.16
ag^-a	Not found							
ag^-g^-	−179.15	−60.34	−67.24	−179.15	58.16	−680.0072888	2.65	5.27
$g^-g^+g^+$	−67.17	60.69	51.17	−174.96	64.34	−680.0078444	4.92	4.92
g^-g^+a	−75.82	68.03	−164.42	−176.67	60.54	−680.0156812	0.00	0.00
$g^-g^+g^-$	Not found							
g^-ag^+	−68.95	170.46	63.92	−177.96	64.23	−680.0089084	4.25	4.25
g^-aa	−72.75	174.08	−164.51	−178.44	58.36	−680.0123034	2.12	2.12
g^-ag^-	−68.76	173.93	−85.69	176.52	52.14	−680.0109917	2.94	2.94
$g^-g^-g^+$	−77.18	−77.25	59.64	177.16	62.88	−680.0086255	4.43	4.43
g^-g^-a	−99.88	−68.03	174.57	−178.75	56.18	−680.0088266	4.30	4.30
$g^-g^-g^-$	−70.55	−55.24	−61.77	176.60	56.78	−680.0087301	4.36	4.36

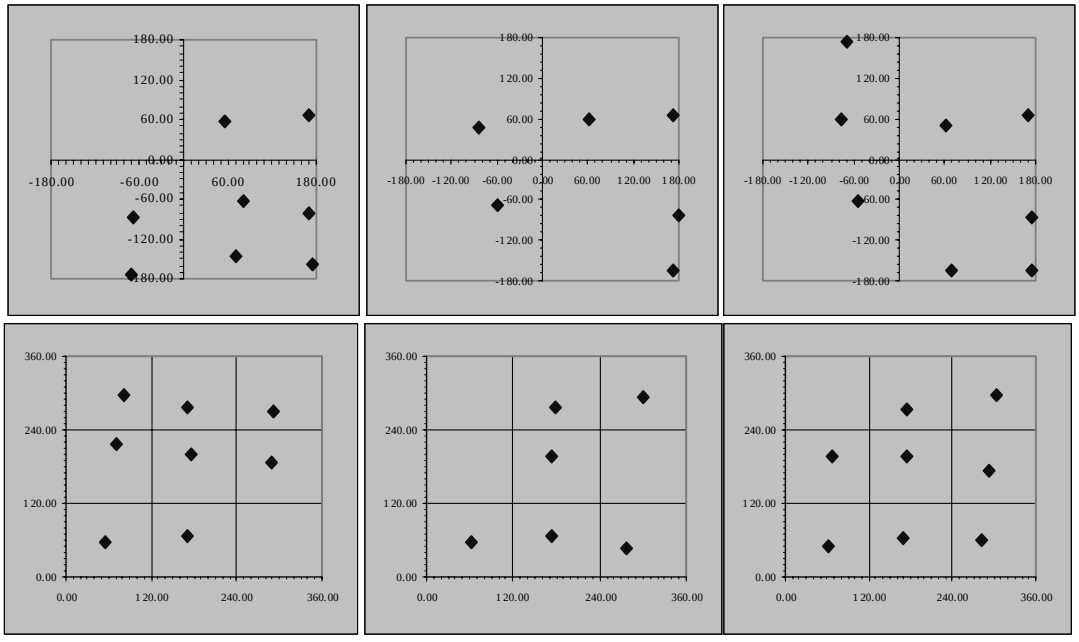


Table 4
Computed conformational characteristics of the (*S*)-2-methyl-3-mercapto-propanamide optimised at HF/3-21G level of theory

	θ	ϕ	ψ	ω	χ	E_{total}	ΔE	$\Delta\Delta E$
$g^+g^+g^+$	70.44	55.21	61.78	−176.63	−56.73	−680.0087301	4.36	4.36
g^+g^+a	99.80	68.03	−174.67	178.80	56.19	−680.0088266	4.30	4.30
$g^+g^+g^-$	77.26	77.29	−59.64	−177.17	−62.86	−680.0086256	4.43	4.43
g^+ag^+	68.76	−173.93	85.69	−176.52	−52.14	−680.0109917	2.94	2.94
g^+aa	72.65	−174.10	164.53	178.40	−58.38	−680.0123034	2.12	2.12
g^+ag^-	68.95	−170.46	−63.92	177.96	−64.23	−680.0089084	4.25	4.25
$g^+g^-g^+$	Not found							
g^+g^-a	75.80	−67.97	164.41	176.65	−60.73	−680.0156813	0.00	0.00
$g^+g^-g^-$	67.12	−60.71	−51.27	174.93	−64.47	−680.0078445	4.92	4.92
ag^+g^+	−180.85	60.34	67.24	−177.04	−58.16	−680.0072888	2.65	5.27
ag^+a	Not found							
ag^+g^-	−158.71	83.27	−47.96	178.89	−62.74	−680.0074613	2.54	5.16
aag^+	−178.94	−169.07	82.53	−176.35	−53.18	−680.0103653	0.72	3.34
aaa	175.51	−172.86	164.66	177.54	−59.84	−680.0115057	0.00	2.62
aag^-	−192.28	−172.20	−65.48	177.62	−66.91	−680.0071224	2.75	5.37
ag^-g^+	162.418	−89.84	53.79	−179.12	−64.44	−680.0105571	0.60	3.22
ag^-a	Not found							
ag^-g^-	−179.46	−61.51	−57.73	−179.83	−65.39	−680.0056265	3.69	6.31
$g^-g^+g^+$	−43.64	68.84	89.11	−178.25	−53.86	−680.0107768	1.82	3.08
g^-g^+a	−70.69	70.03	173.74	177.69	−60.93	−680.013685	0.00	1.25
$g^-g^+g^-$	Not found							
g^-ag^+	−81.05	−170.72	82.04	−176.20	−56.70	−680.0113096	1.49	2.74
g^-aa	−86.80	−175.44	159.35	177.50	−61.92	−680.0118794	1.13	2.39
g^-ag^-	−81.58	−169.72	−66.09	178.07	−68.29	−680.0074812	3.89	5.15
$g^-g^-g^+$	−71.25	−81.96	64.31	177.19	−62.61	−680.0118537	1.15	2.40
g^-g^-a	−75.46	−70.88	144.73	175.96	−59.04	−680.0124754	0.76	2.01
$g^-g^-g^-$	−59.68	−54.82	−56.83	−179.06	−64.63	−680.0077714	3.71	4.96

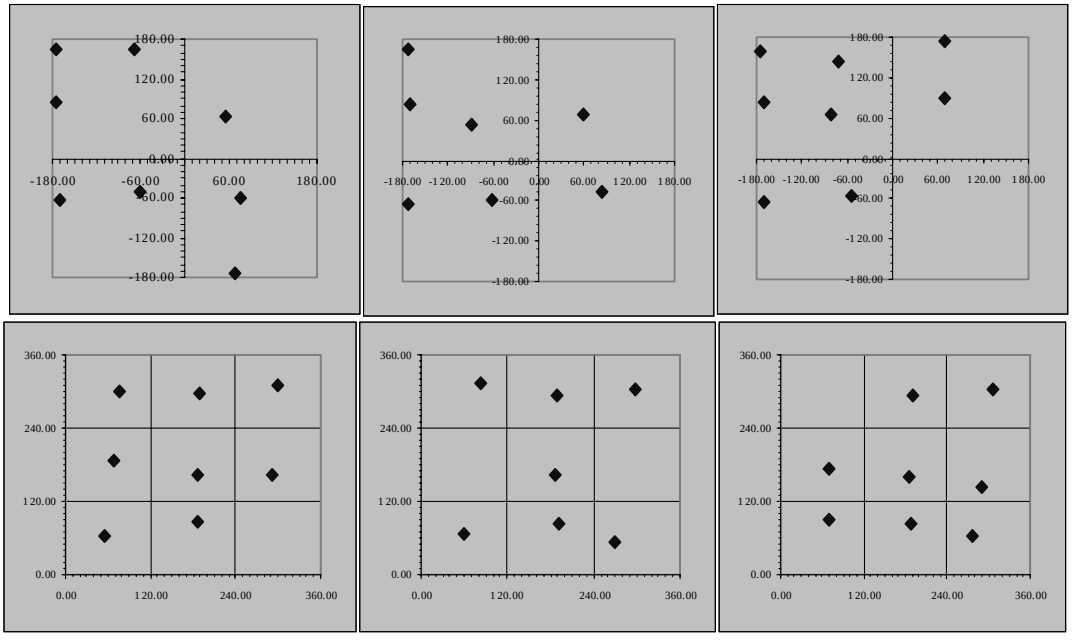
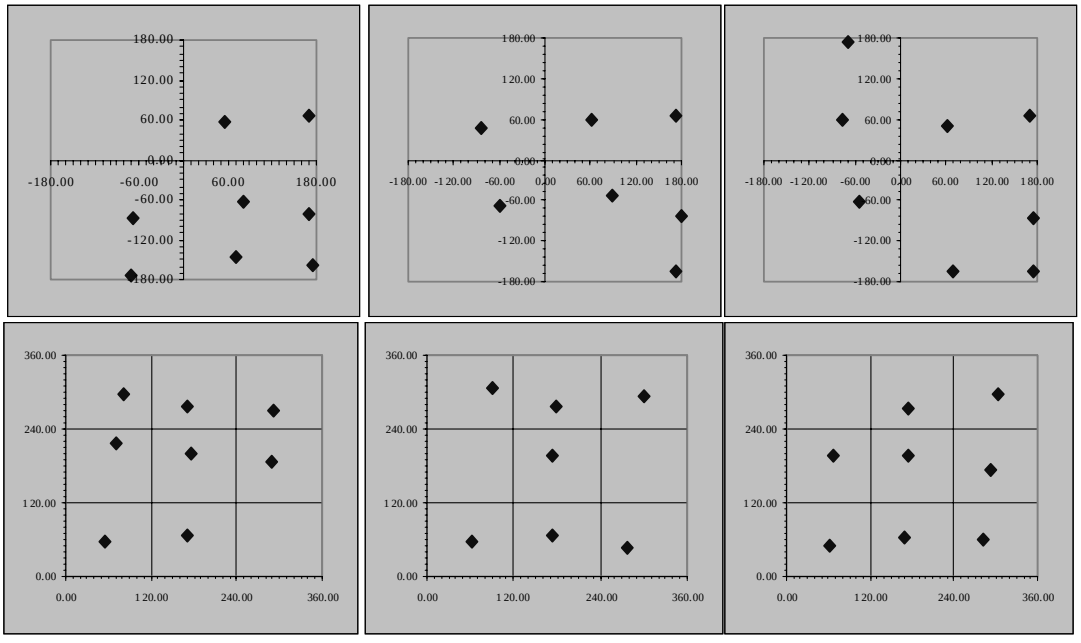


Table 5
Computed conformational characteristics of the (*R*)-2-methyl-3-mercapto-propanamide optimised at HF/3-21G level of theory

	θ	ϕ	ψ	ω	χ	E_{total}	ΔE	$\Delta\Delta E$
$g^+g^+g^+$	59.62	54.85	56.78	179.12	64.63	−680.0077715	3.71	4.96
g^+g^+a	75.46	70.88	−144.73	−175.96	59.04	−680.0124754	0.76	2.01
$g^+g^+g^-$	71.24	81.89	−64.46	−177.07	62.42	−680.0118538	1.15	2.40
g^+ag^+	81.75	169.72	66.10	−178.03	68.19	−680.0074814	3.89	5.15
g^+aa	86.80	175.44	−159.35	−177.50	61.92	−680.0118794	1.13	2.39
g^+ag^-	81.05	170.72	−82.77	176.21	56.72	−680.0113095	1.49	2.74
$g^+g^-g^+$	Not found							
g^+g^-a	70.57	−70.11	−173.72	−177.63	61.04	−680.0136855	0.00	1.25
$g^+g^-g^-$	43.64	−68.84	−89.11	178.25	53.86	−680.0107768	1.83	3.08
ag^+g^+	179.46	61.49	57.67	179.87	65.42	−680.0056264	3.69	6.31
ag^+a	Not found							
ag^+g^-	−162.42	89.84	−53.79	179.12	64.44	−680.0105571	0.60	3.22
aag^+	−167.67	172.23	65.53	−177.61	67.04	−680.0071222	2.75	5.37
aaa	−175.46	172.88	−164.66	−177.59	59.84	−680.0115057	0.00	2.62
aag^-	178.94	178.94	−82.57	176.34	53.19	−680.0103653	0.72	3.34
ag^-g^+	158.71	−83.27	47.96	−178.89	62.74	−680.0074613	2.54	5.16
ag^-a	Not found							
ag^-g^-	−179.15	−60.34	−67.24	−179.15	58.16	−680.0072888	2.65	5.27
$g^-g^+g^+$	−67.17	60.69	51.17	−174.96	64.34	−680.0078444	4.92	4.92
g^-g^+a	−75.82	68.03	−164.42	−176.67	60.54	−680.0156812	0.00	0.00
$g^-g^+g^-$	Not found							
g^-ag^+	−68.95	170.46	63.92	−177.96	64.23	−680.0089084	4.25	4.25
g^-aa	−72.75	174.08	−164.51	−178.44	58.36	−680.0123034	2.12	2.12
g^-ag^-	−68.76	173.93	−85.69	176.52	52.14	−680.0109917	2.94	2.94
$g^-g^-g^+$	−77.18	−77.25	59.64	177.16	62.88	−680.0086255	4.43	4.43
g^-g^-a	−99.88	−68.03	174.57	−178.75	56.18	−680.0088266	4.30	4.30
$g^-g^-g^-$	−70.55	−55.24	−61.77	176.60	56.78	−680.0087301	4.36	4.36



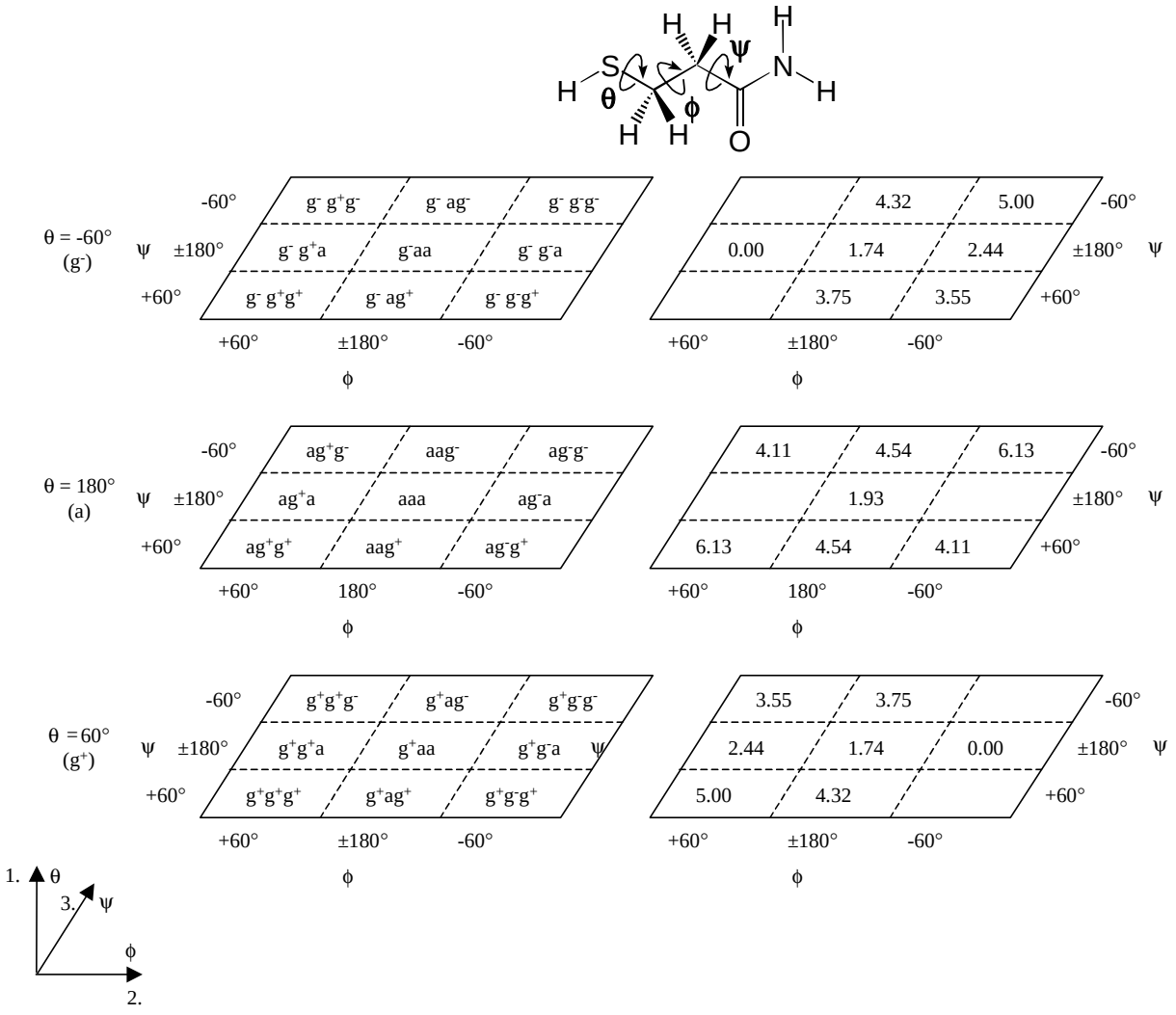
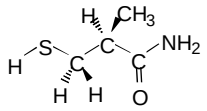
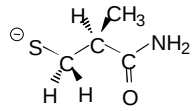


Fig. 4. Expected conformers (left) and computed energies: ΔE (kcal/mol) (right) of 3-mercapto-propanamide structures.

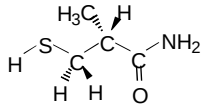
therefore along the variable ψ the amino acid backbone may only have three conformers (γ_L, ϵ_L and α_L) rather than the usual nine. This work has already been published [10]. However, there are additional complications. The nitrogen in proline has two alkyl group attached therefore one would expect similar energies to *cis*- and *trans*-peptide bonds in any proline residue [**6**]. This is in direct contrast to all naturally occurring amino acids. The problem has already been presented at the Fifth World Congress at WATOC [12] and further work is now in progress [13].



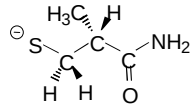
[3a]



[3b]



[4a]



[4b]

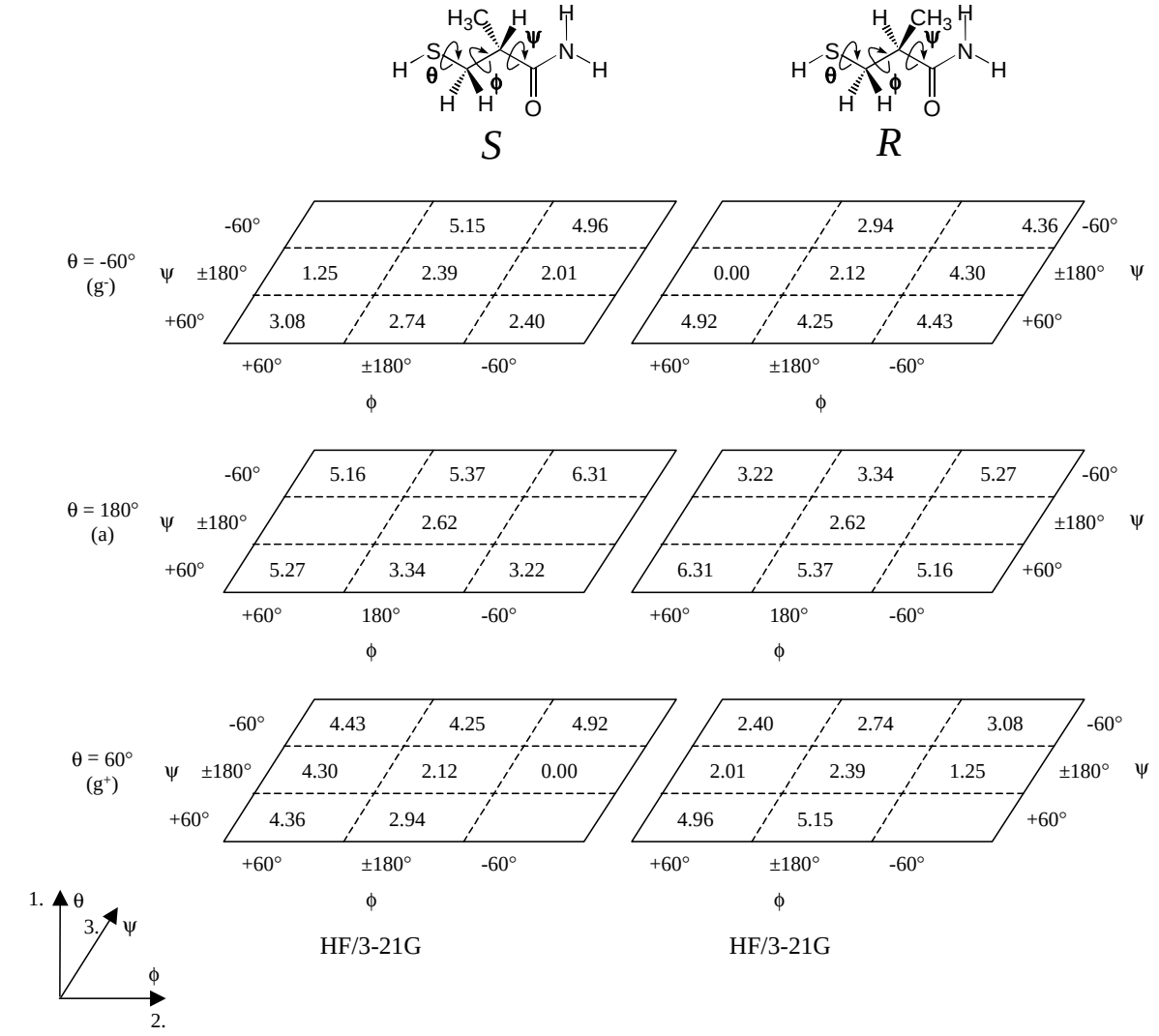
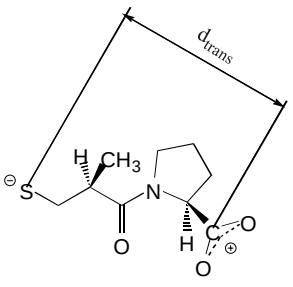
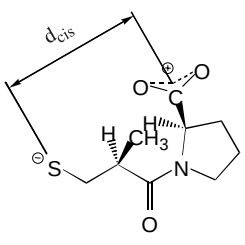


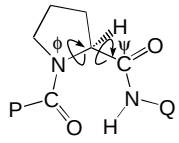
Fig. 5. Computed conformational energies, Δ*E* (kcal/mol) of 2-methyl-3-mercapto-propanamide.



[16]



[10]



[12]

The process of *cis–trans* isomerism may also be important in the docking of captopril. Clearly one would expect a different separation between the two negatively charged terminii.

Obviously, d_{trans} represents a longer separation and d_{cis} a shorter separation. It may be anticipated that the separation (d_{ACE}) of the two points at the active site of the ACE cannot be shorter or larger that d_{cis} and d_{trans}, respectively:

$$d_{cis} < d_{ACE} < d_{trans}$$

In this sense captopril may be regarded to be a molecular "calliper" in establishing certain structural features of the ACE. Ab initio computations on the captopril, as a whole, has to wait until more computing power becomes available.

Acknowledgements

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References

[1] D.W. Cushman, H.S. Cheung, E.F. Sabo, M.A. Ondetti, Biochemistry 16 (1977) 9484.
[2] S.H. Ferreira, Br. J. Pharmacol. Chemother. 24 (1956) 163.
[3] Y.S. Bakhle, Nature (London) 220 (1968) 919.
[4] Y.S. Bakhle, A.M. Reynard, J.R. Vane, Nature (London) 222 (1969) 956.
[5] P.R. Andrews, J.M. Carson, A. Cassali, M.J. Spark, R. Woods, J.Med. Chem. 28 (1985) 393.
[6] D.V.S. Green, I.H. Hillier, G.A. Morris, N. Gensmantel, D.W. Payling, D.H. Robinson, J. Mol. Struct. (Theochem) 251 (1991) 173.
[7] B.T. Luke, J. Mol. Struct. (Theochem) 309 (1994) 1.
[8] B.T. Luke, J. Mol. Struct. (Theochem) 332 (1995) 25.
[9] M.J. Frisch, G.W. Trucks, H.B. Schlegel,.M.W. Gill, B.G. Johnson, M.A. Robb, J.R. Cheeseman, T. Keith, G.A. Petersson, J.A. Montgomery, K. Raghavachari, M.A. Al-Laham, V.G. Zakrzewski, J.V. Ortiz, J.B. Foresman, J. Cioslowski, B.B. Stefanov, A. Nanayakkara, M. Challacombe, C.Y. Peng, P.Y. Ayala, W. Chen, M.W. Wong, J.L. Andres, E.S. Replogle, R. Gomperts, R.L. Martin, D.J. Fox, J.S. Binkley, D.J. Defrees, J. Baker, J.P. Stewart, M. Head-Gordon, C. Gonzalez, J.A. Pople, GAUSSIAN 94, Revision D.2, Gaussian Inc., Pittsburgh PA, 1995.
[10] H.A. Baldoni, A.M. Rodrigues, G. Zamarbide, R.D. Enriz, Ö. Farkas, P. Csaszar, L.L. Torday, C.P. Sosa, I. Jakli, A. Perczel, M. Hollosi, I.G. Csizmadia, J. Mol. Struct. (Theochem) 465 (1999) 79.
[11] A. Perczel, J.G. Angyan, M. Kajtar, W. Viviani, J.L. Rivail, J.F. Marcoccia, I.G. Csizmadia, J. Am. Chem. Soc. 113 (1991) 6256.
[12] WATOC (99) Book of Abstracts, Paper: p 212.
[13] H.A. Baldoni, G. Zamarbide, R.D. Enriz, L.L. Torday, Ö. Farkas, A. Perczel, I. Jakli, C.P. Sosa, I.G. Csizmadia, in preparation.