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Peptide models XXIX. *cis–trans* Isomerism of peptide bonds: ab initio study on small peptide model compound; the 3D-Ramachandran map of formylglycinamide

H.A. Baldoni[a], G.N. Zamarbide[a], R.D. Enriz[a,*], E.A. Jauregui[a], Ö. Farkas[b], András Perczel[b,c], S.J. Salpietro[d], I.G. Csizmadia[d]

[a]*Departamento de Química, Universidad Nacional de San Luis, 5700 San Luis, Argentina*
[b]*Department of Organic Chemistry, Eötvös Lorand University, P.O. Box 32, 112 Budapest, Hungary*
[c]*Department of Biochemistry, University of Oxford, Oxford, UK*
[d]*Department of Chemistry, University of Toronto, Ontario, Canada M5S 3H6*

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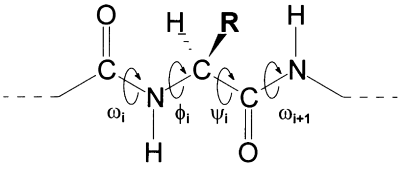
Abstract

Thermodynamic separations for *cis* and *trans*-amides and formylglycinamide range from 0.00 to 4.77 kcal/mol as computed at various levels of theory. The barriers for *trans* → *cis*-isomerization, for the same set of compounds, computed at various levels of theory, were found between 15.69 and 22.67 kcal/mol. The *cis*- and *trans*-Ramachandran maps of formylglycinamide are compared and the topology of the ab initio 3D-Ramachandran map is presented for the first time. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: *trans*- and *cis*-Ramachandran maps; Topology of a 3D-Ramachandran map; Relative stability of *cis*- and *trans*-peptide bonds; Barriers to *trans*- to *cis*-isomerization

1. Preamble

The Ramachandran map is the corner stone of peptide and protein chemistry and biology. Yet every Ramachandran map in the literature is for the *trans*-peptide bond ($\omega_i = 180°$).



(1)

In other words, instead of treating the problem as a three-dimensional (3D)-potential energy hypersurface

$$E = E(\omega_i, \phi_i, \psi_i) \tag{2}$$

a two-dimensional (2D) cross-section is presented as the *trans*-Ramachandran map for $\omega_i = 180°$

$$E = E_{\omega_i=180}(\phi_i, \psi_i) \tag{3}$$

* Corresponding author.
E-mail addresses: hbaldoni@unsl.edu.ar (H.A. Baldoni), gzama@unsl.edu.ar (G.N. Zamarbide), denriz@unsl.edu.ar (R.D. Enriz), ejaure@unsl.edu.ar (E.A. Jauregui), farkas@para.chem.elte.hu (O. Farkas), perczel@para.chem.elte.hu (A. Perczel), ssalpiet@alchemy.chem.utoronto.ca (S.J. Salpietro), icsizmad@alchemy.chem.utoronto.ca (I.G. Csizmadia).

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One of the consequences of this practice is that ω, the angle that measures *trans–cis*-isomerization, has become a forgotten dimension. Yet, there is an uncharted territory along this forgotten dimension, described by the *cis*-Ramachandran map:

$$E = E_{\omega_i=0}(\phi_i, \psi_i) \tag{4}$$

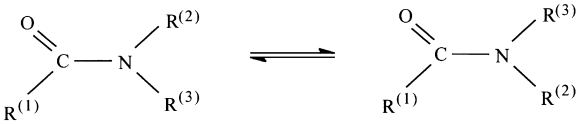
The other serious consequence of this practice is that by the end of the 20th century we have reached such an acute state that one cannot fully trust the X-ray determinated protein structures. This is the consequence of the standard practice that crystallographers are fitting their data with an assumed fully *trans*-polypeptide chain. Consequently, only the relatively few neutron diffraction data can be used to search for the presence of *cis*-peptide bonds in proteins. Yet, there is mounting evidence that *cis*-peptide bonds play significant biological roles in several areas even though their abundance is relatively minor with respect to the *trans*-isomer.

Thus in the new millennium the "exclusively *trans*-peptide" dogma will not be acceptable and the 3D-Ramachandran hypersurface will be law of the 21st century.

We are happy to present here the first 3D-Ramachandran map computed for formylglycinamide ($HCONH–CH_2–CONH_2$) at the HF and DFT levels of theory. We apologize in advance if the topology of the 3D-Ramachandran map reminds you of Spock's 3D-chess in Star Trek.

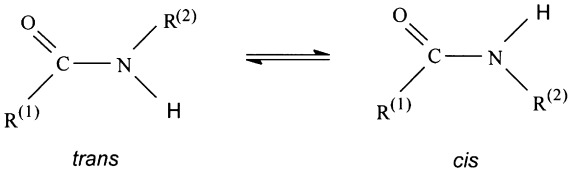
2. Introduction

cis–trans-Isomerizations of peptide bonds (reaction (5)) are of great importance



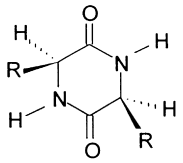
(5)

In most cases $R^{(3)} = H$ and $R^{(1)}$ as well as $R^{(2)}$ are part of the peptide backbone.



(6)

The *trans*-isomer is usually favoured in peptides and proteins; however, under certain circumstances steric requirement may force the –CONH– moiety to *cis* configuration. This is particularly true for small cyclopeptides. In the smallest cyclopeptides, substituted or unsubstituted diketopiperazine (Scheme 1), both peptide bonds must be *cis*, since we are dealing with a six-member ring only.



Scheme 1.

Clearly, the ring must be of a certain size before a *trans* peptide bond may be formed without a major ring strain.

The question of *cis–trans*-isomerization occupied the minds of chemist and biochemist during the second half of the 20th century. As early as 1958 it was proposed [1,2] that protonation of the amide nitrogen would change the hindered rotation (due to the partial double bond character of the peptide bond) to a nearly free rotation of the *N*-protoned peptide bond.

Soon thereafter it was recognised that proline is the most likely amino acid to undergo *cis–trans*-isomerization because its nitrogen has two alkyl groups attached. Although the two carbon atoms attached directly to *N* are not equivalent this is expected to make the *cis*- and *trans*-forms to be comparable on the energy scale. However, even for the proline residue, the *cis–trans*-isomerization of a peptide bond has a long history [3,4]. Nevertheless, it has been acknowledged that, in proteins, proline amides display similar tendency to assume both the *cis* and *trans* conformations [5] of the protein

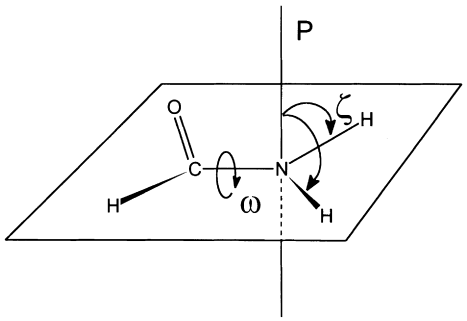
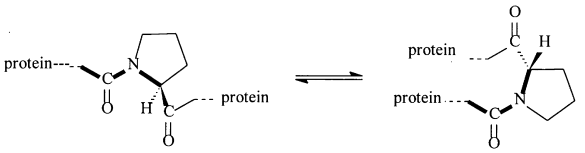


Fig. 1. Definition of rotation (ω) and inversion (ζ) angles for the rotation–inversion PES of formamide.

chain (reaction (7));



(7)

Since only proline amides posses this conformational flexibility, it has been considered that *cis–trans* proline isomerization plays many important biochemical roles. These include controlling the rate of protein folding [6–12], initiating receptor-mediated transmembrane signalling [13–17], being involved in the recognition of peptide antigens [18], and regulating the activation as well as the breakdown of peptide hormones [19–21]. For this reason the *cis–trans*-isomerization is of great importance.

Maigret et al. [22] pioneered the computational study of *cis–trans*-isomerization of prolyl residues in 1970. Such theoretical work by definition implies the study of a gas-phase process. Thus, any energetics (thermodynamic or kinetic), that may be obtained, represent intrinsic properties without the influence of any environmental factors. They were the first to present their conformations for the *cis* and *trans*-isomers of *N*- and *C*- protected proline in terms of potential energy curves:

$$E = f(\psi) \tag{8}$$

and the *cis–trans*-isomerization as a potential energy

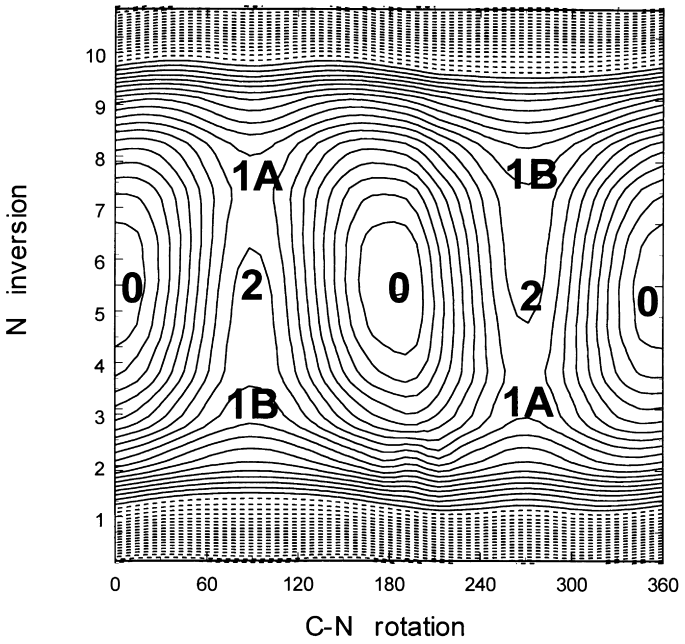


Fig. 2. Energy contour diagram of the rotation–inversion PES of formamide.

Table 1
Total energy values (Hartree) for *cis*- and *trans*-isomers of small peptide (**I**, **II**, **III**, **IV**) and for their interconversion state computed at several levels of theory

Compound	HF/3-21G			HF/6-31G(d)			B3LYP/6-31G(d)		
	cis	TS	*trans*	*cis*	TS	*trans*	*cis*	TS	*trans*
I	− 167.9849004	− 167.9552566	− 167.9849004	− 168.9307027	− 168.9056923	− 168.9307027	− 169.8888412	−169.8602786	−169.8888412
II	−245.6095424	−245.5813168	−245.6095424	−246.9866145	−246.9611539	−246.9866145	−248.5069078	−248.4762919	−248.5069078
III	−206.7961135	−206.7668791	−206.7991112	−207.9584499	−207.9323838	−207.9613495	−209.1972214	−209.1668970	−209.1998893
IV	−373.6401485	−373.6116251	−373.6477487	−375.7413391	−375.7163014	−375.7486527	−377.8953961	−377.8664198	−377.9014523

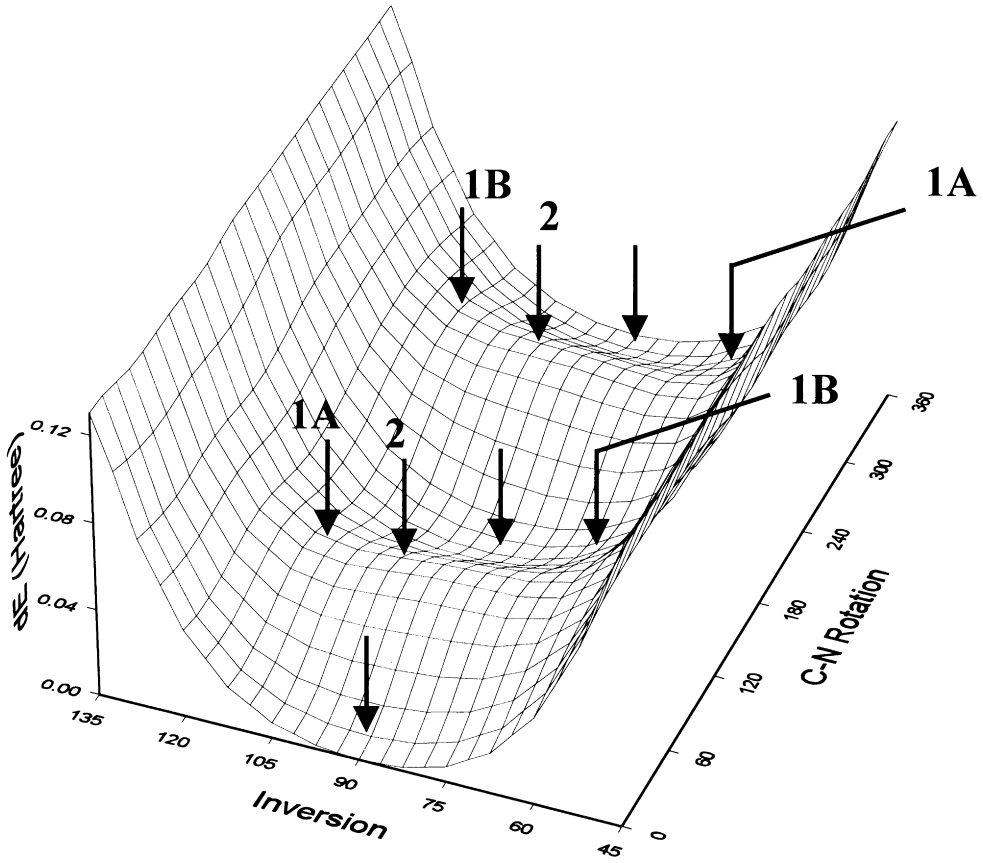


Fig. 3. Rotation–inversion PES landscape for formamide.

surface (PES):

$$E = F(\psi, \omega) \tag{9}$$

Subsequently, Farmer and Hopfinger [23] also presented the *cis–trans*-isomerization in terms of such a PES.

More recently, Karplus and coworkers [24] pointed out how important is the pyramidalization of the amide nitrogen to the process of *cis–trans*-isomerization. If $R^{(2)} = R^{(3)}$ in reaction (5), as exemplified in the case of I and II for $R^{(1)} = H$, then of course the *cis*- and *trans*-isomers have the

Table 2
Relative energy values (kcal/mol) for *cis* and *trans* isomers of small peptide (**I**, **II**, **III**, **IV**) and for their interconversion state computed at several levels of theory

Compound	HF/3-21G			HF/6-31G(d)			B3LYP/6-31G(d)		
	cis	TS	*trans*	*cis*	TS	*trans*	*cis*	TS	*trans*
I	0.00	18.60	0.00	0.00	15.69	0.00	0.00	17.92	0.00
II	0.00	17.71	0.00	0.00	15.98	0.00	0.00	19.21	0.00
III	1.88	20.23	0.00	1.82	18.17	0.00	1.67	20.70	0.00
IV	4.77	22.67	0.00	4.59	20.30	0.00	3.80	21.98	0.00

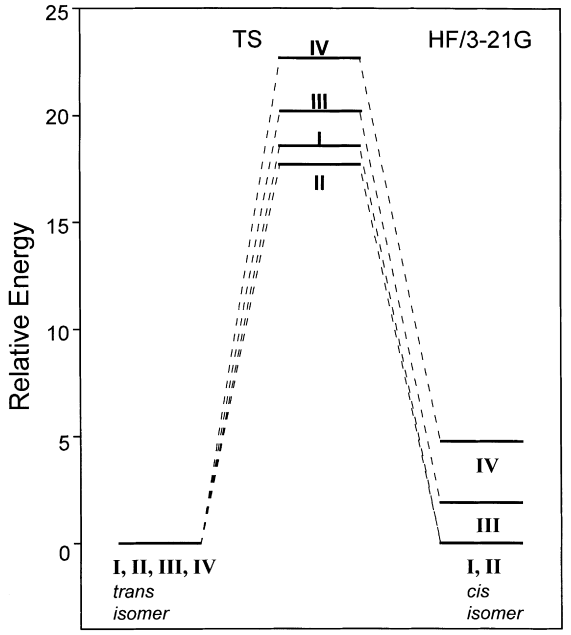


Fig. 4. A schematic representation of *trans–cis* inversion energy profiles for four peptide model compounds using HF/3-21G data points.

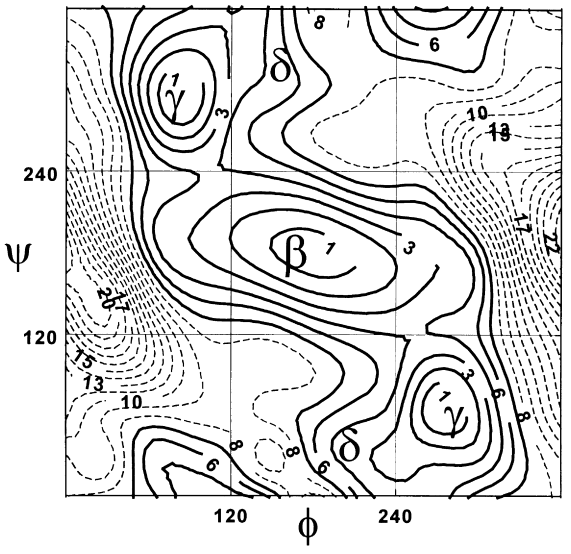
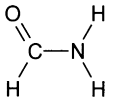
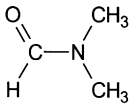


Fig. 5. Ramachandran type energy contour diagram (HF/3-21G) of For-Gly-NH_2 with *trans* backbone. Contour up to 6 kcal/mol are solid lines, above 6 kcal/mol broken lines.

same energy.

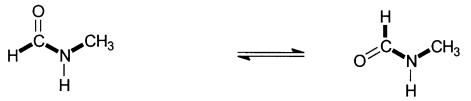


I

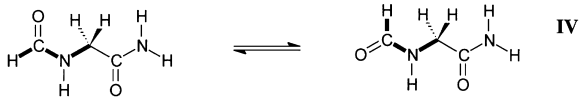


II

Furthermore, the transition state (TS) for the *cis–trans*-isomerization is expected to occur half way through the isomerization reaction co-ordinated. Non-symmetric substitution, i.e. non-identical $R^{(2)}$ and $R^{(3)}$, does not show the same degeneracy. Such general characteristics may be studied using the following set of compounds



trans cis III



trans cis IV

Although ab initio Gaussian SCF computations on formamide (**I**) have been carried out as early [25] as 1968 the *cis–trans*-isomerization of *N*-methyl formamide (**III**) has been studied, perhaps for the first time, by Andrews [26] in 1971 using the PCILO method. More recently Wiberg and Laidig [27] have carried out calculations on formamide (**I**) at several ab initio levels of theory in studying *cis–trans*-isomerization. To the best of our knowledge, nobody studied the *cis–trans*-isomerization of *N*- and *C*- protected glycine at the ab initio level. This means that, as of today, the ab initio *cis*-Ramachandran map of the glycine residue is still unknown.

3. Scope

In the present paper we wish to report our findings with respect to *cis–trans*-isomerization for compounds **I–IV**. The geometry optimized stable *cis*- and *trans*-isomers of compounds **I–IV** will be used to assist in the search for TSs associated with the process of *cis–trans*-isomerization.

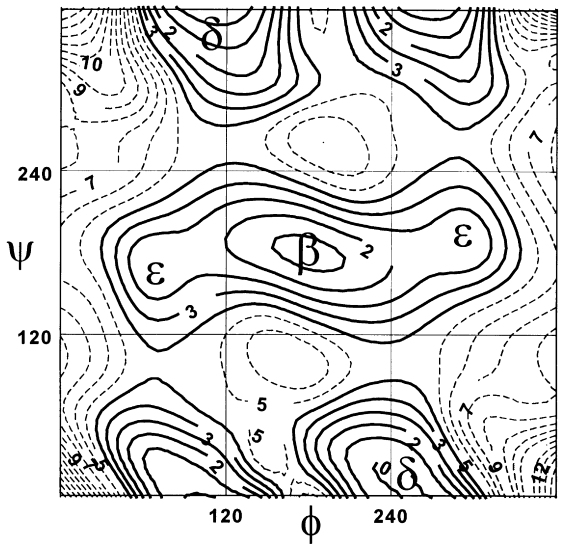
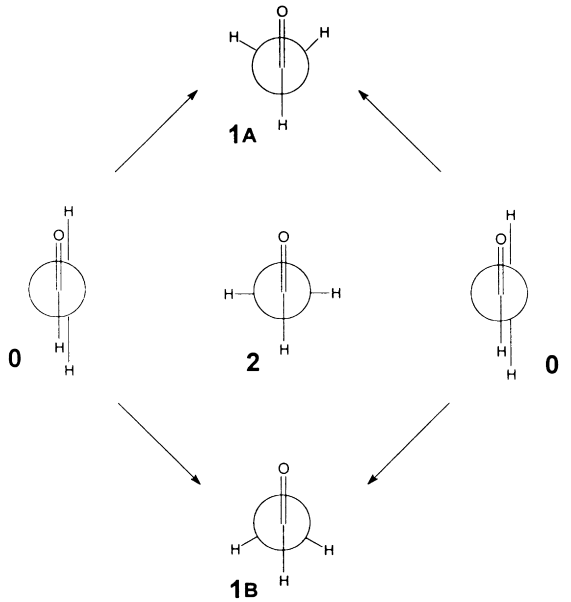


Fig. 6. Ramachandran type energy contour diagram (HF/3-21G) of For-Gly-NH_2 with *cis* backbone. Contour up to 6 kcal/mol are solid lines, above 6 kcal/mol broken lines.



Scheme 2.

4. Method

Ab initio Hartree–Fock (HF) and density functional geometry optimizations have been carried out using the GAUSSIAN 94 program system [28]. Two basis sets 3-21G and 6-31G(d) were employed at the HF level of theory and the B3LYP type DFT procedure were applied using the larger basis set 6-31G(d) only.

5. Results and discussion

The simplest molecule (**I**) can be studied in the greatest detail. Thus for formamide a rotation–inversion potential energy surface has been generated. The rotation (ω) is defined by the dihedral angle associated with the following four atoms: H–C–N–H. The pyramidality of the nitrogen (ζ) is defined in Fig. 1.

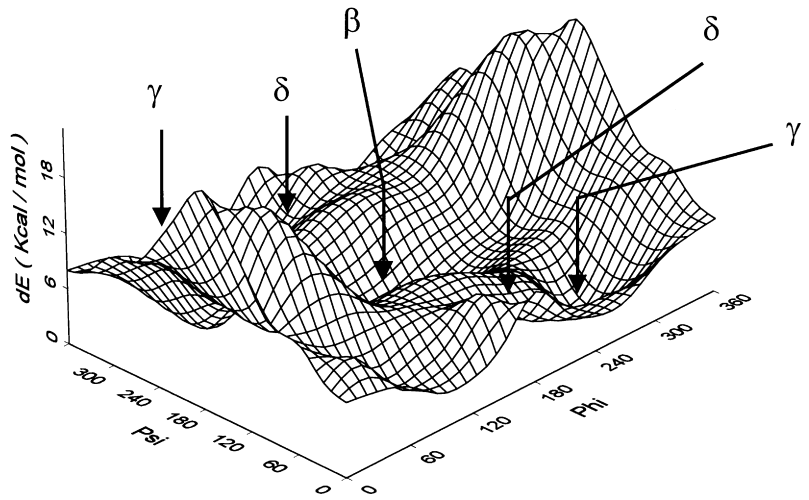


Fig. 7. Ramachandran type potential energy surface of For-Gly-NH_2 with *trans* backbone computed by HF/3-21G.

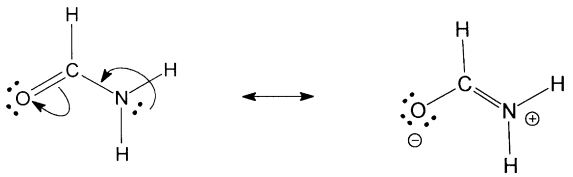
Table 3
Imaginary frequency values of *cis* and *trans* isomerization of compounds (**I**, **II**, **III**, **IV**) computed at several levels of theory

Compound	Imaginary frequencies		
	HF/3-21G	HF/6-31G(d)	B3LYP/6-31G(d)
I	548.40 i	505.63 i	554.32 i
II	256.91 i	260.45 i	299.06 i
III	335.22 i	322.06 i	366.68 i
IV	302.23 i	295.23 i	325.74 i

For the planar nitrogen angle ζ, involving point p, N and H, is 90°. If the two N–H bonds are bent up ζ will be less than 90° while if the two N–H bonds are bent down ζ will assume values greater than 90°. Such a rotation–inversion PES, has been generated at the HF/3-21G level of theory and is shown as a contour diagram in Fig. 2. A landscape representation can also be seen in Fig. 3.

The topology of the above PES is in full agreement with chemical expectations (cf. Scheme 2).

The nitrogen is planar in the peptide due to conjugative stabilization of the adjacent carbonyl (Scheme 3). However, when it is twisted out of coplanarity it does not have to be planar so it assumes its natural pyramidal form. Thus two TSs ($\mathbf{1_A}$ and $\mathbf{1_B}$ in Scheme 3) may be expected. The former ($\mathbf{1_A}$) is the most stable of the pair. In the most stable form ($\mathbf{1_A}$) the C=O is bisecting the HNH angle while in the least stable form ($\mathbf{1_B}$) the C–H is bisecting the HNH angle. In the rest of the paper only the most stable TS will be tabulated.



Scheme 3.

For the *cis–trans*-isomerization of compounds **I**–**IV**, the computed results obtained at several levels of theory are given in Tables 1 and 2. The process is illustrated graphically in Fig. 4 using the HF/3-21G data points.

The imaginary frequencies, along the reaction co-ordinates of *cis–trans*-isomerizations, are presented in Table 3. These imaginary frequencies are associated with the TSs along the reaction co-ordinates which is the curvilinear path as illustrated schematically by the upper pair of arrows in Scheme 3 for formamide. At the TS the vectorial motion associated with the reaction co-ordinate is the rotation about the C–N bond.

Even though there is only one peptide bond which may isomerize in formylglycinamide the problem is

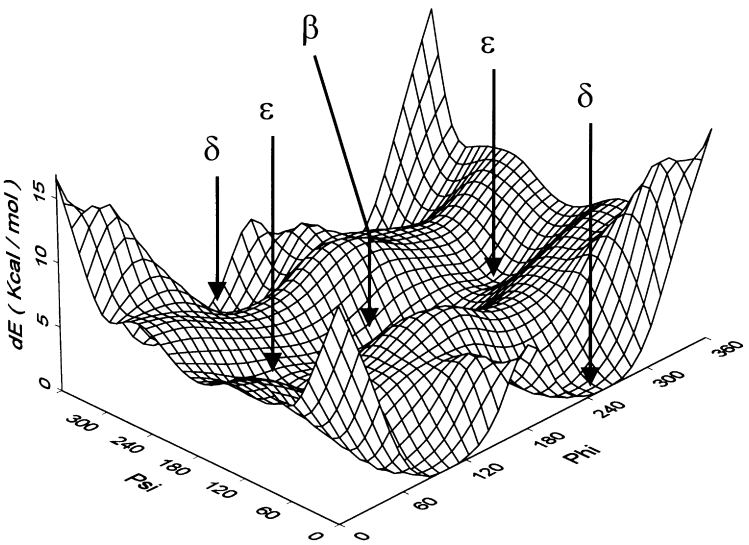


Fig. 8. Ramachandran type potential energy surface of For-Gly-NH_2 with *cis* backbone computed by HF/3-21G.

Table 4
Total energy values of *cis* and *trans* HCO-Gly-NH_2 in several of its geometry backbone (BB) peptide bond conformation computed at the HF/3-21G level of theory

BB	Peptide bond	ϕ	ψ	ω_0	ω_1	E	ΔE	ΔE_{stabil}
α_D	*cis*		Not found			–	–	–
α_D	*trans*		Not found			–	–	–
α_L	*cis*		Not found			–	–	–
α_L	*trans*		Not found			–	–	–
β_L	*cis*	−179.9	−179.9	0.0	0.0	−373.6401490	5.42	5.42
β_L	*trans*	−179.9	179.9	−179.9	179.9	−373.6477487	0.65	0.65
δ_D [a]	*cis*	114.4	−13.6	−5.6	1.7	−373.6414523	4.60	4.60
δ_D	*trans*	121.9	−25.2	174.9	−176.5	−373.6435790	3.27	3.27
δ_L [b]	*cis*	−114.5	13.5	5.7	−1.6	−373.6414523	4.60	4.60
δ_L	*trans*	−121.9	25.2	−174.9	177.8	−373.6435790	3.27	3.27
ϵ_D	*cis*	64.6	169.2	9.0	−3.0	−373.6380966	6.71	6.71
ϵ_D	*trans*		Not found			–	–	–
ϵ_L	*cis*	−64.6	−169.2	−8.9	3.1	−373.6380967	6.71	6.71
ϵ_L	*trans*		Not found			–	–	–
γ_D	*cis*		Not found			–	–	–
γ_D	*trans*	83.4	−64.6	175.6	−179.5	−373.6487902	0.00	0.00
γ_L	*cis*		Not found			–	–	–
γ_L	*trans*	−83.3	64.6	−175.7	−179.5	−373.6487902	0.00	0.00

[a] Even though the $\phi = 114.4°$ and $\psi = 13.4°$ conformation is in the γ_D box, it is structurally closer to the δ_D conformation of the *trans*-glycine than to its γ_D conformation and hence is labelled as δ_D and not as γ_D.

[b] In the same way the $\phi = -114.5°$ and $\psi = 13.5°$ conformation is in the γ_L box, it is structurally closer to the δ_L conformation of the *trans*-glycine than to its γ_L conformation and hence is labelled as δ_L and not γ_L.

Table 5
Total energy values of *cis*- and *trans*-HCO-Gly-NH_2 in several of its geometry backbone (BB) peptide bond conformation computed at the HF/6-31G(d) level of theory

BB	Peptide bond	ϕ	ψ	ω_0	ω_1	E	ΔE	ΔE_{stabil}
α_D	*cis*		Not found			–	–	–
α_D	*trans*		Not found			–	–	–
α_L	*cis*		Not found			–	–	–
α_L	*trans*		Not found			–	–	–
β_L	*cis*	−179.9	179.9	0.0	0.0	−375.7413393	4.59	4.59
β_L	*trans*	−179.9	179.9	−179.8	−179.9	−375.7486522	0.00	0.00
δ_D [a]	*cis*	118.1	−11.3	−9.5	−1.2	−375.7434359	3.27	3.27
δ_D	*trans*		Not found			–	–	–
δ_L [a]	*cis*	−118.0	11.4	9.6	1.4	−375.7434359	3.27	3.27
δ_L	*trans*		Not found			–	–	–
ϵ_D	*cis*	73.8	163.6	16.4	−4.1	−375.7405225	5.10	5.10
ϵ_D	*trans*		Not found			–	–	–
ϵ_L	*cis*	−73.2	−163.6	16.3	4.1	−375.7405224	5.10	5.10
ϵ_L	*trans*		Not found			–	–	–
γ_D	*cis*		Not found					
γ_D	*trans*	84.9	−66.8	177.9	177.8	−375.7479423	0.45	0.45
γ_L	*cis*		Not found					
γ_L	*trans*	−84.9	66.8	−177.9	−177.8	−375.7479422	0.45	0.45

[a] Even though the $\phi = 118.1°$ and $\psi = 11.3°$ conformation is in the γ_D box, it is structurally closer to the δ_D conformation of the *trans*-glycine than to its γ_D conformation and hence is labelled as δ_D and not γ_D.

[b] In the same way the $\phi = 118.0°$ and $\psi = 11.4°$ conformation is in the γ_L box, it is structurally closer to the δ_L conformation of the *trans*-glycine than to its γ_L conformation and hence is labelled as δ_L and not γ_L.

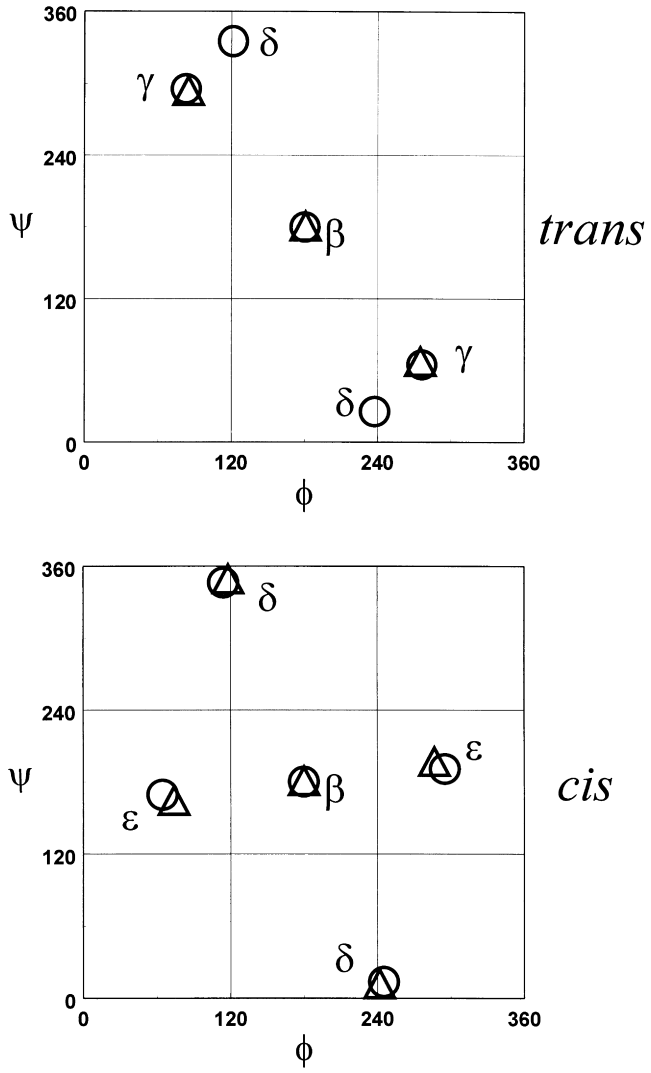


Fig. 9. Topological pattern for optimized conformers for For-Gly-NH_2 in its *trans*-(upper) and *cis*-(lower) backbone configuration. Geometries were computed at the HF/3-21G (○) and HF/6-31G(d) (△) level of theory.

considerably more involved because torsional angles ϕ and ψ may also be varied. The contour diagram of the *trans*- as well as the *cis*-Ramachandran map for $HCONH–CH_2–CONH_2$ are shown in Figs. 5 and 6, respectively. The same information is presented as PES-landscape for the *trans*- and *cis*-isomers in Figs. 7 and 8, respectively. The optimized structures computed at HF/3-21G as well as HF/6-21G(d) levels of theory are given in Tables 4 and 5.

Fig. 9 summarises the topology of the *trans*- and *cis*-Ramachandran maps for formylgycinamide shown in Figs. 5 and 7 as well as Figs. 6 and 8, respectively.

Fig. 10 shows, in a schematic way, the idealised topology of the backbone conformational potential energy surface (PES) of an amino acid residue. Two full cycles ($-360° \leq \phi \leq +360°$ and $-360° \leq \psi \leq +360°$) of rotation are shown. The broken line square, at the centre, depicts the cut made according to the IUPAC-IUB convention ($-180° \leq \phi \leq +180°$ and $-180° \leq \psi \leq +180°$). The four quadrants are identical and we use the upper right hand quadrant as the

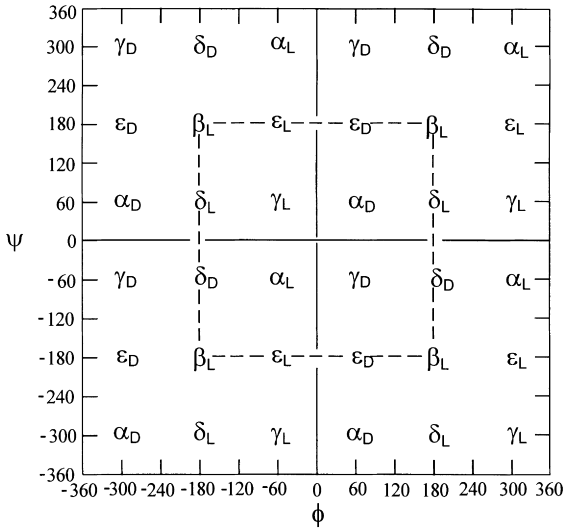


Fig. 10. Idealized topology of the Ramachandran map showing two full cycles of rotation. The IUPAC-IUB recommended cut is shown at the centre as a square of broken lines.

traditional cut ($0° \leq \phi \leq +360°$ and $0° \leq \psi \leq +360°$). Figs. 5–8 are presented as the traditional cut of the *cis*- and *trans*-Ramachandran maps.

Double Ramachandran maps; analogous to the schematic pattern of Fig. 10 are shown for the *trans*- and *cis*-formyl glycine in Figs. 11 and 12, respectively. These maps were generated at the HF/3-21G level of theory.

In order to assess the relative reliability of the HF/3-21G results, energy separations computed at higher levels of theory were plotted against the HF/3-21G values (cf. Fig. 13). The upper position of the figure shows the *cis–trans*-isomerization energies (thermodynamic separation) and barriers to *cis–trans*-isomerization (kinetic separation) for compounds **I**–**IV**. The lower portion of the figure shows relative energies of the various conformers of *cis–trans*-formylglycinamide. While the scatter is more noticeable in the case of kinetic separation (barrier heights) than in the case of thermodynamic separation (*cis–trans*-isomerization)

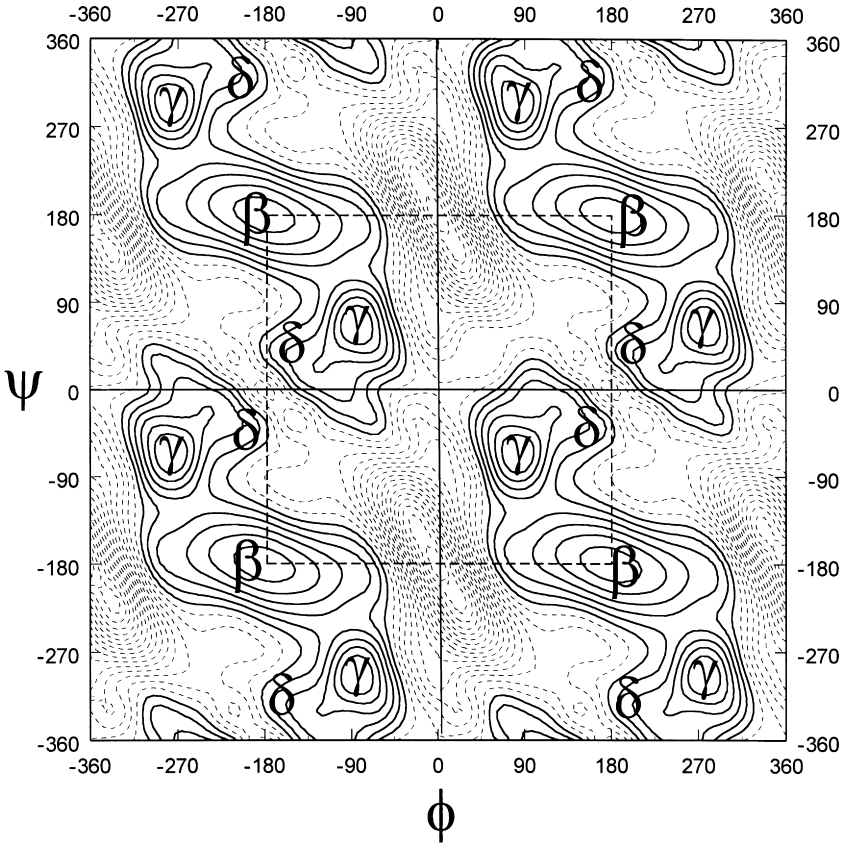


Fig. 11. Double *trans*-Ramachandran map for formylglycinamide computed at the HF/3-21G level of theory.

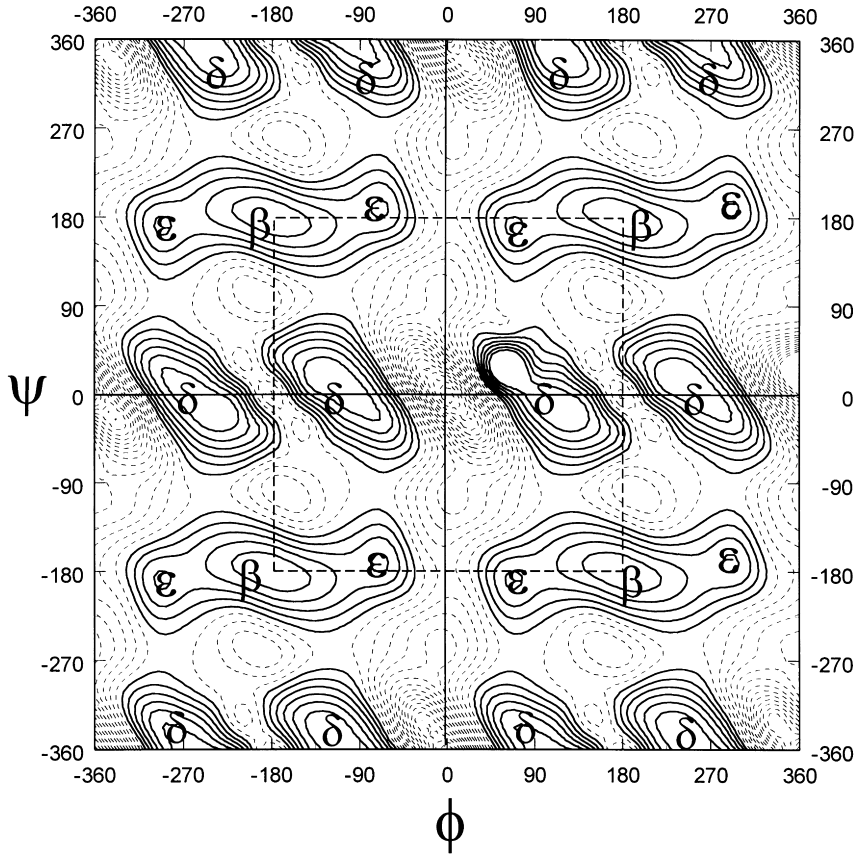


Fig. 12. Double *cis*-Ramachandran map for formylglycinamide computed at the HF/3-21G level of theory.

nevertheless the trend is well reproduced by the lower level of theory (i.e. HF/3-21G).

6. Conclusions

The energies of the *cis*-isomers of non-symmetrically substituted peptide bonds are somewhat higher that the energies of the *trans* peptide bond. In the case of *N*-methyl formamide (**III**) the *cis*-isomer is 1.88 kcal/mol, higher than the *trans* isomers at the HF/3-21G level of theory. For the β-conformation of *N*-formylglycinamide (**IV**) the corresponding value is 4.77 kcal/mol.

Although the actual magnitude for thermodynamic stability may vary with the basis set and method used, nevertheless, these ΔE values will always be relatively small energy differences. In fact the above numbers represent the worst case scenario because the higher level calculations already reduced 1.88 to 1.67 kcal/mol and 4.77 to 3.80 kcal/mol. Thus, the Boltzmann distribution would always predict the presence of some *cis*-form on the basis of thermodynamic stability.

It is of course a fundamental question if the barrier height for *cis–trans*-isomerization will permit equilibration of the two isomers. The barrier height for the *cis–trans*-isomerization of the above two compounds (**III** and **IV**) were computed at the HF/3-21G level of theory to be 20.23 and 22.67 kcal/mol. Again this is reduced to 18.17 and 20.30 kcal/mol, respectively, when the computations were carried out at the HF/6-31G(d) level of theory. Thus, kinetically the *cis–trans*-isomerization is not out of question when the experiment is carried out in solution.

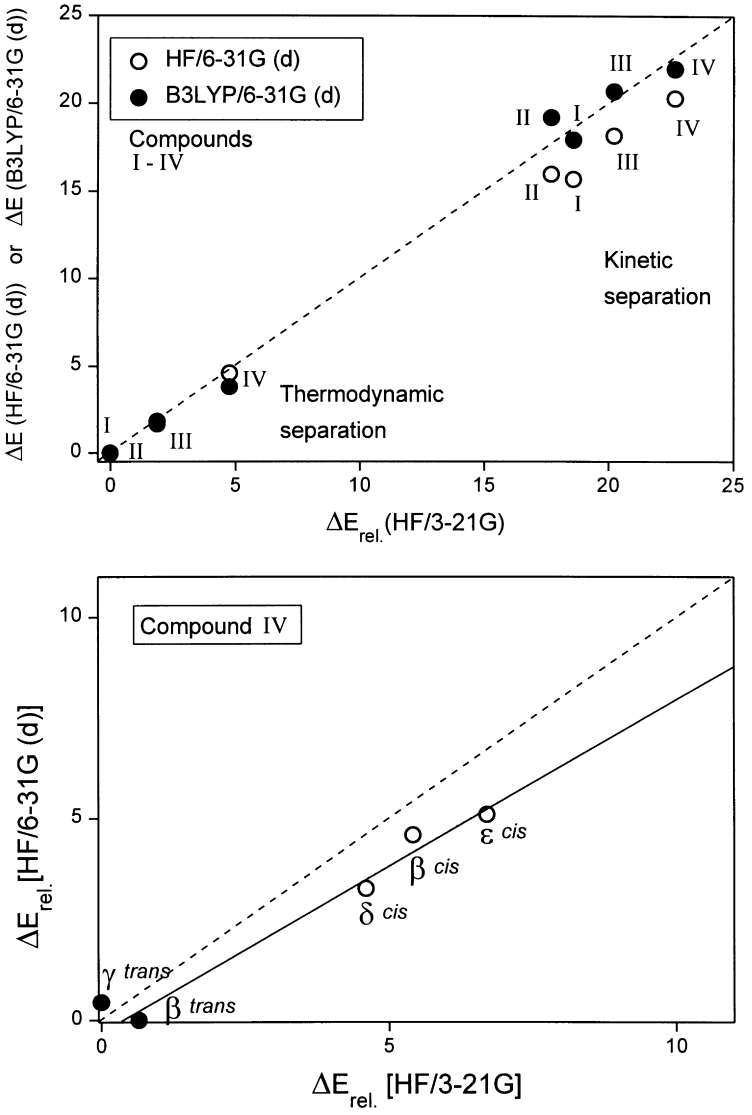


Fig. 13. Correlation of energy separations computed at higher levels of theory with those obtained at the HF/3-21G level of theory.

The results reported here allow one to present the topology of the 3D-Ramachandran map, which is shown in Fig. 14 using the HF/3-21G data points. The TS energy 22.67 kcal/mol computed at the HF/3-21G level of theory is not shown in Fig. 14 but occupies the position between the *trans*- and the *cis*-β-backbone conformation. For the *trans*- and *cis*-isomerism the following energetic may be calculated in kcal/mol with respect to the γ-global minimum energy backbone conformation:

$$\underset{trans\text{-}\beta}{0.65} \rightarrow \underset{TS}{23.32} \rightarrow \underset{cis\text{-}\beta}{5.42}$$

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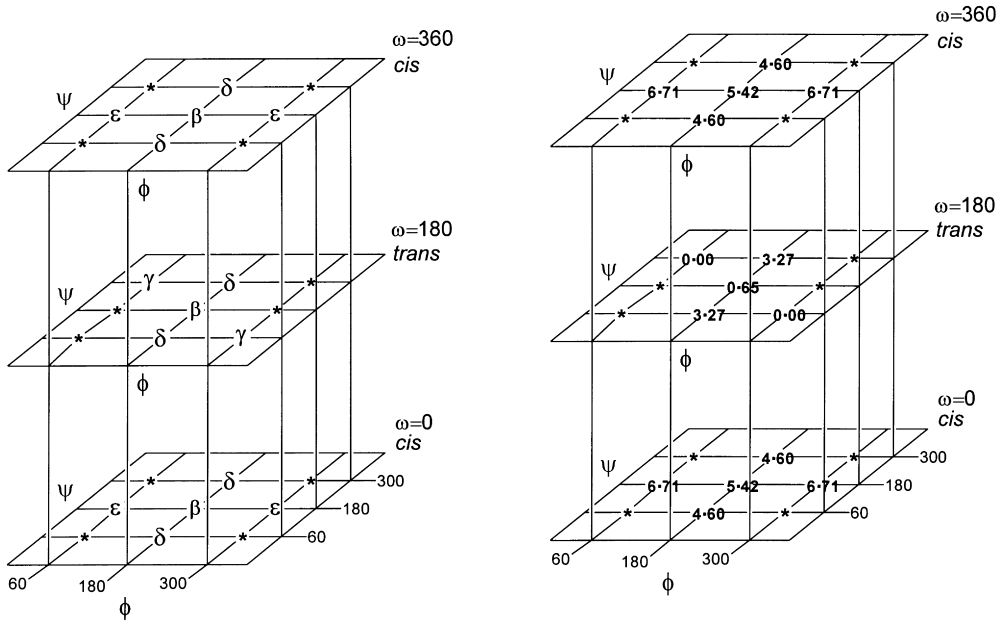

Fig. 14. Topology of the 3D-Ramachandran map for formylglycinamide at the HF/3-21G level of theory. The TS from the *trans*- to the *cis*-β-backbone conformations are not shown but understood to be above the 0.65 kcal/mol value by 22.67 kcal/mol. The anhililated conformations are denoted by stars.

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