

## An ab initio computational study on selected lycopene isomers

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Received 15 December 2000; accepted 12 February 2001

### Abstract

Lycopene is an effective antioxidant in vivo. Although lycopene is present in its all-*trans* isomeric form in fruits and vegetables, serum and tissue samples show a predominance of various *cis*-isomers of lycopene. The present study was undertaken to investigate the molecular structure of several *cis*-isomers of lycopene using an ab initio molecular modeling procedure. The relative stability of selected *cis*-isomers of lycopene with respect to the all-*trans* isomer, was studied. The following sequence of stability was observed.

5-*cis* > all-*trans* > 9-*cis* > 13-*cis* > 15-*cis* > 7-*cis* > 11-*cis*

The first four of these isomers had relative energies within +1 kcal mol<sup>-1</sup>, but the fifth isomer (i.e. 15-*cis*) was within 3 kcal mol<sup>-1</sup>. However, the last two isomers were less stable than the all-*trans*-isomer with more than 5 kcal mol<sup>-1</sup>, difference in energy. The optimized molecular conformational study structures indicated that the central conjugated part of every lycopene isomer is planar. However, the two tail ends of the molecules, each containing three single C–C bonds, avoid coplanarity. © 2001 Elsevier Science B.V. All rights reserved.

**Keywords:** All *trans*-lycopene; Selected *cis*-isomers of lycopene; Thermodynamic stability of lycopene isomers; Computations of lycopene isomers; Ab initio MO theory

### 1. Introduction

#### 1.1. Biological background

Oxidative stress is now recognized as an important

etiological factor in the causation of several chronic diseases, amongst which are cancer and cardiovascular diseases. Antioxidants are effective in mitigating the damaging effect of free radicals. Lycopene is a carotenoid antioxidant, present in tomatoes and other fruits and vegetables. Recent studies have shown that it acts as an antioxidant in vivo, providing protection against the oxidation of lipids, proteins and DNA [1,2]. A recently published paper [3] indicated a

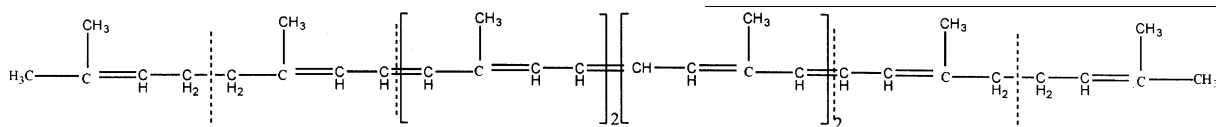
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significant inverse correlation between the intake of lycopene or serum concentrations of lycopene and the risk of several concerns. The isomeric forms of lycopene have been suggested to be important factors influencing its absorption and bioavailability.

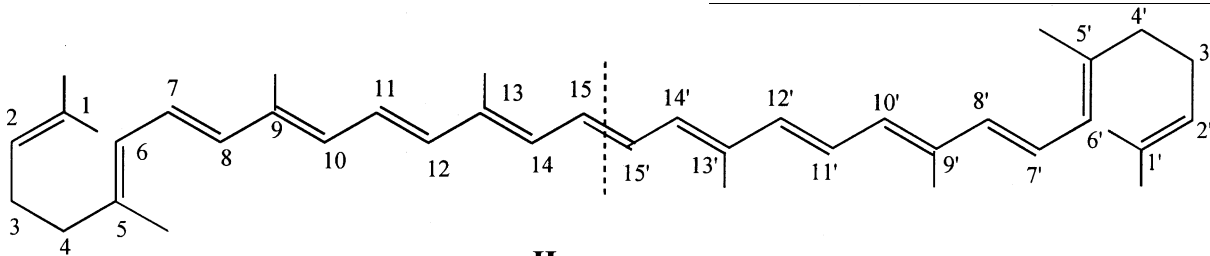
### 1.2. Structural background

Lycopene [ $C_{40}H_{56}$ ] consists of eight isoprenic units, so its skeleton is related to tetraterpenes [ $C_{40}H_{64}$ ], even though it contains fewer hydrogens. Its composition is shown in **I**.



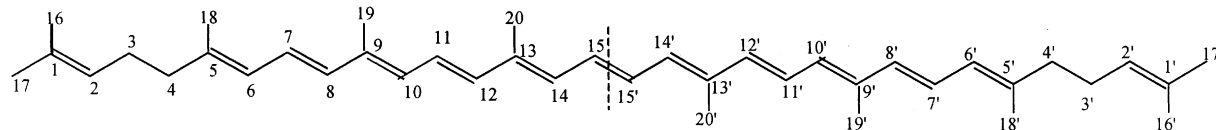
**I**

As such, lycopene is closely related to  $\alpha$ -,  $\beta$ -, and  $\gamma$ -carotenes. Sometimes, the structure of lycopene is presented in a pre-folded form (**II**) to show its structural similarity to  $\beta$ -carotene. Due to the internal molecular symmetry, it has been traditional to number the chain from the two ends as shown in **II**.



**II**

The all-*trans* lycopene has also been presented, traditionally, in its fully extended form (**III**).



**III**

All of these representations imply a planar molecular form.

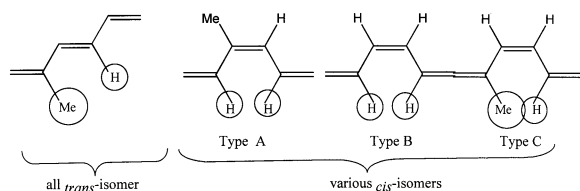
Isolation procedures for lycopene were first reported in 1910 [4] and its structure was determined during the period of 1928–1931 [5–8].

The spectral characteristics of stereoisomeric carotenoids, including lycopene, were studied [9] in 1943. The ease of isomerization of the  $C_{40}H_{56}$  carotenoids has been noticed by Zechmeister and Tuzson [10] as early as 1938. An isomerization equilibrium can only be reached very slowly but the process starts immediately after the crystalline carotene is dissolved. This indicates that the all-*trans*- and various *cis*-isomers are very close on the free-energy scale, but nevertheless require appreciable energy of activation for such a non-catalyzed inter-conversion. Subsequently, *trans* to *cis* isomerization of lycopene [11] and other

compounds were studied using iodine as the catalyst. [11–13]. In 1943, Pauling pointed out [14] that *trans* to *cis* isomerization could be a result of the overlapping of the methyl group of a carbon atom adjacent to a double bond and the hydrogen. Not all *cis*-isomers may be of equal stability due to a number of possible

1,4 interactions as shown by the structures of Scheme 1. Clearly, on the basis of relative group sizes, the  $-CH_3 \cdots H-$  interaction (type C) appears to be the most destabilizing.

There are a number of possible geometrical



Scheme 1.

isomers. Zechmeister indicated [13] the possible presence of 20  $\beta$ -carotene, 32  $\alpha$ -carotene, 64  $\gamma$ -carotene and 72 lycopene geometrical isomers. No X-ray structure of lycopene has been determined as yet. There are, however, two X-ray structures of  $\beta$ -carotene in the literature [15,16].

## 2. Aim of study

Although lycopene is present in its all-*trans* isomeric form in fruits and vegetables, *cis*-isomers constitute the predominant form present in the serum and tissues [17,18]. The biological significance of lycopene isomerization is not well understood. The aim of our study was to investigate the structure and stability of different isomeric forms of lycopene using ab initio molecular modeling, and to gain a better understanding of lycopene isomerization requirements. In addition to geometrical *cis/trans* isomerism, the conformations of the two tails of the molecule were also analyzed.

## 3. Method

This computational study involved semi-empirical (AM1) geometry optimization, which was followed by an ab initio study carried out at the HF/3-21G level of theory.

The computations were carried out using the GAUSSIAN 94 program system [19]. Standard geometry optimizations were performed on the all-*trans*- as well as six selected *cis*-isomers. The optimized molecular conformations were also compared to the results obtained from a lycopene model compound [20].

Fig. 1 shows the all-*trans*- and selected *cis*-isomers of lycopene. The all-*trans*- and the selected six *cis*-isomers (5-, 7-, 9-, 11-, 13- and 15-) were explored in their molecular entirety (containing 296 electrons and

96 atoms, which corresponds to 282 geometrical parameters to be optimized). Thus, lycopene is among the largest organic molecules being investigated using ab initio molecular computation with the current computational technology.

## 4. Results

The relative energies, which measure thermodynamic stabilities of the lycopene isomers, computed at the HF/3-21G level of theory, are summarized in Table 1. The expected stabilities, on the basis of molecular structures, are given in Table 2. The values of the torsional angles ( $\tau_{1'2'3}$  as well as  $\tau_{1'2',3}$ ) of the three pairs of single bonds ( $C^2-C^3$ ,  $C^3-C^4$ ,  $C^4-C^5$  as well as  $C^{2'}-C^{3'}$ ,  $C^{3'}-C^{4'}$ ,  $C^{4'}-C^{5'}$ ) are summarized in Table 3,

## 5. Discussion

### 5.1. Molecular configurations

The relative energies, which measure thermodynamic stabilities of lycopene isomers, are summarized in Table 1 and are depicted in Fig. 2. We notice four categories for *cis*-isomers, which are summarized in Table 2. The computed relative stabilities of the four categories of the *cis*-isomers, are listed below.

*Type A'* involves the 5-*cis*-isomer. This is the only *cis*-isomer which is slightly more stable (within  $-0.5 \text{ kcal mol}^{-1}$ ) than the all-*trans* form.

*Type A* involves the 9-*cis* and 13-*cis*-isomers. These *cis*-isomers are slightly less stable (within  $1.0 \text{ kcal mol}^{-1}$ ) than the all-*trans*-form.

*Type B* involves the 15-*cis*-isomer, which is only about  $3 \text{ kcal mol}^{-1}$  less stable than the all-*trans* form.

*Type C* involves the 7- and 11-*cis*-isomers. These *cis*-isomers are about  $6 \text{ kcal mol}^{-1}$  higher on the energy scale than the all-*trans*-form.

*Cis*-isomers of lycopene in *Types A'* and *A* and the *trans* lycopene have similar energies, since we are dealing with triply substituted double bonds as shown in Table 2.

Type *A* structures (see Fig. 1) are only slightly

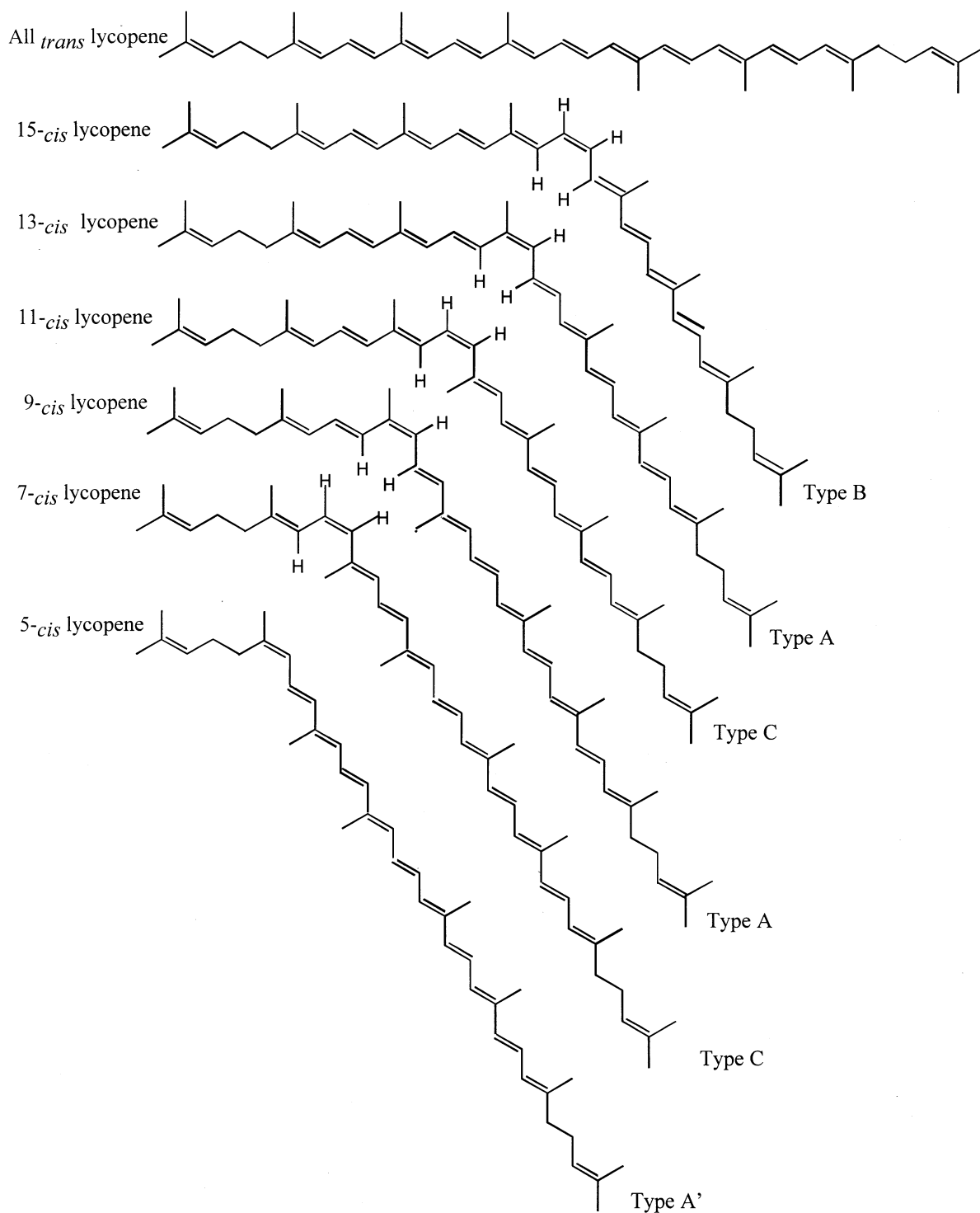


Fig. 1. Geometrical isomers of lycopene.

Table 1  
Computed total energy and Relative Energy Values of Various Isomers of Lycopene, at HF/3-21G level of theory

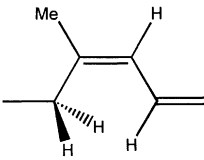
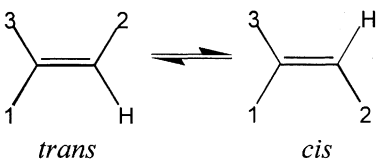
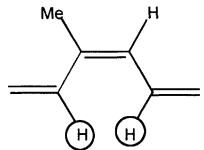
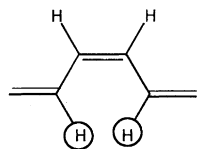
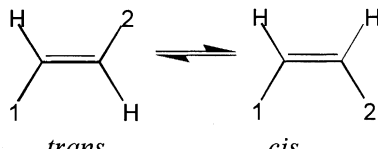
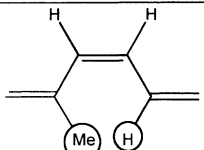
Isomer	Energy (Hartree)	Relative energy (kcal mol <sup>-1</sup> )
All- <i>trans</i>	-1538.5731249	0.000
5- <i>Cis</i>	-1538.5737548	-(0.395) <sup>a</sup>
7- <i>Cis</i>	-1538.5636899	5.921
9- <i>Cis</i>	-1538.5722460	0.552
11- <i>Cis</i>	-1538.5634789	6.053
13- <i>Cis</i>	-1538.5721338	0.622
15- <i>Cis</i>	-1538.5693098	2.394

<sup>a</sup> Global minimum.

higher on the energy scale (see Fig. 2) than the all-*trans*-isomer. Type A' is extremely similar to Type A, except that the hydrogens on the 1,4 positions (denoted as carbon 4 and 7) are not eclipsed but staggered. This is shown in Scheme 2.

Table 2

Classification of various *cis*-lycopene isomers according to 1,4-non-bonded interactions and extent of substitution about the carbon-carbon double bond involved. NB: Clearly, on the basis of relative group sizes, the -CH<sub>3</sub>···H- interaction (type C) appears to be the most destabilizing. The order of expected stability is the following: A' > A > B > C

1,4-non bonded interaction		Isomers	Isomerisation with different degree of substitution
Type	<i>cis</i> structure		
A'		5- <i>cis</i>	
A		9- <i>cis</i> and 13- <i>cis</i>	
B		15- <i>cis</i>	
C		7- <i>cis</i> and 11- <i>cis</i>	

Type B, there is only one example- the 15-*cis*-isomer. The 1,4 interaction involves the *cis* double bond which has only two alkyl substituents as shown in Table 2.

Type C has the two least stable structures, the 7-*cis* and 11-*cis*-isomers. In accordance with Fig. 2, the relative energies measuring stabilities are therefore as follows in Scheme 3

In view of the foregoing, one only may wonder if the thermodynamic stability of the lycopene isomers, as well as the kinetic stability of the isomerization transition states, will predetermine the relative concentrations of these isomers in tissues and plasma.

## 5.2. Molecular conformations

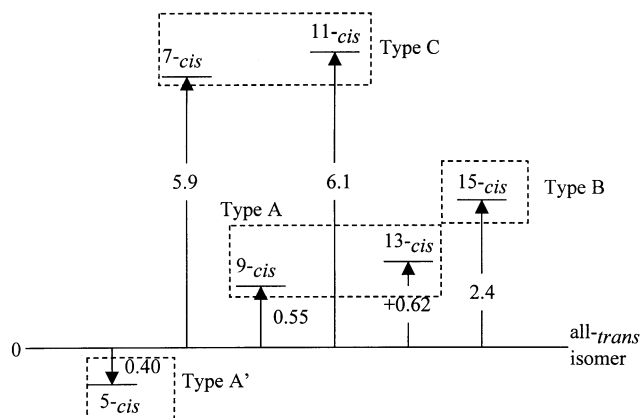
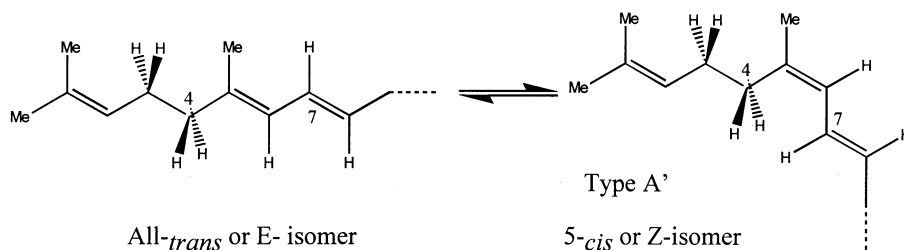
When a planar moiety is rotated about a tetrahedral carbon, it may be either eclipsed with a tetrahedral

Table 3

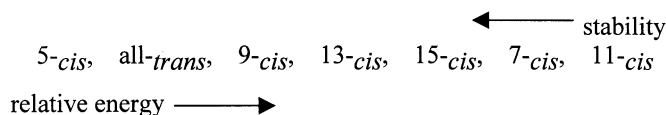
Optimized torsional angles and selected orbital energies for various isomers of lycopene, calculated at RHF/3-21G level of theory

Parameter <sup>a</sup>	Dihedral	all- <i>trans</i>	5- <i>cis</i>	7- <i>cis</i>	9- <i>cis</i>	11- <i>cis</i>	13- <i>cis</i>	15- <i>cis</i>
$\chi_1$	D5	-106.596	103.040	-106.539	-106.605	-106.440	-106.409	-106.393
$\chi_2$	D6	-176.424	176.517	-176.567	-176.479	-176.430	-176.524	-176.473
$\chi_3$	D7	-100.364	90.063	-100.548	-100.368	-100.340	-100.393	-100.459
$\chi_1'$	D31	106.368	106.440	106.515	106.460	106.394	106.474	106.475
$\chi_2'$	D30	176.452	176.460	176.480	176.460	176.4637	176.504	176.456
$\chi_3'$	D29	100.377	100.406	100.468	100.415	100.448	100.415	100.421
$\phi$	D#	N/A	1.388	-5.854	-0.016	5.945	-0.0005	0.016
HOMO	-	-0.23712	-0.23320	-0.23387	-0.23347	-0.23508	-0.23422	-0.23459
LUMO	-	+0.06964	+0.05102	+0.05144	+0.05255	+0.06867	+0.05331	+0.05284
$\Delta$	-	0.30676	0.28422	0.28531	0.28602	0.30375	0.28753	0.28743

<sup>a</sup>  $\chi$  denotes the dihedral angle value for the single bonds, from the outsides inwards ( $\chi_1$  corresponds to the first single bond, closest to the terminal end of the molecule).  $\phi$  corresponds to the value of the dihedral angle about which the isomerisation has occurred, for each particular *cis*-isomer. Thus,  $\phi$  measures deviation from coplanarity of the *cis* double bond. HOMO is highest occupied MO energy, measuring the ionisation energy (IE) in terms of Koopman's theorem. LUMO is lowest unoccupied MO energy and  $\Delta$  is the difference LUMO–HOMO in Hartree atomic units.

Fig. 2. A schematic illustration of the relative energies (kcal mol<sup>-1</sup>) of the various *cis*-isomers of lycopene studied relative to the all-*trans* form.

Scheme 2.



Scheme 3.

bond or perpendicular to that bond. This has been revealed by the study on ethyl benzene [21].

In the case of lycopene isomers, in most cases, the olefinic moiety seems to favor a compromising position, having  $\chi^1$  and  $\chi^3$  in the range of 90–107°. Thus, it is either roughly perpendicular to the C<sup>3</sup>–C<sup>4</sup> bond or near to a position of eclipsing with one of the two C–H bonds of the CH<sub>2</sub> moieties of C<sup>3</sup> and C<sup>4</sup>. These conformers are shown in Scheme 4. The optimized values of the torsional angles are summarized in Table 3.

Fig. 3 shows the optimized structures of lycopene in the all-*trans* as well as in the selected *cis*-isomeric forms. The results (see Fig. 3 and Table 3) clearly indicate that while the conjugated double bonded segment of lycopene from C<sup>5</sup> to C<sup>5'</sup> is planar or nearly planar, the two terminal positions of the molecule (from C<sup>1</sup> to C<sup>5</sup> as well as from C<sup>1'</sup> to C<sup>5'</sup>) are rotated out of plane.

### 5.3. Deviation from coplanarity

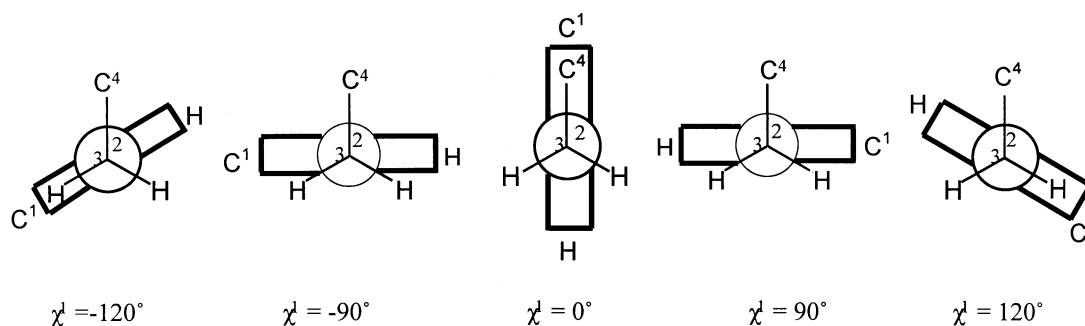
Sometimes the reactivity of an unsaturated compound is related to its not completely planar forms. This is particularly true for *cis*-double bonds. Deviation from coplanarity is within about 6° at the HF/3-21G level of theory as shown by the data in Table 3 by the entry  $\phi$ . The deviation from coplanar-

ity ( $\Delta\phi$ ) at the corresponding double bonds in the all-*trans*-form is considerably smaller as shown by the data given in Table 4. Such non-planarity implies a weakening of the  $\pi$ -bond, which in turn is related to reactivity. Such an enhanced reactivity is certainly related to *trans*–*cis* isomerization. However, it is not clear at this time if such structural differences may also imply enhanced radical scavenging ability.

## 6. Perspectives

Lycopene from natural plant sources exists predominantly in the all-*trans* configuration. For this reason, it may have been assumed to be the thermodynamically most stable form. However, all one can conclude is that the biosynthesis in the plants leads to the all-*trans*-form and this is independent of its thermodynamic stability. In human plasma, lycopene is an isomeric mixture, containing at least 60% of the total lycopene as *cis*-isomers (Table 5). All-*trans*, 5-*cis*, 9-*cis*, 13-*cis* and 15-*cis* are the most commonly identified isomeric forms of lycopene [18]. The relative biological significance in terms of absorption and effectiveness of various geometric isomers of lycopene is unclear at present.

Epidemiological studies have supported the hypothesis that consumption of heat-processed



Scheme 4.

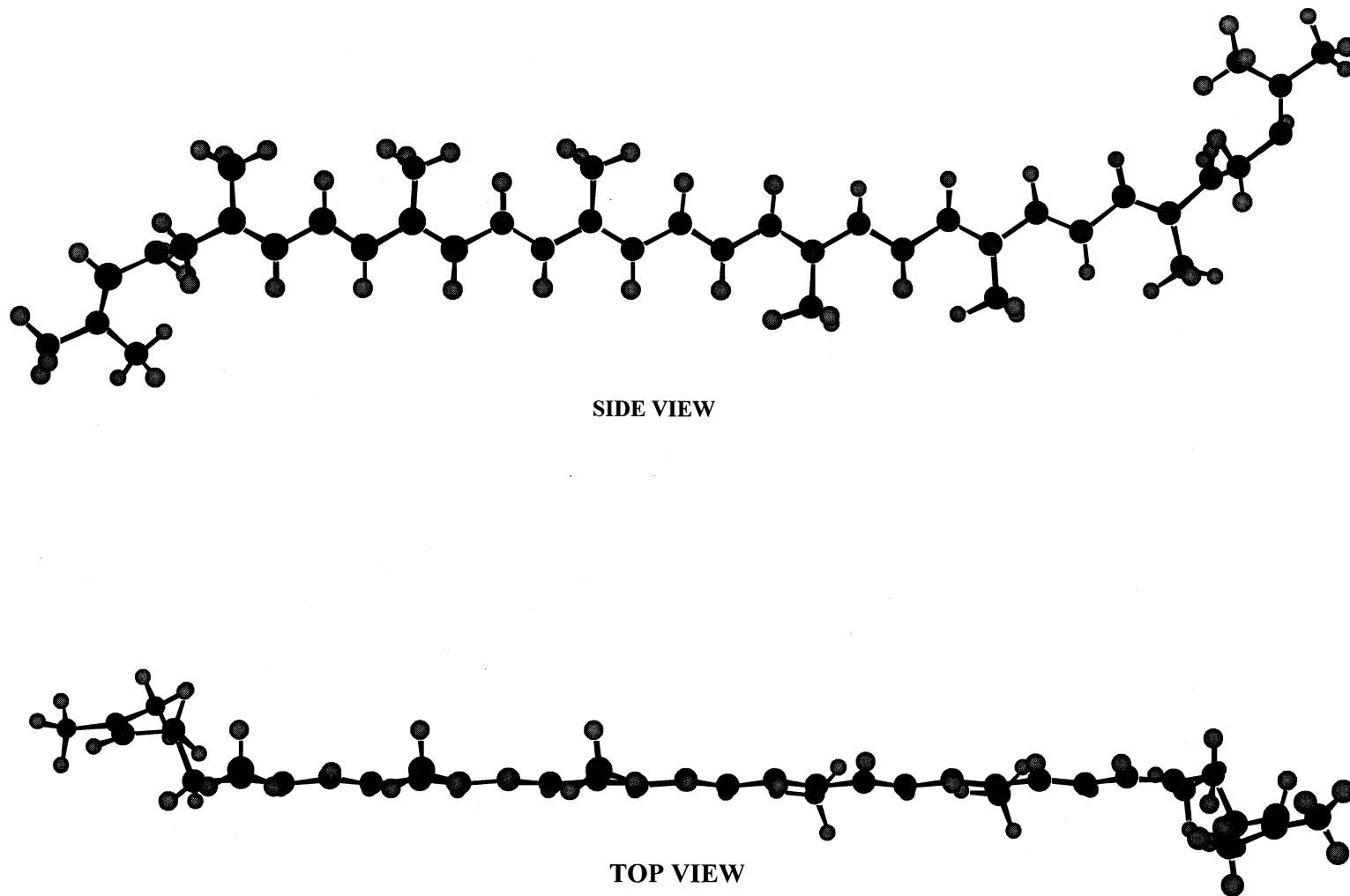


Fig. 3. (a) Side and top views of optimized all-*trans* lycopene Structure, (b) side and top views of optimized 5-*cis* lycopene structure.



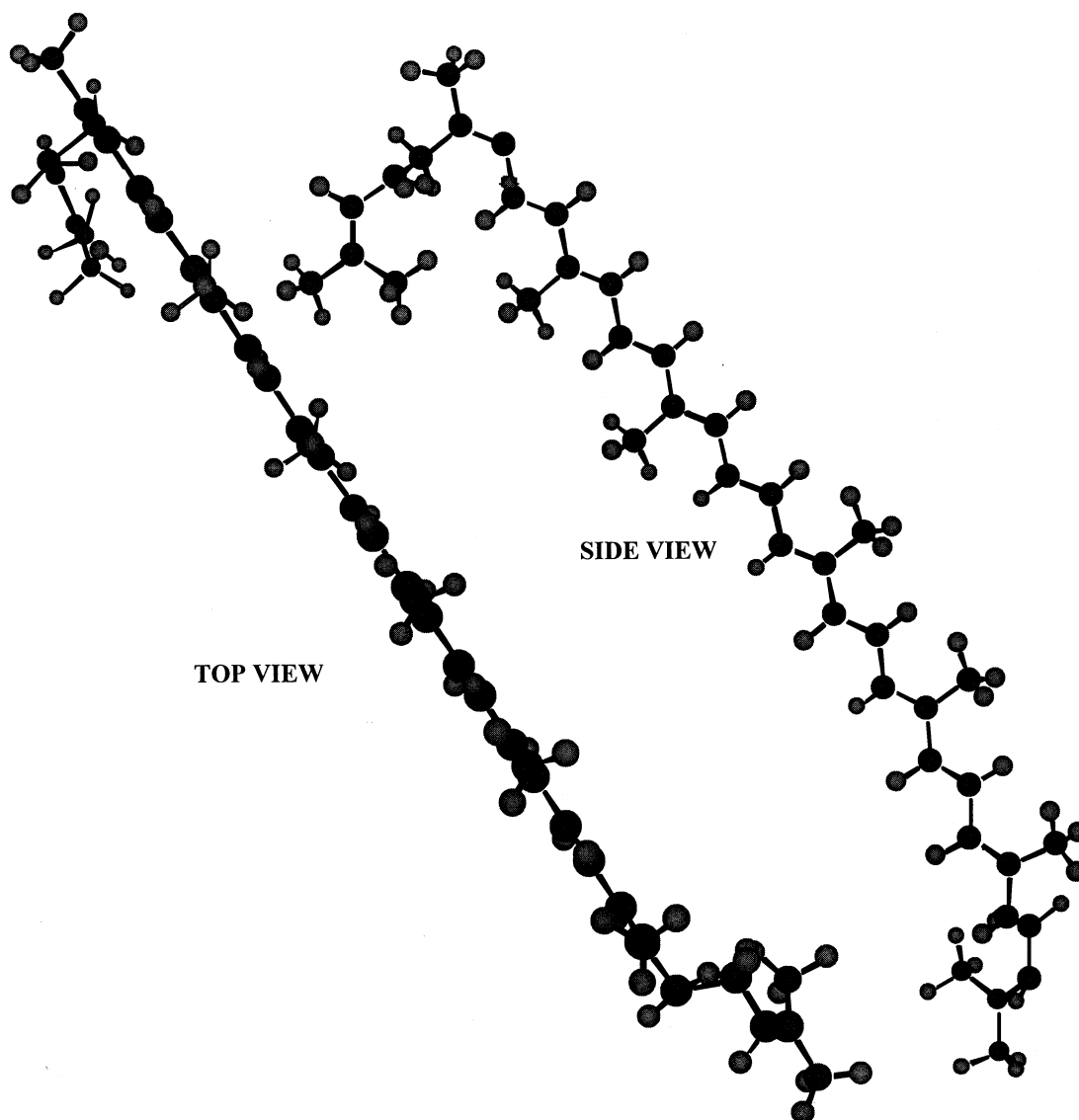


Fig. 3. (continued)

tomatoes, such as in the Mediterranean diet, may reduce the risk of coronary heart disease by preventing the oxidation of the low-density lipoprotein [1,2]. Giovannucci et al. [22] have also suggested that only the intake of processed tomato products was related to reduced risk of prostate cancer, probably because of their high content of lycopene [21] *cis*-isomer. The observation that high concentrations of *cis*-isomers are present in

human serum and prostate tissue, also suggests that *cis*-isomers might be biologically more active than the all-*trans*-isomer.

Of all the *cis*-isomers, the 5-*cis*-form appears to be the most stable. Furthermore, our calculations suggest that it is thermodynamically more stable than the all-*trans*-isomer. This suggests that the 5-*cis*-isomer has the highest concentration when equilibrium is reached.

Table 4

Torsional angles for the *trans*-peptide bonds in the all-*trans* lycopene, computed at RHF/3-21G level of theory.

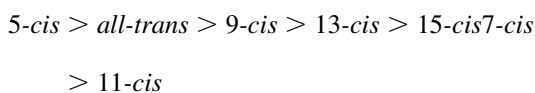
Bond	Dihedral ( $\phi$ )	$\phi$	$\Delta\phi^a$
C <sup>1</sup> –C <sup>2</sup>	D4	178.955	1.045
C <sup>5</sup> –C <sup>6</sup>	D8	178.645	1.355
C <sup>7</sup> –C <sup>8</sup>	D10	179.943	1.057
C <sup>9</sup> –C <sup>10</sup>	D12	–179.999	–0.001
C <sup>11</sup> –C <sup>12</sup>	D14	179.999	0.001
C <sup>13</sup> –C <sup>14</sup>	D16	179.998	0.002
C <sup>15</sup> –C <sup>15'</sup>	D18	180.000	0.000
C <sup>14'</sup> –C <sup>13'</sup>	D20	179.997	0.003
C <sup>2'</sup> –C <sup>11'</sup>	D22	180.000	0.000
C <sup>10'</sup> –C <sup>9'</sup>	D24	180.000	0.000
C <sup>8'</sup> –C <sup>7'</sup>	D26	179.060	0.940
C <sup>6'</sup> –C <sup>5'</sup>	D28	–178.623	–0.377
C <sup>2'</sup> –C <sup>1'</sup>	D32	–178.925	–0.075

<sup>a</sup> Deviation from coplanarity measured as follows:  $\Delta\phi = 180^\circ - \phi$  (for  $\phi > 0$ ),  $\Delta\phi = -180^\circ - \phi$  (for  $\phi < 0$ ).

All of these are in general agreement with the biological observations. Thus, one can project that in the future, quantum chemical computations will be able to enhance, considerably, our understanding of the antioxidant activity of lycopene.

## 7. Conclusions

As far as configuration stability is concerned, the following sequence has been established at the HF/3-21G level of ab initio computations.



The conformational analyses indicated that the central skeleton of conjugated double bonds is practically planar for all seven isomers. However, the tail-end with C–C single bonds are flexible and their conformations avoid coplanarity with the central skeleton.

## Acknowledgements

The authors are grateful to Professor A. Kuczman for helpful discussions. We also wish to thank Keneth P. Chasse (math@velocet.ca), Graydon Hoare (graydon@pobox.com) and Velocet Communications for database management, network support, software

Table 5

Amounts of lycopene in various substances and the percentages of *trans*- and *cis*-isomers present

	Total lycopene <sup>a</sup>	% <i>trans</i> (of total)	% <i>cis</i> (of total)
Raw tomato	233.58 ± 2.98 μM	89.70	10.30
Tomato juice	189.25 ± 1.12 μM	90.62	9.38
Heated tomato juice	178.08 μM	71.94	28.06
Human serum	422.1 ± 22.9 nM	32.37	67.63
Rat serum	36.41 ± 5.62 nM	37.74	62.26
Rat prostate	316.66 ± 55.88 nM	33.38	66.62

<sup>a</sup> Consider the density of animal and plant tissues as 1, MW of lycopene as 536.85.

and distributive processing development. A special thanks is also extended to Andrew M. Chasse (fixy@fixy.org) for his continuing and ongoing development of novel scripting and coding techniques, helping to bring about a reduction in the necessary number of CPU cycles for each computations.

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