



Ab initio-MO Study of Route-Map to Biosynthesis of Bicyclomonoterpenes

MAHBOUBEH TAHERKHANI

Department of Chemistry, Takestan Branch, Islamic Azad University, Takestan, Iran

Corresponding author: Tel: +98 912 5039918; E-mail: mah.taherkhani@tiau.ac.ir, mahtaherkhani@yahoo.com

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The biogeneses of cyclic terpenes are usually assumed to involve classical and non-classical carbocation intermediates resulting from dissociation of the geranylpyrophosphate **1**. Formation of carbocations and consequent rearrangements and formation of stereoisomers, explain the cyclization to several cyclic monoterpenes. To study the route map of biosynthesis as well as synthesis of bicycle-monoterpenes from geranylpyrophosphate **1**, possible intermediates and bicycle-products were designed. Afterwards *ab initio* calculations were carried out at HF/6-31G** level of theory using Gaussian software. The results indicated that among cyclic carbocations, classical carbocation **7** was the most stable isomer. However the non-classical carbocation **5** was the least stable one. In regard with studied bicyclo-monoterpenes, **24** was more unstable (21.36 kcal/mol) than **26**. The results indicated that among products, the fenchane **26** was the most stable isomer; however the pynene type **24** was the least stable one. The results indicated that kinetic considerations control the outcome of reaction and thermodynamic rules have less roll in route map of biosynthesis.

Key Words: *Ab initio* calculations, Bicyclomonoterpenes, Biosynthesis.

INTRODUCTION

The biological and ecochemical functions of terpenes have not yet been fully investigated. Many plants produce volatile terpenes in order to attract specific insects for pollination or otherwise to expel certain animals using these plants as food. Less volatile but strongly bitter-tasting or toxic terpenes also protect some plants from being eaten by animals (antifeedants). Last, but not least, terpenes play an important role as signal compounds and growth regulators (phytohormones) of plants, as shown by preliminary investigations.

EXPERIMENTAL

Biosynthetic pathways

Isoprene rule: The earliest attempt to rationalize the pattern of structures of the monoterpenes was the rule proposed by Wallach in 1887 who envisaged such compounds to be constructed from isoprene units **a**. Some 30 years later, Robinson extended this isoprene rule by pointing out that in monoterpenes and such higher terpenes as were then known, the units were almost invariably linked in a head-to-tail fashion as shown for limonene **b** and camphor **c**. However, many higher terpenes and a few monoterpenes were later found not to obey this amended rule and Ruzicka and his collaborators proposed¹, a biogenetic isoprene rule¹ (Fig. 1).

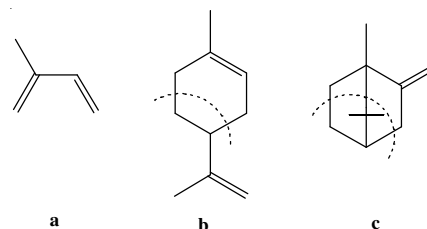


Fig. 1. Isoprene rule

Bicyclimonoterpenes (BCMT) are an important class of terpenes which, bicyclic cyclopropanes carane and thujane, bicyclic cyclobutane pinane and bicyclo[2.2.1]heptanes such as caphane, isocamphane and fenchane are the most important skeletons of naturally occurring bicyclic monoterpenes.

The biogeneses of cyclic and polycyclic terpenes are usually assumed to involve intermediate carbenium ions, but evidence for this *in vivo* was given only in some specific cases. In the simple case of monocyclic monoterpenes such as limonene the allylic cation remaining after separation of the pyrophosphate anion cyclizes to a cyclohexyl cation, which is deprotonated to (R)- or (S)-limonene (Fig. 2). After dissociation of the pyrophosphate anion, the remaining acyclic cation undergoes a 1,3-sigmatropic hydrogen shift and thereby cyclizes to a monocyclic carbenium ion which, itself, isomerises to the ionic precursor of another skeleton.

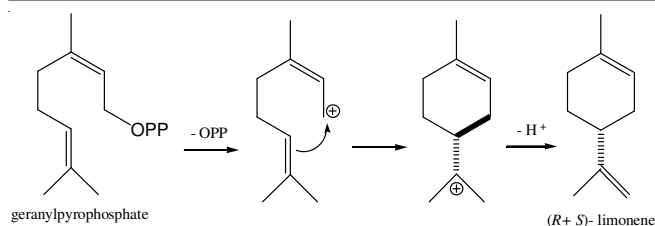


Fig. 2. Biogenesis of (R+ S)- limonene from geranylpyrophosphate

Ab initio calculation by HF method of 6-31g** level of theory were carried out for bicyclomonoterpenes as well as their cationic intermediate. It is well known that precursors of terpenes is geranylpyrophosphate. this compound produces geranyl carbocation that it can isomerises and rearrangement to other chain, monocyclic and bicyclic carbocations. Within biosynthetic route to terpenes, some of them convert to bicyclomonoterpenes. Bicyclomonoterpenes (BCMT) are an important class of terpenes, which Bicyclic cyclopropanes carane and thujane, bicyclic cyclobutane pinane and bicyclo[2.2.1]heptanes such as camphene, isocamphane and fenchane are the most important skeletons of naturally occurring bicyclic monoterpenes.

Computational methods: In this investigation possible isomers of bicyclomonoterpenes and their intermediate were designed and their structures were optimized without any restrictions at HF/6-31g** level using Gaussian 98 program. Considering zero point energy (ZPE) and heat of formations (HF) including zero point energies carried out for all isomers. Relative energy E_{rel} (kcal/mol) for all isomers calculated are given in Tables 1 and 2.

TABLE-1
CALCULATED HEATS OF FORMATIONS AND ZERO-POINT VIBRATIONAL ENERGIES (HARTREE), ZERO-POINT CORRECTION AND RELATIVE ENERGIES (INCLUDING ZERO-POINT ENERGY, kcal/mol) FOR DIPHOSPECINES FOR CARBOCATIONS. (HF/6-31G** Opt Freq)

Structure	HF (hartree)	ZPE (hartree)	ZPC (hartree)	E_{rel} (Kcal/mol)
1	-388.322547	-388.063482	0.2359066	15.86
2	-388.3237951	-388.064409	0.276103	15.28
3	-388.3176741	-388.055280	0.262394	21.01
4	-388.341998	-388.080276	0.261722	5.32
5	-388.3008449	-388.041625	0.259219	29.57
6	-388.305353	-388.044439	0.260914	27.81
7	-388.3534294	-388.08876	0.264669	0
8	-388.3451859	-388.085881	0.261449	1.81
9	-388.3392642	-388.077324	0.261941	7.17
10	-388.3407983	-388.078814	0.261985	6.24
11	-388.3321631	-388.068353	0.263810	12.80
12	-388.33686	-388.07278	0.264079	10.02
13	-388.3494832	-388.087034	0.262449	1.08
14	-388.3268398	-388.065103	0.261737	14.84
15	-388.3394933	-388.076694	0.262800	7.57
16	-388.33105	-388.066653	0.264397	13.87

RESULTS AND DISCUSSION

The nonclassical version of the intermediate carbenium ion (also referred to as a carbonium ion) resulting upon dissociation of the pyrophosphate anion from geranylpyrophosphate explains the cyclization to several cyclic carbenium ions, as

TABLE-2
CALCULATED HEATS OF FORMATIONS AND ZERO-POINT VIBRATIONAL ENERGIES (HARTREE), ZERO-POINT CORRECTION AND RELATIVE ENERGIES (INCLUDING ZERO-POINT ENERGY, kcal/mol) FOR DIPHOSPECINES FOR PRODUCTS (HF/6-31G** OPT FREQ)

Structure	HF (hartree)	ZPE (hartree)	ZPC (hartree)	E_{rel} (Kcal/mol)
17	-389.1867389	-388.908538	0.278201	2.64
18	-389.1833966	-388.904693	0.278703	5.05
19	-389.1828475	-388.904092	0.278756	5.43
20	-389.1682112	-388.892108	0.276103	12.95
21	-389.1673184	-388.891123	0.276195	13.57
22	-389.166914	-388.890083	0.276831	14.22
23	-389.1666438	-388.889802	0.276841	14.39
24	-389.1565713	-388.878703	0.277868	21.36
25	-389.1610238	-388.883203	0.277821	18.53
26	-389.1905586	-388.912749	0.277810	0.00

demonstrated for some monoterpenes². (Fig. 3) Additional diversity arises from 1,2-hydride and 1,2-alkyl shifts (Wagner-Meerwein rearrangements) and sigmatropic reactions (cope rearrangements) on the one hand and on the other hand from the formation of diastereomers and enantiomers provided that the cyclizations generate new asymmetric carbon atoms (Fig. 3).

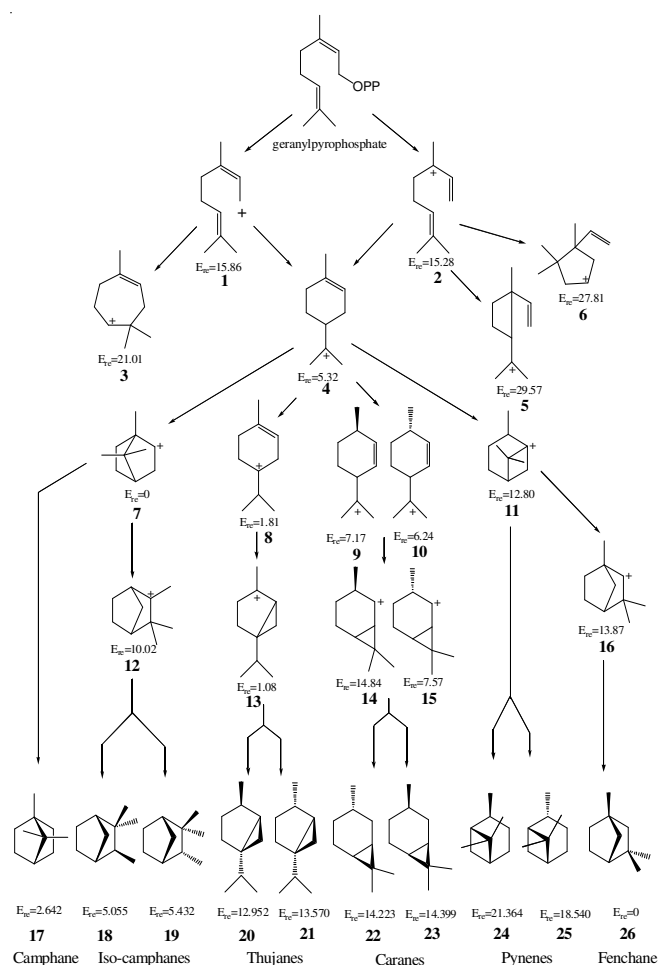
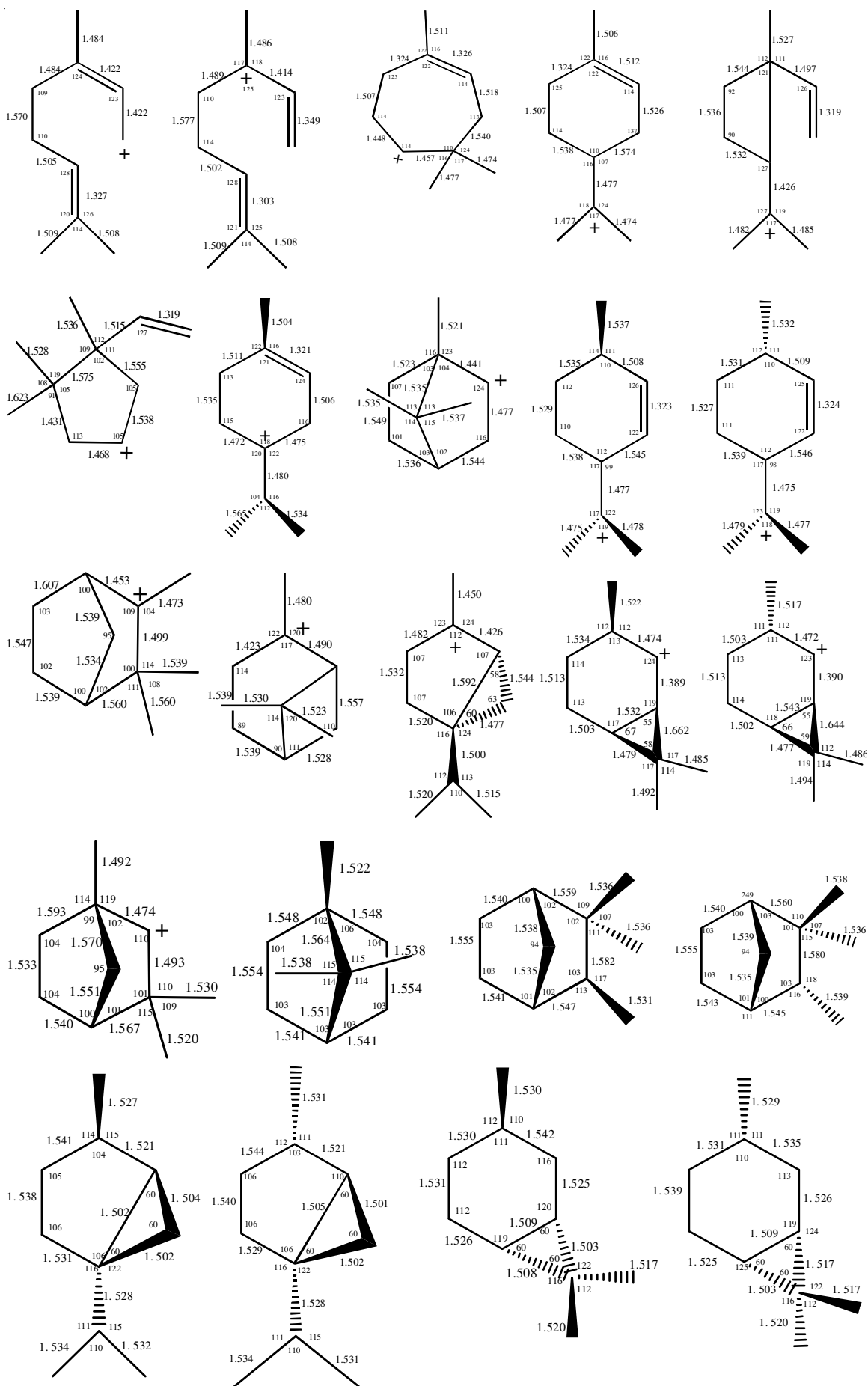
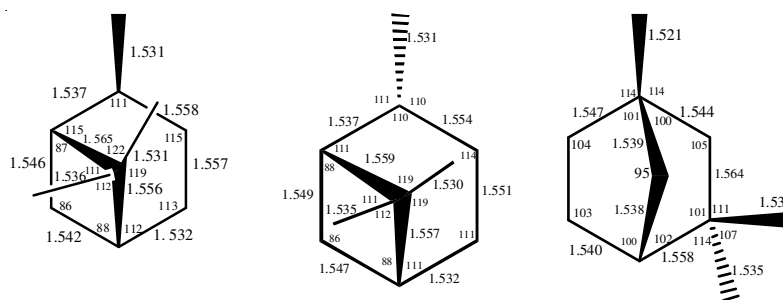


Fig. 3. Biogenesis of bicyclic monoterpenes from geranylpyrophosphate

MO calculation at the 6-31G** level indicated that among cyclic carbocations, classical carbocation 7 was the most stable isomer. In contrast, the non-classical carbocation 5 was the





Scheme-I HF/6-31G** optimized bond lengths (Å) and bond angles (°). Optimized structures are not planar

least stable one. In regard with studied bicyclo-monoterpenes, **24** was more unstable (21.36 kcal/mol) than **26**. Table-1 presents data on relative energy of carbocations. The sequence of stability for carbocations were $7 > 13 > 8 > 4 > 10 > 9 > 15 > 12 > 11 > 16 > 14 > 2 > 1 > 3 > 6 > 5$.

On the other hand, the results indicated that among products, the fenchane **26** was the most stable isomer. However the pyrene type **24** was the least stable one. The results indicated that kinetic considerations control the outcome of reaction and thermodynamic rules have less roll in route map of biosynthesis. The sequence of stability for carbocations were $26 > 17 > 18 > 19 > 20 > 21 > 22 > 23 > 25 > 24$.

Calculations

Semiempirical calculations were carried out using AM1 method [*]. Energy minimum geometries were located by energy minimizing, with respect to all geometrical coordinates and without imposing any symmetry constrains. The AM1 results were used as input for the *ab initio* calculations, which were carried out³ using Gaussian 98 at the HF/6-31G** level of theory for geometry optimization calculations. Vibrational frequencies were calculated at 6-31 G** level for all geom-

etries, which were confirmed to have zero imaginary frequency. The frequencies were scaled by a factor of 0.9135 for HF method and used for computation of the zero-point vibrational energies⁴. NBO calculations were carried out on optimized structures at HF/6-31G** level [***] (**Scheme-I**).

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