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The conformation of levopimaric acid investigated by high-level ab initio MO calculations. Possibility of the CH/π hydrogen bond☆

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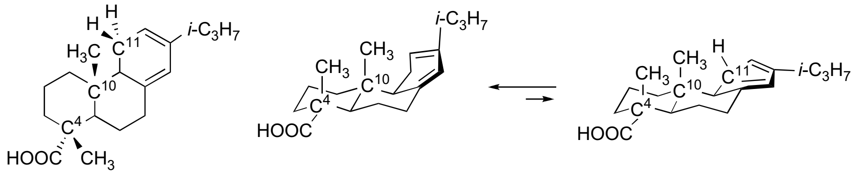
ABSTRACT

Ab initio MO calculations were carried out, at the MP2/6-311G(d,p) level of approximation, to investigate the conformation of levopimaric acid. It has been found that the folded conformation is more stable than the extended conformation. The result is consistent with the documented experimental data. The reason for the relative stability of the folded conformation has been sought in the context of the CH/π hydrogen bond. Short non-bond distances have been disclosed between CHs in the 10β angular methyl group and sp^2 carbons of the conjugated diene ring in the more stable folded conformers of model compounds. We suggest that the folded conformation of levopimaric acid is a consequence of an attractive molecular force, the CH/π hydrogen bond.

1. Introduction

Levopimaric ($\Delta^{6,8(14)}$-abietadienoic) acid **1** has long been known to exist, in solution, in the unusual folded conformation **1a**, as opposed to the extended conformation **1b** (Scheme 1).[1] In 1972, the crystal conformation of **1** was shown to be similar to that found in solution.[2] To accommodate the relative stability of the folded conformation, Burgstahler and co-workers once postulated the possibility of an attractive interaction between the 10β angular methyl group in **1a** and the conjugated diene moiety. However, the same authors superseded this explanation by another one, based on the relief of repulsion between the 10β-methyl group and the 11β-hydrogen in **1b**; the buttressing effect by the C4β methyl group might enhance the effect.[3]

The explanation based on the relief of steric repulsion between the 10β-methyl group and 11β-hydrogen seemed reasonable. We, however, thought that the above folded conformation of **1** may be a consequence of the CH/π interaction;[4] this molecular force is a weak hydrogen bond occurring between a CH (soft acid) and a π-group (soft base).[5] In the present case, the stabilizing interaction may occur between CHs of the 10β-methyl group and the conjugated π-system in the cyclohexadiene ring. To test this possibility, we examined the conformation of **1** by the high-level ab initio MO method. We suggest that the seemingly peculiar molecular



1 **1a** (folded) **1b** (extended)

Scheme 1. Conformational equilibrium of levopimaric acid **1**.

☆ A comprehensive literature list for the CH/π hydrogen bond is available on the website http://www.tim.hi-ho.ne.jp/dionisio.

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structure **1a** (in view of the usual stereochemical considerations) is attributed to CH/π hydrogen bonds occurring between the 10β angular methyl group and the π-system. This is important since the implication of the present result will extend to conformational and chiroptical problems of many terpenic and steroidal dienes.[6–11]

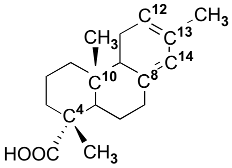
2. Method

The Gaussian 03 program[12] was used. Electron correlation energies were calculated by applying the second order Møller-Plesset (MP2) perturbation theory. The geometry of the model compounds was optimized at the MP2/6-311G(d,p) level of approximation. Using these geometries, single point calculations were performed, at the same level, to estimate the energy of the conformers. Vibrational frequencies were calculated using the analytical second derivatives at the same level of the geometry optimization for each conformer. Using these results, the thermal energy corrections were added to the total Gibbs free energy at 298.15 K and 1 atm of pressure.

3. Results and discussion

3.1. Conformation of levopimaric acid 1

Since **1** is too large in performing high-level calculations, a simpler structure **2** (13-methyl, instead of isopropyl in **1**) was calculated.



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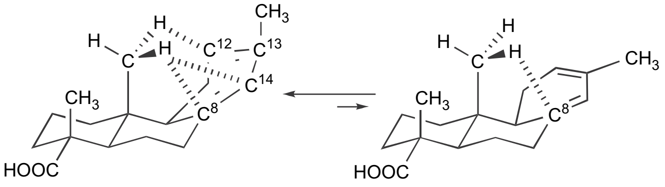


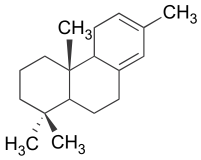
2a **2b**

Scheme 2. CH/π hydrogen bonds in folded **2a** and extended **2b** conformation.

A folded conformation **2a** has been found to be more stable, by 3.32 kcal mol^{-1}, than the extended conformation **2b**. In **2a**, the torsion angle τ defined by C^8–C^{14}–C^{13}–C^{12} has been found to be −10.4°. This compares with the experimental values (−9.1°, −11.8°) reported for the molecules of **1** in the crystalline state.[13] Short CH/π distances, 2.67, 2.84, 3.13, and 2.65 Å, respectively, to C^8, C^{14}, C^{13}, and C^{12} have been noted between hydrogen atoms of the 10β-methyl group and sp^2 carbons in the conjugated diene [Scheme 2 and Fig. 1a].

In the less stable extended conformation **2b** (τ +11.1°), a short CH/π distance, 2.61 Å, has only been noted between a hydrogen atom of the 10β-methyl group and C^8. The distance between one of the hydrogen atoms in 10β-methyl group and 11β-hydrogen is 2.07 Å [Fig. 1b].

To see the effect of simplification of the structure, we calculated model structures **3**, **4**, and **5**. Table 1 compares the results. In Table 2, the interatomic distances between H (in 10β-CH_3) and C^8, C^{14}, C^{13}, and C^{12} are given.



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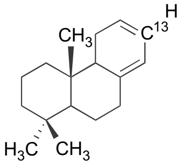

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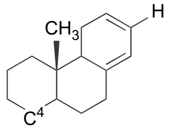

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Table 1
Relative conformational Gibbs energies $\Delta G_{folded-extended}$ (kcal mol^{-1}) of **2**, **3**, **4**, and **5**. In the parentheses are the torsion angle (°) defined by the atomic sequence C^8–C^{14}–C^{13}–C^{12}

	2	3	4	5
Folded	−3.32 (−10.4)	−1.69 (−10.6)	−2.56 (−9.8)	−2.33 (−10.2)
Extended	0 (+11.1)	0 (+11.3)	0 (+10.4)	0 (+9.8)

Table 2
Interatomic distances (Å) between C–H (in 10β-CH_3) and C^8, C^{14}, C^{13}, and C^{12}

	2	3	4	5
Folded	2.67, 2.84, 3.13, 2.65	2.65, 2.80, 3.09, 2.69	2.65, 2.81, 3.09, 2.71	2.61, 2.72, 2.94, 2.85
Extended	2.61, 3.32, 4.04, 3.98	2.61, 3.32, 4.05, 3.99	2.61, 3.32, 4.03, 3.98	2.63, 3.33, 4.02, 3.98

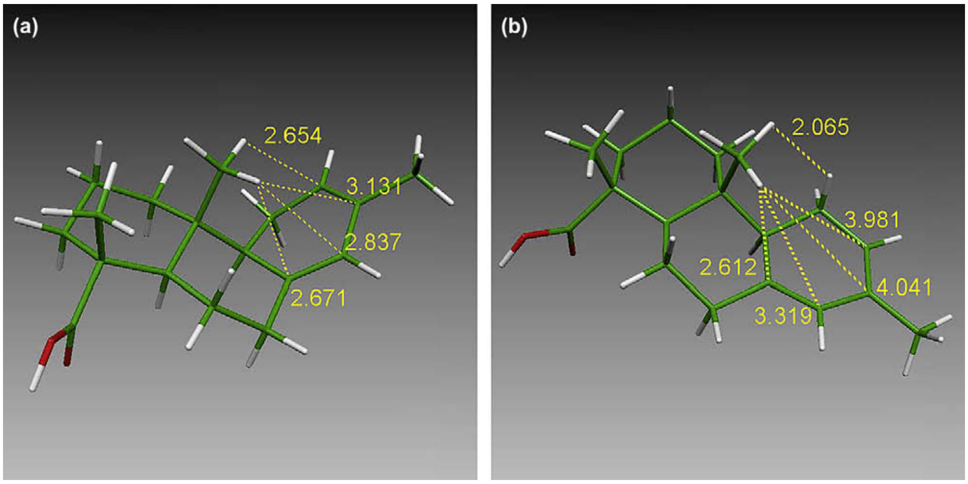


Figure 1. Conformation of **2**, suggested by the MP2/6-311G(d,p) level of optimization. (a) More stable, folded conformation **2a**. (b) Less stable, extended conformation **2b**.

Table 3
Relative conformational Gibbs energies $\Delta G_{\text{folded-extended}}$ (kcal mol^{-1}) of 9α-methyl **6**, 9α,10β-dimethyl **7**, and 9,10-nor compound **8**. In the parentheses are the torsion angle τ (°) defined by the atomic sequence C^8–C^{14}–C^{13}–C^{12}

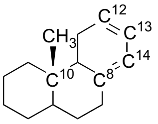
	5	6	7	8
Folded	−2.33 (−10.2)	1.90 (−12.2)	0.89 (−7.8)	0.31 (−12.5)
Extended	0 (+9.8)	0 (+14.4)	0 (+12.0)	0 (+15.6)

Table 4
Short CH/π distances (Å) disclosed in model structures **6** and **7** between C–H and sp^2 carbons

6a (negative τ)	10β-CH_3	
6b (positive τ)	9α-CH_3	2.97 (C^{12}), 2.96 (C^{13}), 2.81 (C^{14})
7a (negative τ)	10β-CH_3	2.57 (C^8), 2.68 (C^{14}), 2.82 (C^{13}), 2.78 (C^{12})
7b (positive τ)	9α-CH_3	2.76 (C^{12}), 2.97 (C^{13}), 2.99 (C^{14})

Replacement of COOH by CH_3 (**3**) decreased, though not significantly, the relative stability of the folded conformation $\Delta G_{\text{folded-extended}}$ (3.32–1.69=1.63 kcal mol^{-1}), while the geometric parameters remained almost unchanged. Deletion of the methyl groups at C^{13} (**4**) and C^4 (**5**) did not appreciably affect the computational output; the so-called buttressing effect by the C4β methyl group seems to give little effect on the relative stability of the conformations. Therefore, one must seek another reason for the relative stability of the folded conformation of **1**–**5**. We hypothesized that this is a consequence of the attractive CH/π hydrogen bonds, which may occur between the 10β-methyl group and the conjugated diene moiety.

To investigate the importance of the 10β angular methyl group in stabilizing the folded conformation of **1**–**5**, we calculated the conformational energy of 9α-methyl compound **6**, 9α,10β-dimethyl compound **7**, and 9,10-nor compound **8**. Table 3 compares the results. It is remarkable that, in 9α-methyl compound **6**, the extended conformation (**6b**, τ +14.4°) is more stable, by 1.90 kcal mol^{-1}, than the folded one (**6a**, τ −12.2°); this is contrary to the results obtained for 10β-methyl compounds **1**–**5**. Table 4 lists the short CH/π distances disclosed in model structures **6** and **7**. The distances from CH(9α-CH_3) to sp^2 carbons (2.97, 2.96, and 2.81 Å, respectively, for C^{12}, C^{13}, and C^{14} in **6b**, 2.76, 2.97, and 2.99 Å in **7b**) are somewhat longer than those estimated for the folded conformation of **2** (2.67–2.84 Å). Being consistent with this effect, the difference in the conformational Gibbs energy $\Delta G_{\text{folded-extended}}$ of **5** (−2.33 kcal mol^{-1}) is larger than that of **6** (+1.90), though slightly. We think this to reflect the contribution of CH/π hydrogen bonds.



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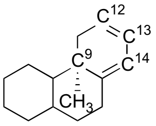

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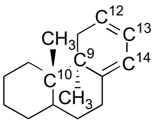

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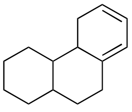

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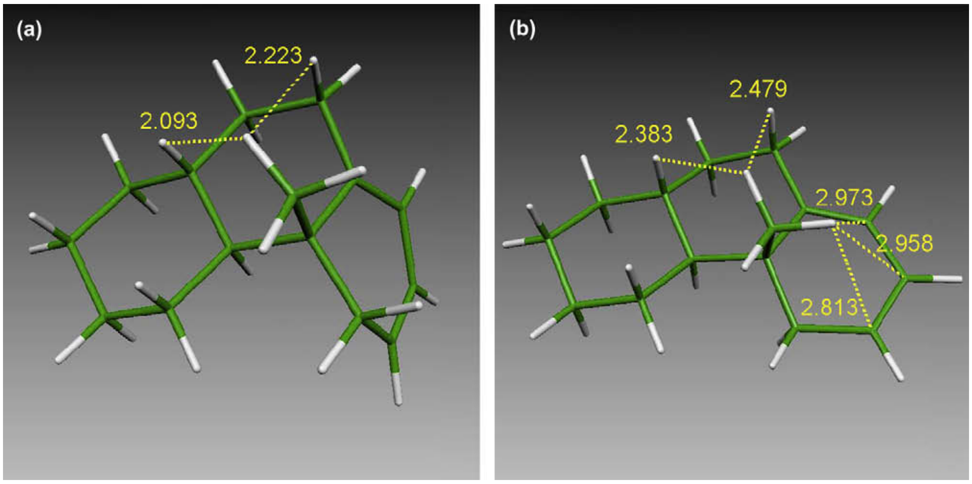


Figure 2. Calculated conformations of the 9-methyl compound **6**. (a) **6a** and (b) **6b**.

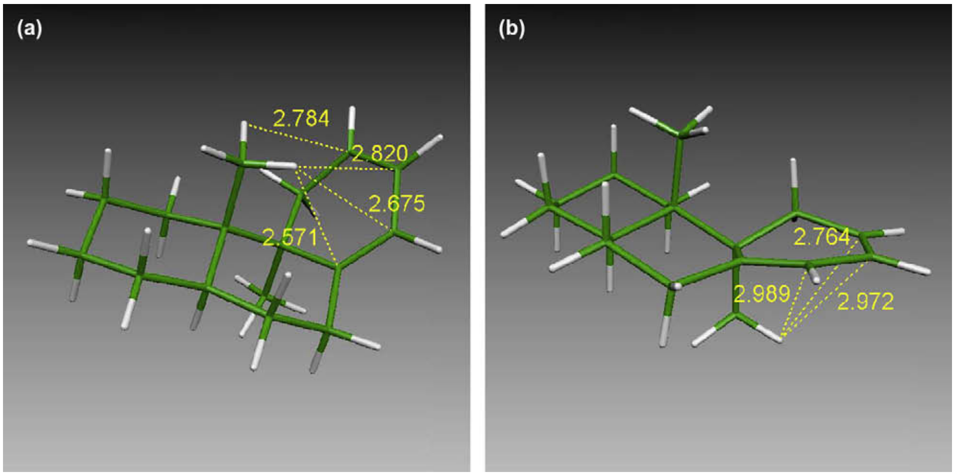
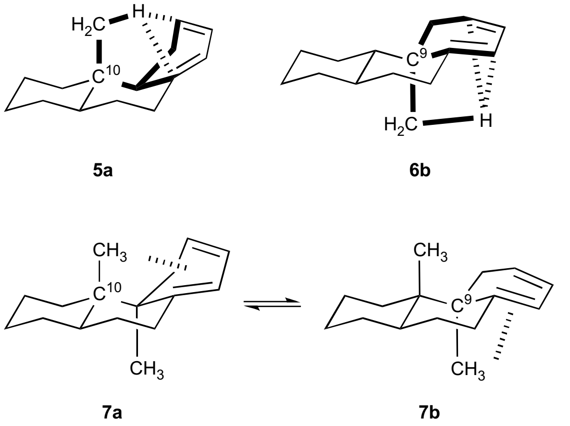


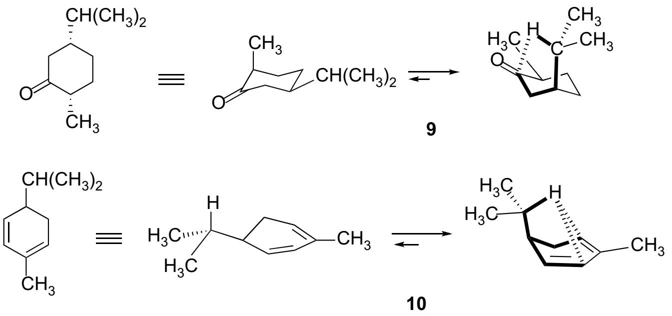
Figure 3. Calculated conformations of the 9,10-dimethyl compound **7**. (a) **7a** and (b) **7b**.



5a **6b**

7a **7b**

Scheme 3. CH/π hydrogen bonds suggested for 10β-methyl **5**, 9α-methyl **6**, and 9α,10β-dimethyl compound **7**. Notice that in the more stable conformation of **5** (**5a**) and **6** (**6b**), formation of five-membered CH/π hydrogen bonds (intensified) is possible.



9

10

Scheme 4. Experimental and calculated conformational equilibria of isocarvomenthone **9** and α-phellandrene **10**. Five-membered CH/π hydrogen bonds are intensified.

Figure 2 illustrates the conformations of 9α-methyl compound **6**. Notice that, in **6b**, CH/π hydrogen bonds may occur from the other side of the molecular plane, while such an interaction is absent in **6a**. The extended conformation **6b** is more stable than **6a**, accordingly.[†]

Figure 3 shows the conformation of 9α,10β-dimethyl compound **7**. In **7a** (τ −7.8°) and **7b** (τ +12.0°), the interaction of 10β-Me and 9α-Me groups occurs from the opposite sides of the molecular plane. The difference in the conformational energy $\Delta G_{\text{folded-extended}}$ becomes smaller ($0.89\ \text{kcal mol}^{-1}$), accordingly. Scheme 3 illustrates this. CH/π hydrogen bonds do not occur in compound **8**; $\Delta G_{\text{folded-extended}}$ is insignificant in this case ($0.31\ \text{kcal mol}^{-1}$). This also is reasonable.

The present result is consistent with our recent findings that the folded conformation of isocarvomenthone **9**[14] and α-phellandrene **10**[15] is stabilized by five-membered CH/π hydrogen bonds (Scheme 4).

4. Conclusions

Ab initio MO calculations were carried out, at the MP2/6-311G(d,p) level, to investigate the conformation of model compounds of levopimaric acid **1**. In agreement with the documented crystallographic and spectroscopic data, **1** has been suggested to exist in the folded conformation. Short non-bond distances have in fact been disclosed, in the stable conformers of model compounds **2**–**5**, between a CH in the 10β methyl group and sp^2 carbons of the conjugated diene ring. We conclude that the stability of the folded conformation of levopimaric acid is attributed to an attractive molecular force, the CH/π hydrogen bond.

Acknowledgements

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Supplementary data

Atomic coordinates of **3** and **4** calculated at the MP2/6-311G(d,p) level of approximation are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.02.014.

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[†] The distances from hydrogen of the 9α-methyl group to the hydrogens at the 1,3-diaxial positions are 2.09 and 2.22 Å in **6a**, and 2.38 and 2.48 Å in **6b**. The larger H/H distances in **6b** may be a consequence of CH/π hydrogen bonds (see Fig. 2b). In **6a**, unfavorable 1,3-diaxial interactions may play some role in destabilizing this conformation.