Origin of the Axial-Alkyl Preference of (*R*)-α-Phellandrene and Related Compounds Investigated by High-Level Ab Initio MO Calculations. Importance of the CH/π Hydrogen Bond[#]

Osamu Takahashi,[*,a] **Katsuyoshi Yamasaki,**[a] **Yuji Kohno,**[*,b] **Kazuyoshi Ueda,**[b] **Hiroko Suezawa**[c] **and Motohiro Nishio**[*,d]

[a] *Department of Chemistry, Graduate School of Science, Hiroshima University, Kagamiyama, Higashi-Hiroshima-shi, 739-8526 Japan.*
[b] *Department of Materials Chemistry, Graduate School of Engineering, Yokohama National University, 79-5 Tokiwadai, Hodogaya-ku, Yokohama, 240-8501 Japan.*
[c] *Ministry of Education, Culture, Sports, Science and Technology, Kasumigaseki, Chiyoda-ku, Tokyo, Japan*
[d] *The CHPI Institute, 705-6-338 Minamioya, Machida-shi, Tokyo, 194-0031 Japan.*

Abstract

Ab initio MO calculations were carried out, at the MP2/6-311++G(d,p)//MP2/6-311G(d,p) level, to investigate the Gibbs energy of conformational isomers of (*R*)-α-phellandrene and related 5-alkyl-1,3-cyclohexadienes. It has been found that the conformer bearing the 5-alkyl group in axial orientation is more stable than the equatorial congener. The result is consistent with experimental evidence that the axial-isopropyl conformer prevails in the conformational equilibrium of α-phellandrene. The reason for the stability of the folded conformer has been sought in the context of the CH/π hydrogen bond. A number of short non-bond distances have been disclosed in the axial conformers, between CHs in the 5-alkyl group and sp2-carbons of the cyclohexadiene ring. The helical sense of the conjugated dienes in the axial conformers has been shown to be left-handed, whereas that of the equatorial conformers is right-handed. We suggest that the stability of the folded conformation often observed in conjugated diene compounds of natural origin, such as α-phellandrene and levopimaric acid, is attributed to an attractive molecular force, the CH/π hydrogen bond.

1. Introduction

[#] A comprehensive literature list for the CH/π hydrogen bond is available on the following website. http://www.tim.hi-ho.ne.jp/dionisio
[*] Corresponding authors. Tel.: +81 82 424 7497; fax: +81 82 424 0727. E-mail addresses: shu@hiroshima-u.ac.jp (O. Takahashi), kohnoy@ynu.ac.jp (Y. Kohno), dionisio@tim.hi-ho.ne.jp (M. Nishio).

Understanding of the factors influencing the relative stability of substituted cyclohexanes has long been a subject of controversy in stereochemistry. The difference in the conformational Gibbs energies between axial- and equatorial-alkyl cyclohexanes ($\Delta G_{ax\text{-}eq}$) is 1.74, 1.79, 2.21 and 4.7 kcal mol^{-1}, respectively, for methyl, ethyl, isopropyl and *t*-butyl cyclohexane.[1] These numbers are referred to as the *A*-values, though there are variations depending on the experimental condition.

The above *A*-values, however, are valid only for the saturated cyclohexane system. For instance, shifts in the equilibrium have been reported for structurally related carbonyl compounds.[2] Namely, the axial conformers in 2-alkyl[3,4,5] and 3-alkyl cyclohexanones[6] are relatively favored as compared to those in alkyl cyclohexanes. This is known as the alkylketone effect. The alkylketone effect is important in stereochemistry since implication of this effect extends to conformational problems of terpenic ketones such as isomenthone (*cis*-2-isopropyl-5-methylcyclohexanone) **1** and isocarvomenthone (*cis*-2-methyl-5-isopropylcyclohexanone) **2**. For isomenthone, the axial-isopropyl conformation (ae-**1**) has been reported to be an important contributor in the equilibrium (Scheme 1a). For isocarvomenthone, it has been shown that the isopropyl-axial conformer (ae-**2**) prevails in the equilibrium (Scheme 1b).[7]

(a)

ae-**1**   ea-2

(b)

ae-**2**   ea-**2**
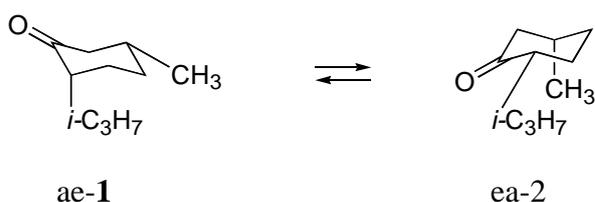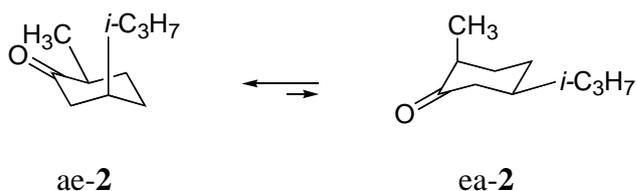
Scheme 1. Conformational equilibrium of (a) isomenthone **1** and (b) isocarvomenthone **2**.

The above results are remarkable in view of the severe "steric constraint" expected in the axial-alkyl conformer of these compounds. Effort has since been made by many workers to explore the origin of this phenomenon. The earlier interpretations were based, basically, on the relief of a 1,3-diaxial repulsion, which may be brought about by replacing a methylene group of cyclohexane with a carbonyl group. Thus, replacement of a CH$_2$ by a C=O group might stabilize the axial alkyl substituent, relative to the equatorial conformation.

In a previous paper, we presented another interpretation for the alkylketone effect. Thus, the difference in the conformational Gibbs energy ($\Delta G_{ax\text{-}eq}$) was estimated, by high-level ab initio MO calculations, for 2- and 3-alkylcyclohexanones, isomenthone **1** and isocarvomenthone **2**.[8] The $\Delta G_{ax\text{-}eq}$ values have been found much smaller than the corresponding data of saturated cyclohexanes. In every axial alkyl conformer, short interatomic distances have been noted between a CH hydrogen of the alkyl group and the carbonyl carbon atom. Figure 1 illustrates this, schematically, for **1** and **2**. The proportion of the axial-isopropyl conformer in the equilibrium has been estimated to be more than 50% and 75%, respectively, for **1** and **2**; the computed result is consistent with documented experimental data.[9]

ax-*i*-Pr-**1**   ax-*i*-Pr-**2**
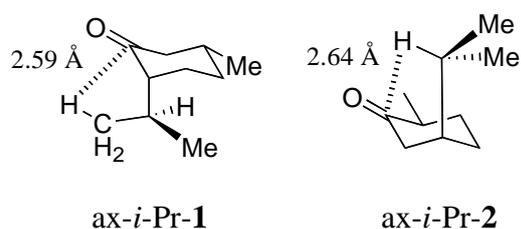
Figure 1. Short CH/C=O distances disclosed in a stable conformer (axial-isopropyl and equatorial-methyl) of isomenthone **1** and isocarvomenthone **2**.

In view of the above finding, we concluded that the relative stability of the axial alkyl groups in alkyl cyclohexanones is a consequence of an attractive molecular force, the CH/π hydrogen bond.[10,11,12] The CH/π hydrogen bond is a weak molecular force occurring between a CH (soft acid) and a π-group (soft base). There, the stabilizing interaction occurs between a CH of the alkyl group and the carbonyl π-system in the cyclohexanone ring.

With respect to unsaturated cyclohexane systems such as 5-alkyl-1,3-cyclohexadienes, it has been known that an appreciable concentration of a conformer with a quasi-axial 5-alkyl group exists in the conformational equilibrium (Scheme 2).
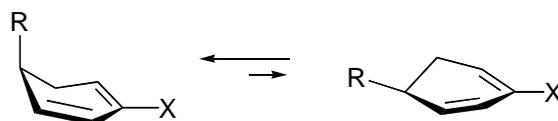
Scheme 2. Conformational equilibrium of 1,3-cyclohexadienes

For instance, in α-phellandrene, (*R*)-(-)-5-isopropyl-2-methyl-1,3-cyclohexadiene (**3**, R = *i*-C$_3$H$_7$), the conformer bearing a quasi-axial isopropyl group has been reported to prevail in solution[13,14,15] (Scheme 3). The genesis of the stability of the axial conformation remained unexplained, however.

axial-i-C$_3$H$_7$ equatorial-i-C$_3$H$_7$

Scheme 3. Conformational equilibrium of α-phellandrene

Herein, we present our interpretation that the above peculiar phenomenon (in view of the usual stereochemical considerations) is a consequence of the CH/π hydrogen bond, which occurs between CHs of the alkyl group and the conjugated diene moiety. This suggestion is important since the implication of this effect will extend to the stereochemical problem of terpenic and steroidal dienes, including levopimaric acid and cholesta-2,4-diene.

2. Method

The Gaussian 03 program[16] was used. Electron correlation energies were calculated by applying the second order Møller-Plesset (MP2) perturbation theory. The geometry of axial and equatorial conformers was optimized at the MP2/6-311G(d,p) level of approximation. Using these geometries, single point calculations were performed, at the MP2/6-311++G(d,p) 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 atmosphere of pressure.

3. Results and Discussion

3.1. Conformational Equilibrium of 1,3-Cyclohexadienes

Table 1 summarizes the relative Gibbs energies (G_{rel}) and abundance of the conformational isomers of 5-alkyl-1,3-cyclohexadienes **3** (X = CH$_3$) and **4** (X = H). Three axial and equatorial conformers were found when R = C$_2$H$_5$ and i-C$_3$H$_7$. The difference in the conformational energies (ΔG_{ax-eq}) for the ethyl and isopropyl compounds was calculated, therefore, by taking account of the abundance of all the conformers.

Table 1. Relative Gibbs free energies (G_{rel} in kcal mol^{-1}) and abundance (%) of the conformational isomers of 1,3-cyclohexadienes

R	**3** (X = CH$_3$)		**4** (X = H)	
	G_{rel}	abundance	G_{rel}	abundance

ax-CH$_3$	0.00	*53.0*	0.02	*49.4*
eq-CH$_3$	0.07	*47.0*	0.00	*50.6*
$\Delta G_{\text{ax-eq}}$ [a]	-0.07		0.02	
ax-C$_2$H$_5$(1)	0.00	30.6	0.00	28.1
ax-C$_2$H$_5$(2)	0.06	27.6	0.09	24.1
ax-C$_2$H$_5$(3)	0.98	5.8	0.70	8.7
		64.0 [b]		*60.9* [b]
eq-C$_2$H$_5$(1)	0.40	15.6	0.32	16.3
eq-C$_2$H$_5$(2)	0.46	14.0	0.36	15.3
eq-C$_2$H$_5$(3)	0.93	6.4	0.78	7.5
		36.0 [b]		*39.1* [b]
$\Delta G_{\text{ax-eq}}$ [c]	-0.34 [c]		-0.26 [c]	
ax-i-C$_3$H$_7$(1)	0.00	57.2	0.00	54.4
ax-i-C$_3$H$_7$(2)	0.70	17.5	0.81	13.8
ax-i-C$_3$H$_7$(3)	0.80	14.9	0.90	11.9
		89.6 [b]		*80.1* [b]
eq-i-C$_3$H$_7$(1)	1.55	4.2	1.12	8.3
eq-i-C$_3$H$_7$(2)	1.59	3.9	1.16	7.6
eq-i-C$_3$H$_7$(3)	1.90	2.3	1.55	4.0
		10.4 [b]		*19.9* [b]
$\Delta G_{\text{ax-eq}}$ [a]	-1.27 [c]		-0.83 [c]	
ax-t-C$_4$H$_9$	0.00	*64.7*	0.06	*47.3*
eq-t-C$_4$H$_9$	0.36	*35.3*	0.0	*52.7*
$\Delta G_{\text{ax-eq}}$ [a]	-0.36		0.06	

[a] G_{ax} - G_{eq}
[b] Total abundance is given in italics.
[c] Calculated by taking account of the abundance of three axial and three equatorial conformers.

Table 1 reveals several interesting points. First, the proportion of the axial-alkyl conformer is larger in **3** (X = CH$_3$) than in **4** (X = H). We think this to reflect the difference in the π-density of the diene system. Introduction of a methyl group to position 2 might have increased the electron density of the conjugated π-system.

Second, it is noted that in every case, except for **4**, R = CH$_3$ and t-C$_4$H$_9$, the axial conformer is more stable (negative $\Delta G_{\text{ax-eq}}$) than the respective equatorial congener. The proportion of the axial-ethyl and axial-isopropyl conformer is rather high. Thus, the population of the axial conformer increases on going from R = methyl to ethyl and isopropyl, and then drops when R = t-butyl group: 53 æ 64 æ 90 æ 65% for **3** and 49 æ 61 æ 80 æ 47% for **4**. It is remarkable that the axial conformer prevails in the

equilibrium of the *t*-butyl derivative of **3**. The above result is in conflict with the general understanding that an increase of the bulkiness of a substituent will disfavor the axial conformation. We will discuss on this point later.

3.2. CH/C(π) Nonbond Distance

In view of the above results, we thought that an attractive molecular interaction, the CH/π hydrogen bond, plays a crucial role in bringing about the folded conformation of **3** and **4** stable. To test this idea, we examined the interatomic distance and angle parameters of relevant C-H and sp2-C in the conjugated diene moiety. Table 2 lists the results. Figure 2 illustrates the most stable axial conformers of **3**.
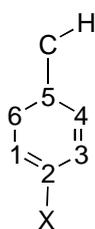
Table 2. Nonbond distances d and angles θ between CH hydrogens in the axial alkyl group and sp2-carbons of cyclohexa-1,3-dienes **3** and **4**

Table 2. Nonbond distances H-C(sp2) (d) and angles $\angle$C-H…C (θ) between CH hydrogens in the axial alkyl group and sp2-carbons of cyclohexa-1,3-dienes **3** and **4**.

R	d [a]	Ratio [b]	N [c]	θ [d]	d [a]	Ratio [b]	N [c]	θ [d]
	X = CH$_3$ **3**				X = H **4**			
CH$_3$	2.83 (C1)	53.0	5	96.6	2.84 (C1)	49.4	5	96.2
	3.01 (C2)		6	106.8	3.00 (C2)		6	106.2
	3.07 (C3)		5	90.3	3.07 (C3)		5	90.3
C$_2$H$_5$(1)	2.80 (C1)	30.6	5	98.0	2.74 (C1)	28.1	6	106.5
	2.97 (C2)		6	108.5	2.95 (C2)		7	106.4
	3.06 (C3)		5	91.7	2.85 (C3)		6	116.0
	2.73 (C4)		5	95.0	2.81 (C4)		5	96.9
C$_2$H$_5$(2)	2.81 (C1)	27.6	5	97.4	2.82 (C1)	24.1	5	97.1
	2.95 (C2)		6	108.9	2.95 (C2)		6	108.3
	3.01 (C3)		5	92.6	3.02 (C3)		5	92.6
C$_2$H$_5$(3)	2.72 (C1)	5.8	6	106.4	2.81 (C1)	8.7	5	97.6
	2.93 (C2)		7	106.6	2.97 (C2)		6	108.0
	2.84 (C3)		6	116.1	3.06 (C3)		5	91.7
	2.81 (C4)		5	97.0	2.72(C4)		5	95.0
i-C$_3$H$_7$(1)	2.80 (C1)	57.2	5	97.1	2.82 (C1)	54.4	5	96.8
	2.91 (C2)		6	110.4	2.91 (C2)		6	109.8
	2.98 (C3)		5	94.9	2.99 (C3)		5	94.7
i-C$_3$H$_7$(2)	2.67 (C1)	17.5	6	108.4	2.68 (C1)	13.8	6	108.5

	2.94 (C2)		7	105.1	2.96 (C2)		7	104.8
	2.85 (C3)		6	115.3	2.87 (C3)		6	115.2
	2.81 (C4)		5	97.1	2.81 (C4)		5	97.1
i-C_3H_7(3)	2.76 (C1)	14.9	6	103.5	2.77 (C1)	11.9	6	103.1
	2.85 (C2)		7	111.7	2.87 (C2)		7	111.5
	2.81 (C3)		6	118.7	2.83 (C3)		6	118.7
	2.80 (C4)		5	97.5	2.80 (C4)		5	97.4
t-C_4H_9	2.70 (C1)	64.7	6	105.1	2.71 (C1)	47.3	6	105.0
	2.85 (C2)		7	110.1	2.87 (C2)		7	110.0
	2.84 (C3)		6	118.0	2.85 (C3)		6	117.9
	2.82 (C4)		5	97.7	2.82 (C4)		5	97.7

[a] Nonbond distances (Å). In the parentheses is the carbon atom interacting with a C-H hydrogen (CH or CH_3).
[b] Abundance (%) of the rotamer.
[c] Number of atoms forming the shortest circle of the intramolecular CH/π hydrogen bond.
[d] C-H…C(sp2) angle (°)

Notice that a number of short CH/C(sp2) distances are found in every axial conformer. These values are, in most cases, shorter than the sum of the van der Waals radii (1.2 Å for H and 1.77 Å for sp2-C = 2.97 Å).[17,18] In many cases the number of atoms forming the CH/π hydrogen bond (N) is 5 or 6, but formation of 7-membered CH/π hydrogen bond seems possible. Table 2 also lists an angle parameter θ, defined by the C-H and an interacting sp2-carbon (C1, C2, C3, or C4). The angle θ falls between ca. 90-98° for N = 5, while this is ca. 103-119° for N = 6. This is comprehensible since most intramolecular weak hydrogen bonds (OH/π,[19,20,21] NH/π,[22] CH/O[23,24]) occur in such a range. From the above results we suggest that the axial conformation of **3** and **4** is stabilized by an attractive molecular force, the CH/π hydrogen bond.[25] The abundance of the axial-isopropyl conformer for α-phellandrene (89.6%) is understood in terms of the concurrent action of several CH/π hydrogen bonds [see Figures 2 (c), 2 (d), and 2 (e)].

8
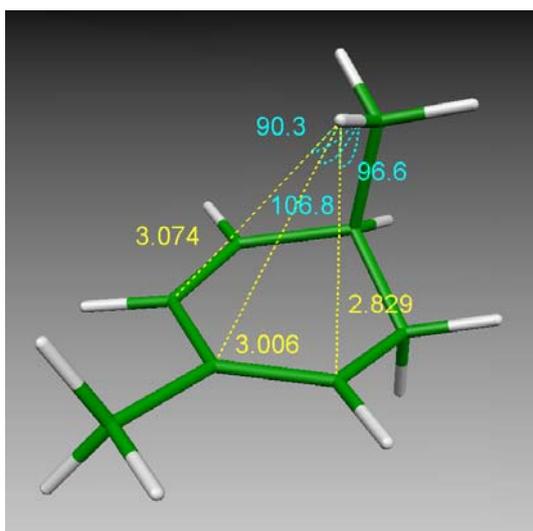
(a) CH₃
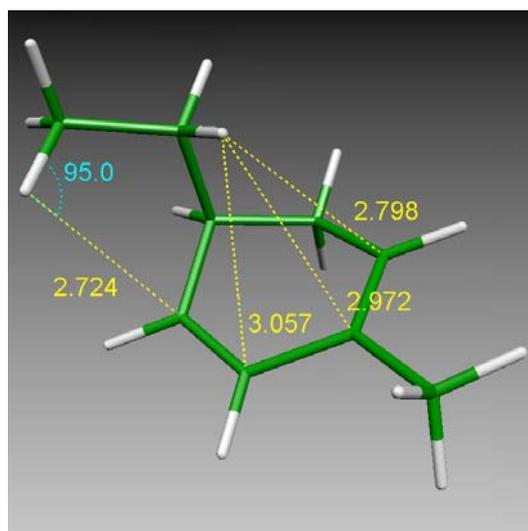
(b) C₂H₅ (ax1)
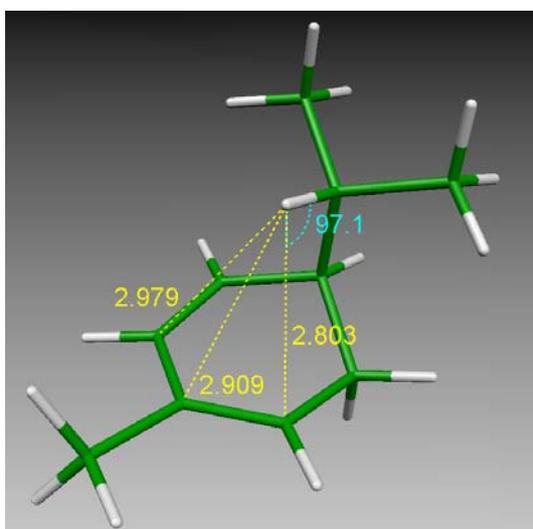
(c) *i*-C₃H₇ (ax1)
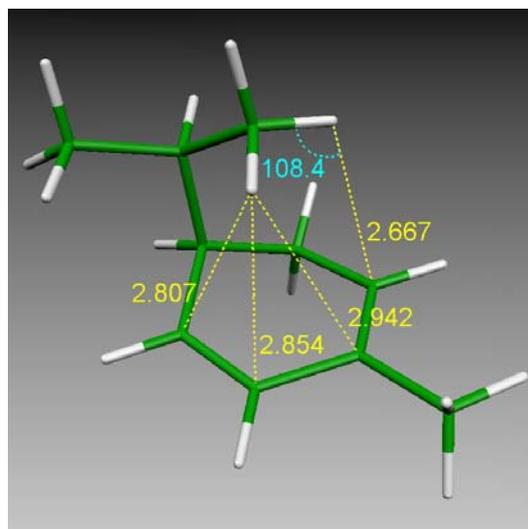
(d) *i*-C₃H₇ (ax2)
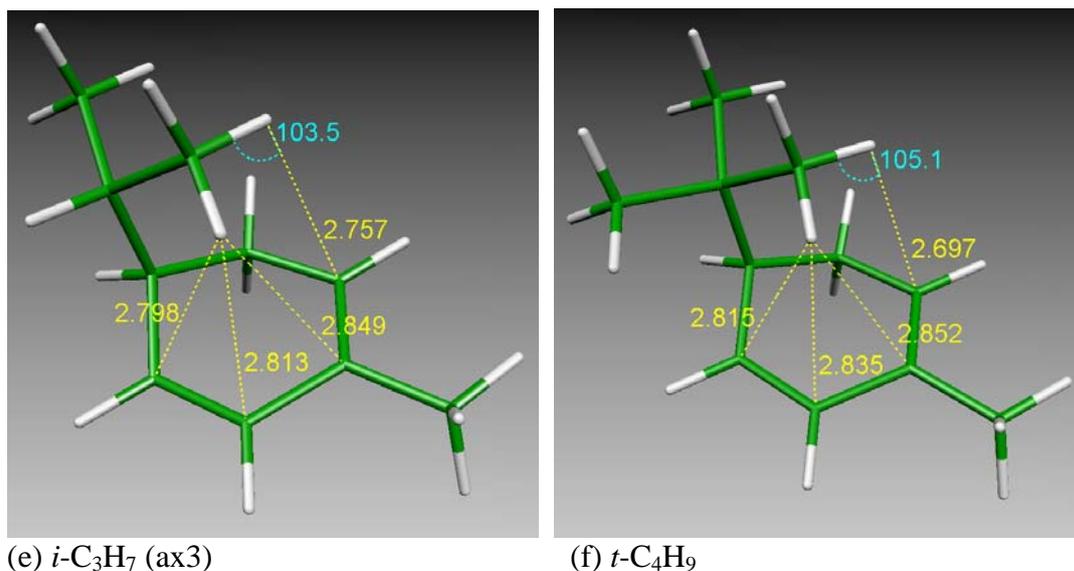
(e) i-C_3H_7 (ax3)   (f) t-C_4H_9

Figure 2. CH/π short distances disclosed in the most stable conformers of **3**. (a) R = CH_3, (b) C_2H_5 (ax1), (c) i-C_3H_7 (ax1), (d) i-C_3H_7 (ax2), (e) i-C_3H_7 (ax3), (f) t-C_4H_9. The yellow dotted line indicate short CH/π contacts (Å); the C-H…C(π) angles (º) are shown by blue.

3.3. Comparisons with Experimental Data

In 1961, Burgstahler, Ziffer and Weiss reported that α-phellandrene exists in the folded conformation in solution and the sense of the diene helix is left-handed.[26] It has been shown, by variable-temperature CD measurements, that the conformer bearing the axial isopropyl group preponderates. In agreement with the above suggestions,[13-15,21] the present calculated result (ΔG_{ax-eq} –1.27 kcal mol^{-1}) shows that the axial conformation is preferred (ca. 90%) to the equatorial conformer (ca. 10%). Lightner et al.[27] estimated the Gibbs energy difference (ΔG_{ax-eq}) to be < 0.05 kcal mol^{-1} for (+)-(5R)-methyl-1,3-cyclohexadiene (**4**, R = CH_3) and ca. 0.4 kcal mol^{-1} for (+)-(5R)-t-butyl-1,3-cyclohexadiene (**4**, R = t-C_4H_9). The conformational equilibrium of (-)-(R)-α-phellandrene (**3**, R = i-C_3H_7) was also studied and they reported a positive value (ca. 0.25 kcal mol^{-1}) for ΔG_{ax-eq}. These data are at variance, however, with the suggestions by other workers.[13-15]

3.4. Helicity of the Diene Moiety

Table 3 summarizes the dihedral angles τ defined by atomic sequence C1-C2-C3-C4 in these compounds. Figure 3 illustrates this for the axial and equatorial conformers of **3** (R = CH_3 and t-C_4H_9).

Table 3. Dihedral angles τ[a] defined by the atomic sequence C1-C2-C3-C4 in the axial and equatorial conformers of **3** and **4**

Table 3. Dihedral angles τ [a] defined by the atomic sequence C1-C2-C3-C4 in the axial and equatorial conformers of **3** and **4**

R	3	4
ax-CH$_3$	*-15.3*	*-14.5*
eq-CH$_3$	*17.7*	*16.9*
ax-C$_2$H$_5$	-16.0	-15.2
	-16.0	-11.7
	-12.8	-15.1
Average [b]	*-15.7*	*-13.8*
eq-C$_2$H$_5$	18.2	17.5
	17.5	16.6
	17.4	16.7
Average [b]	*17.8*	*17.0*
ax-i-C$_3$H$_7$	-17.5	-16.7
	-13.5	-12.6
	-13.0	-11.8
Average [b]	*-16.0*	*-15.3*
eq-i-C$_3$H$_7$	17.3	16.6
	18.0	17.3
	18.6	17.7
Average [b]	*17.9*	*17.1*
ax-t-C$_4$H$_9$	*-14.6*	*-13.5*
eq-t-C$_4$H$_9$	*17.8*	*17.1*

[a] C1-C2-C3-C4 torsion angle (º)
[b] Weighted mean of τ (º)

(a)   (b)
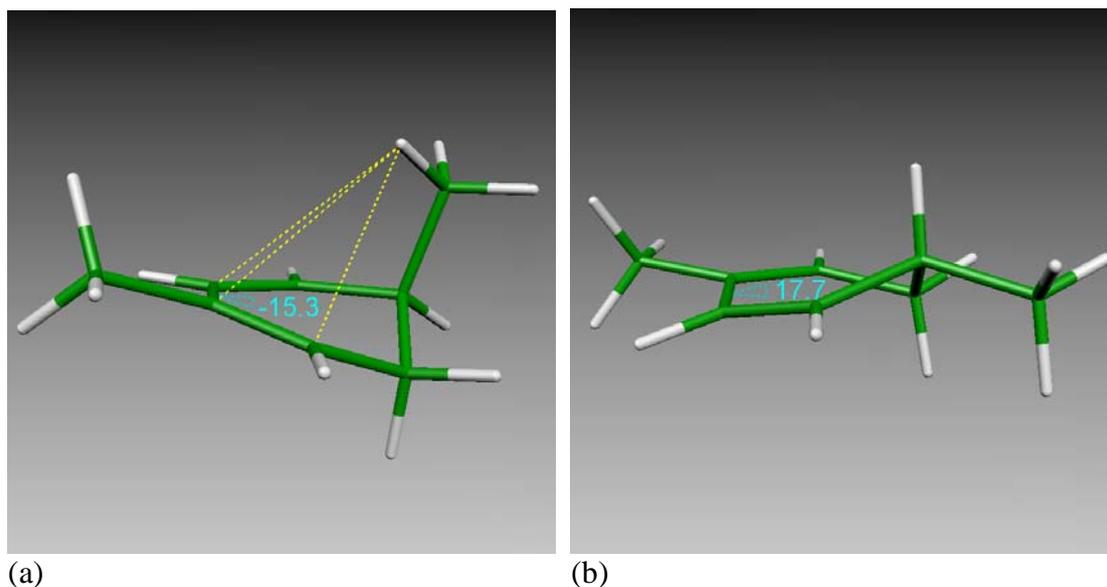
Figure 3. Dihedral angles of the axial and equatorial conformers of **3**. (a) axial-CH$_3$, (b) equatorial-CH$_3$.

The sense of the diene helicity has been shown to be left-handed in the axial conformers, while it is right-handed in the equatorial conformers. This agrees with the so-called diene-helicity rule.[28,29,30] We do not mean, however, the above result to show the rightness of this rule. The diene-helicity rule, in its original form, states that the sign and amplitude of the Cotton effect is determined, primarily, by the sense and the amount of the diene helicity. This has been criticized later by Burgstahler and coworkers;[31] they found that influence of neighboring alkyl groups overrides the effect of the diene skewness. This is especially true when an alkyl (mostly methyl) group is present at the homo-allylic position[10] to the diene system.

Another notable feature of the present result is that the twist angle $|\tau|$ of the diene is smaller in the axial conformers (13.5-16.0°) than in the equatorial conformers (16.9-17.9°). We feel that the conformational equilibrium and the chiroptical property of α-phellandrene and related 1,3-cyclohexadienes should be re-investigated[32] in view of the above findings that the difference in the skewness is not trivial between the axial and equatorial conformers. Further, the contribution of CH/π hydrogen bonds is different among the alkyl derivatives, depending of the nature (CH or CH$_3$, 5- or 6-membered) and the number of interacting C-H groups. The π or π* orbital of the diene chromophore may be perturbed in different ways, by virtue of the CH groups that are suitably oriented for an interaction to take place; the Cotton effect at the π/π* transition will be influenced, accordingly.[33,34,35]

4. Conclusions

Ab   initio   MO   calculations   were   carried   out,   at   the MP2/6-311++G(d,p)//MP2/6-311G(d,p) level, to investigate the Gibbs energy of

conformational isomers of 5-alkyl-1,3-cyclohexadiene compounds. The result is consistent with previous experimental data that the axial-isopropyl conformer of α-phellandrene predominates in the conformational equilibrium. The reason for the stability of the axial-alkyl conformers has been sought in the context of the CH/π hydrogen bond. In agreement with this hypothesis, a number of short non-bond distances (with proper angle parameters) have been disclosed, between CHs in the alkyl group and the sp2-carbons, in the stable conformers of 5-alkyl-1,3-cyclohexadienes. We conclude that the stability of the folded conformation in these compounds is understood in terms of an attractive molecular force, the CH/π hydrogen bond.

Acknowledgments

References and Notes

[1] Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, **1993**, New York, Table 11.7.

[2] Klyne, W. *Experientia* **1956**, *15*, 119.

[3] Allinger, N. L.; Blatter, H. M. *J. Am. Chem. Soc*. **1961**, *83*, 994.

[4] Rickborn, B. *J. Am. Chem. Soc.* **1962**, *84*, 2414.

[5] Cotterill, W. D.; Robinson, M. J. T. *Tetrahedron* **1964**, *20*, 777.

[6] Allinger, N. L.; Freiberg, L. A. *J. Am. Chem. Soc.* **1962**, *84*, 2201.

[7] Cotterill, W. D.; Robinson, M. J. T. *Tetrahedron* **1964**, *20*, 765.

[8] Takahashi, O.; Yamasaki, K; Kohno, Y.; Ueda, K.; Suezawa, H.; Umezawa, Y.; Nishio, M. *Tetrahedron* **2008***, 64*, 2433.

[9] Djerassi, C. *Optical Rotatory Dispersion,* McGraw-Hill, New York, 1960, p.187.

[10] Nishio, M.; Hirota, M. *Tetrahedron* **1989**, *45*, 7201.

[11] Nishio, M.; Hirota, M.; Umezawa, Y. *The CH/π Interaction, Evidence, Nature, and Consequences*, Wiley-VCH, 1998, New York.

[12] Nishio, M. *CrystEngComm* **2004**, *6*, 130.

[13] Ziffer, H.; Charney, E.; Weiss, U. *J. Am. Chem. Soc*. **1962**, *84*, 2961.

[14] Horsman, G.; Emeis, C. A. *Tetrahedron* **1966***, 22*, 167.

[15] Snatzke, G.; sz. Kovats, E.; Ohloff, G. *Tetrahedron Lett*. **1966**, *38*, 4551.

[16] Gaussian 03, Revision C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.;

13

Jaramillo, J.; Gomperts, R. ; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Wallingford CT, 2004.

[17] Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.

[18] Rowland, R. S.; Taylor, R. *J. Phys. Chem.* **1996**, *100*, 7384.

[19] Nakatsu, K.; Yoshioka, H.; Kunimoto, K.; Kinugasa, T.; Ueji, S. *Acta Crystallogr., Sect. B.* **1978**, *34*, 2357.

[20] Ueji, S.; Nakatsu, K.; Yoshioka, H.; Kinoshita, K. *Tetrahedron Lett.* **1982**, *23*, 1173.

[21] Desiraju, G. R.; Steiner, T. *The Weal Hydrogen Bond in Structural Chemistry and Biology,* Oxford Univ. Press, New York, 1999, pp.145-152.

[22] Drew, M. G. B.; Wiley, G. R. *J. Chem. Soc.*, *Perkin Trans. 2* **1986**, 215.

[23] Steiner, T.; Saenger, W. *J. Am Chem. Soc*. **1992**, *114*, 10146.

[24] Jeffrey, G. A. *An Introduction to Hydrogen Bonding,* Oxford Univ. Press, New York, 1997, p.89.

[25] Nishio, M. *Top. Stereochem.* **2006**, *25*, 255.

[26] Burgstahler, A. W.; Ziffer, H.; Weiss, U. *J. Am. Chem. Soc*. **1961**, *83*, 4660.

[27] Lightner, D. A.; Bouman, T. D.; Gawronski, J. K.; Gawronska, K.; Chappui, J. L.; Hansen, A. E. *J. Am Chem. Soc*. **1981**, *103*, 5315.

[28] Moscowitz, A.; Charney, E.; Weiss, U.; Ziffer, H. *J. Am. Chem. Soc*. **1961**, *83*, 4661.

[29] Weiss, U.; Ziffer, H.; Charney, E. *Tetrahedron* **1965**, *21*, 3105.

[30] Charney, E. *Tetrahedron* **1965**, *21*, 3127.

[31] Burgstahler, A. W.; Weigel, L. O.; Gawronski, J. K. *J. Am. Chem. Soc*. **1976**, *98*, 3015.

[32] The conformational equilibrium was investigated with an assumption that the CD amplitude of the axial and equatorial conformers is the same, which is not necessarily warranted.

[33] Zushi, S.; Kodama, Y.; Fukuda, Y.; Nishihata, K.; Nishio, M.; Hirota, M.; Uzawa, J. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2113.

[34] Araki, S.; Seki, T.; Sakakibara, K.; Hirota, M.; Kodama, Y.; Nishio, M. *Tetrahedron: Asymm.* **1993**, *4*, 555.

[35] Ref. 10 and Chapter 6 of Ref. 11.