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The conformation of alkyl cyclohexanones and terpenic ketones. Interpretation for the 'alkylketone effect' based on the CH/π(C=O) hydrogen bond

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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 free energy of the conformational isomers of 2-alkyl, 3-alkyl, and 4-alkyl cyclohexanones. The calculation gave results consistent with the general trend experimentally found. The genesis of stabilization of the axial conformers in 2- and 3-alkyl cyclohexanones, as compared to the structurally corresponding cyclohexane derivatives, was sought in the context of the attractive CH/π(C=O) hydrogen bond. In support of this hypothesis, short nonbonded distances have been noted between CHs in the alkyl group and the carbonyl carbon in the relevant axial conformers. Calculations were also carried out to study the conformational energies of several terpenic ketones. For isomenthone, more than a half molecular fraction (ca. 55%) has been suggested to be in the isopropyl-axial conformation, while for isocarvomenthone ca. 77% has been suggested to be in the axial-isopropyl conformation; this is consistent with bibliographic experimental data. A crystallographic database search has provided results compatible with this conclusion. We suggest that the relative stability of the axial alkyl substituent, often observed in terpenic and steroidal ketones is rationalized in terms of an attractive molecular force, the CH/π(C=O) hydrogen bond.

1. Introduction

In 1955, Robins and Walker reported that axial alkyl groups in 2-alkyl (**2**) and 3-alkyl (**3**) cyclohexanones are stabilized, relative to the parent hydrocarbons **1**. In other words, a shift is observed in the conformational equilibrium of **2** (Scheme 1; R=CH_3, C_2H_5) and **3** (Scheme 1; R=CH_3, C_2H_5, *i*-C_3H_7) leading to an increase in content of the axial conformer, relative to the structurally corresponding cyclohexanes.[1] Klyne studied this issue and termed the phenomena as the '2-alkyl and 3-alkylketone effect'.[2]

The alkylketone effect is important in stereochemistry since implication of this effect extends to conformational issues of natural organic compounds such as terpenic and steroidal ketones. For instance, the isopropyl group in isomenthone (*cis*-2-isopropyl-5-methylcyclohexanone) and isocarvomenthone (*cis*-2-methyl-5-isopropylcyclohexanone) has been known to prevail in the axial conformation; the reason for this phenomenon, however, has not been elucidated thus far.

Effort was since made by many workers to explore the origin of the alkylketone effects, and the problem has been considered to be rather settled. The interpretation was based

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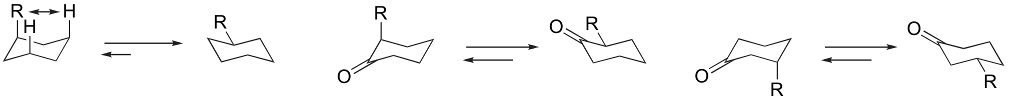


1 **2** **3**

Scheme 1. Conformation of alkyl cyclohexanes **1**, 2-alkyl cyclohexanones **2**, and 3-alkyl cyclohexanones **3**.

on the relief of a severe 1,3-diaxial repulsion in **2** and **3**; this may be brought about by replacing a methylene group of **1** by a carbonyl group. Substitution of a CH_2 moiety by C=O might stabilize the axial alkyl substituent, relative to the equatorial conformation. The above interpretation seemed reasonable on steric grounds and has been long accepted.

Herein, we present a hypothesis that the relative stability of axial alkyl groups in **2** and **3** is one of the consequences of an attractive interaction occurring between CH(s) of the alkyl group and the carbonyl π-system in the cyclohexanone ring (in addition to the decrease of unfavorable 1,3-diaxial interactions). The axial preference of isopropyl group in natural organic compounds, such as isomenthone and isocarvomenthone, can reasonably be explained on the same grounds.

2. Method

2.1. Computational method

The Gaussian 03 program[3] 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 atm of pressure.

2.2. Crystallographic database search

The Cambridge Structural Database (CSD version 5.28, November 2006 release) was used. The relevant data were retrieved by using ConQuest version 6.0 and analyzed by VISTA version 2.0. Only organic crystal data with *R*-factor <0.1 were considered.

3. Results and discussion

3.1. Computational results

Table 1 summarizes the conformational Gibbs free energies of 2-alkyl cyclohexanones **2**, 3-alkyl cyclohexanones **3**, and 4-alkyl cyclohexanones **4**. The data calculated for parent hydrocarbons **1** are also included for comparison. The equatorial (eq1, eq2, eq3) and axial conformers (ax1, ax2, ax3) are arranged, in each series, in the order of increasing conformational energy, since three stable conformers in the ethyl and isopropyl derivatives were found.

Table 1
Conformational Gibbs free energies (kcal mol^{-1}) of (a) 2-alkyl cyclohexanones **2**, (b) 3-alkyl cyclohexanones **3**, (c) 4-alkyl cyclohexanones **4**, and (d) alkyl cyclohexanes **1**

	eq1	eq2	eq3	ax1	ax2	ax3
(a) Relative conformational energies of 2-alkyl cyclohexanones **2**						
CH_3	0.00			1.94		
C_2H_5	0.00	0.30	0.99	1.15	1.84	4.69
i-C_3H_7	0.00	0.30	0.61	0.30	3.62	3.82
t-C_4H_9	0.00			3.88		
(b) Relative conformational energies of 3-alkyl cyclohexanones **3**						
CH_3	0.00			1.00		
C_2H_5	0.00	0.06	0.80	0.72	0.94	3.98
i-C_3H_7	0.00	0.06	0.19	0.63	3.39	3.68
t-C_4H_9	0.00			3.81		
(c) Relative conformational energies of 4-alkyl cyclohexanones **4**						
CH_3	0.00			1.53		
C_2H_5	0.00	0.00	0.85	1.36	1.36	5.85
i-C_3H_7	0.00	0.09	0.09	1.05	5.40	5.40
t-C_4H_9	0.00			5.64		
(d) Relative conformational energies of alkyl cyclohexanes **1**						
CH_3	0.00			1.91		
C_2H_5	0.00	0.00	0.84	1.76	1.77	4.73
i-C_3H_7	0.00	0.06	0.06	1.47	5.54	5.54
t-C_4H_9	0.00			5.11		

As anticipated, the equatorial conformers have been found to be more stable than the axial congeners. In order to compare the stability of the equatorial and axial conformations, contribution from all the conformers should be taken into account, since several conformers are possible in the ethyl and isopropyl derivatives. In these cases, contribution from all the possible conformers should be considered. The difference in the conformational energies for the ethyl and isopropyl compounds was calculated by taking into account of the abundances of all the equatorial and axial conformers. Table 2 lists the conformational energies of **1**, **2**, **3**, and **4** thus estimated. Experimental data for **1** (*A*-value)[4] are included for comparison.

The calculated values for parent alkyl cyclohexanes ΔG_{ax-eq} **1** agree well with the experimental data (*A*-values); this was expected. The values of 4-alkyl cyclohexanones **4** are not much different from those of **1**; this also is reasonable since the alkyl group in **4** is remote from the carbonyl function and the stereochemical influence might be small. In contrast, the magnitude of ΔG_{ax-eq} for **2** (except for R=CH_3) and **3** has been shown to be much smaller (italicized) than the corresponding values of **1** and **4**.

In Table 3, the abundance of the equatorial and axial conformers is compared for **1**, **2**, **3**, and **4**. The proportion of the axial conformers is appreciably larger in 2-ethyl, 2-isopropyl, 3-methyl, 3-ethyl, and 3-isopropyl cyclohexanones (italicized), than in the parent hydrocarbons **1**.

Table 2
Conformational Gibbs free energies of alkyl cyclohexanes **1**, 2-alkyl cyclohexanones **2**, 3-alkyl cyclohexanones **3**, and 4-alkyl cyclohexanones **4**

R	*A*-value[a]	ΔG_{ax-eq} **1**	ΔG_{ax-eq} **2**	$\Delta\Delta G_{\mathbf{1-2}}$[b]	ΔG_{ax-eq} **3**	$\Delta\Delta G_{\mathbf{1-3}}$[c]	ΔG_{ax-eq} **4**	$\Delta\Delta G_{\mathbf{1-4}}$
CH_3	1.74	1.91	1.94	−0.03	*1.00*	0.91	1.53	0.38
C_2H_5	1.79	1.83	*1.33*	0.50	*0.87*	0.96	1.43	0.40
i-C_3H_7	2.21	2.08	*0.80*	1.28	*1.19*	0.89	1.64	0.44
t-C_4H_9	4.7	5.11	3.88	1.23	3.81	1.30	5.64	−0.53

[a] ΔG_{ax-eq} (kcal mol^{-1}) at 300 K in the equatorial–axial equilibrium of a substituted cyclohexane; Ref. 4.

[b] 2-Alkylketone effect: ΔG_{ax-eq} (alkylcyclohexane **1**)−ΔG_{ax-eq} (2-alkylcyclohexanone **2**).

[c] 3-Alkylketone effect: ΔG_{ax-eq} (alkylcyclohexane **1**)−ΔG_{ax-eq} (3-alkylcyclohexanone **3**).

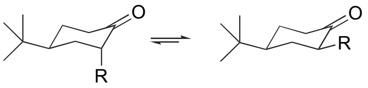
Table 3
Abundance of the equatorial and axial conformers, calculated for 2-alkyl (**2**), 3-alkyl (**3**), 4-alkyl cyclohexanones (**4**), and alkyl cyclohexanes (**1**)

	1		**2**		**3**		**4**	
R	eq	ax	eq	ax	eq	ax	eq	ax
CH_3	96.2	3.8	96.4	3.6	84.4	*15.6*	92.9	7.1
C_2H_5	95.7	4.3	90.5	*9.5*	81.2	*18.8*	91.8	8.2
i-C_3H_7	97.1	2.9	76.4	*23.6*	88.2	*11.8*	94.1	5.9
t-C_4H_9	99.98	0.02	99.86	0.14	99.84	0.16	99.99	0.01

Below, we will compare the above computational results with available experimental data.

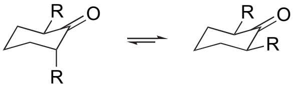
3.2. 2-Alkylketone effect

Allinger studied the effect of substituent,[5] by equilibrating 2-alkyl 4-*tert*-butyl cyclohexanones with sodium methoxide (Scheme 2). The 2-alkylketone effect has been shown to be significant for R=C_2H_5 and *i*-C_3H_7, but was insignificant for R=CH_3.



Scheme 2. Conformational equilibrium of 2-alkyl 4-*tert*-butyl cyclohexanones.

Rickborn studied the cis/trans equilibrium of 2,6-dialkyl cyclohexanones by alkali treatment (Scheme 3).[6] Cotterill and Robinson reported the 2-alkylketone effect for 2-ethylcyclohexanone as 0.9 kcal mol^{-1}.[7]



Scheme 3. Conformational equilibrium of 2,6-dialkyl cyclohexanones.

Table 4 summarizes the above results, together with the calculated data for comparison. In short, the present computational results are consistent with the experimental data. The 2-alkylketone effect is more important in the isopropyl (1.4–1.5 kcal mol^{-1} by experiments vs 1.3 kcal mol^{-1} by calculations) than in the ethyl cyclohexanones (0.5–0.9 vs 0.5 kcal mol^{-1}). It is negligible when R=CH_3.

3.3. 3-Alkylketone effect

Allinger[8] studied the equilibration of 3,5-dimethylcyclohexanone with a palladium-on-carbon catalyst and obtained $\Delta G_{eq-ax}=-1.36$ kcal mol^{-1} and $\Delta S_{eq-ax}=-1.4$ e.u. (Scheme 4). This gave an estimate of the 3-alklylketone effect of ca. 0.6 kcal mol^{-1} for R=CH_3.

Table 4
2-Alkylketone effect: experimentally determined and calculated values

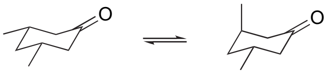
R	ΔG_{ax-eq}[a]	ΔG_{ax-eq}[b]	$\Delta\Delta G_{\mathbf{1-2}}$[a]	$\Delta\Delta G_{\mathbf{1-2}}$[b]	$\Delta\Delta G_{\mathbf{1-2}}$[c]	$\Delta\Delta G_{calcd}$[d]
CH_3	1.56	1.82				−0.03
C_2H_5	1.09	1.21	0.46	0.9	0.9	0.50
i-C_3H_7	0.59	0.56	1.41	1.5		1.28
t-C_4H_9	1.62	1.52	0.82	2.9		1.23

[a] Ref. 5.

[b] Ref. 6. Corrected by adding *RT*ln 2 (0.41 kcal mol^{-1}, *T*=300 K) for the DL (*trans*) compounds.

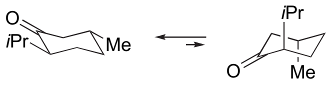
[c] Ref. 7.

[d] 2-Alkylketone effect (calculated value).



Scheme 4. Equilibration of 3,5-dimethylcyclohexanone by palladium catalyst.

Cotterill and Robinson reported that the 3-alkylketone effect is ca. 0.5 kcal mol^{-1} for 3-methyl cyclohexanone (Scheme 5, R=Me).[9] For 3-isopropylcyclohexanone (R=*i*-Pr), Djerassi co-workers found ca. 0.9 kcal mol^{-1}.[10] The present calculated data for 3-alkyl cyclohexanones (0.91, 0.96, and 0.89 kcal mol^{-1}, respectively, for R=CH_3, C_2H_5, and *i*-C_3H_7) are compatible with the above experimental data. To summarize, the 3-alkylketone effect is sizeable in every case, including the methyl analog.



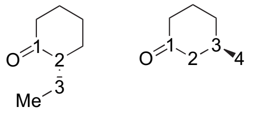
ee-**5** aa-**5**

Scheme 5. Conformational equilibrium of menthone **5**.

3.4. Origin of the alkylketone effects

Our hypothesis is that the alkylketone effect is a consequence of the CH/π(C=O) interaction, occurring between

Table 5
Short CH/C=O distances disclosed in axial conformers of 2-alkyl (**2**) and 3-alkyl cyclohexanones (**3**)



R	Conformer	Abundance[a]	$\tau1$[b]	$\tau2$[c]	d/Å[d]
2-C_2H_5	ax1	7.3	58		2.70
2-*i*-C_3H_7	ax1	23.5	55		2.59
3-CH_3	ax1	15.6		−69	2.72
3-C_2H_5	ax1	11.1		−66	2.70
	ax2	7.7		−69	2.67
3-*i*-C_3H_7	ax1	11.6		−64	2.64

[a] Population of the conformer.
[b] C^1–C^2–C^3–Me torsion angle (°).
[c] C^1–C^2–C^3–C^4 torsion angle (°).
[d] Nonbonded distance between H and C^1.

the alkyl group and the carbonyl π-moiety, which is suitably located for this interaction to take place. The significance of this type of CH/π hydrogen bond in conformational issues of simple organic compounds has been shown by the present authors.[11,12] To test this possibility in the alkylketone effect, we examined the nonbonded distance between the CHs of the alkyl group and the carbonyl group in the axial conformers of **2** and **3**. Table 5 summarizes these results.

Short CH/π(C=O) atomic distances have in fact been shown between the relevant C–*H* and *C*=O atoms, which are separated by four covalent bonds (intensified in Fig. 1) in the axial conformers of 2-ethyl and isopropyl-**2**, and 3-methyl-, ethyl, and isopropyl-**3**. Formation of a five-membered nonbonded interaction is possible in this molecular circumstance. Note that this type of geometry is disfavored in view of ordinary stereochemical considerations. In Figures 2 and 3 are given illustrative examples.

3.5. Conformational equilibrium of menthone

Djerassi and co-workers studied the conformational equilibrium of menthone (*trans*-2-isopropyl-5-methylcyclohexanone) **5** and concluded that **5** exists almost exclusively in the diequatorial conformation (ee-**5** in Scheme 5).[13] Later, Moscowitz, Lightner and co-workers showed that the diequatorial conformation ee-**5** is dominant, by the vibrational CD technique.[14] This conclusion is reasonable but in the same paper they reported that the mole fraction of the diaxial conformer (aa-**5**) is not necessarily trivial; ca. 3% of the diaxial conformer was suggested to exist in the conformational mixture, according to the CD measurements. This seems noteworthy in view of the severe 1,3-diaxial interactions in this molecular circumstance.

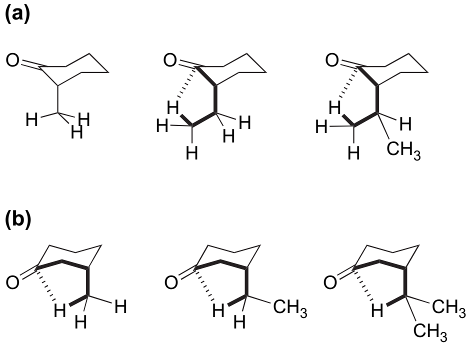


Figure 1. Five-membered CH/π(C=O) interaction in axial conformers of (a) 2-alkyl cyclohexanones **2** and (b) 3-alkyl cyclohexanones **3**.

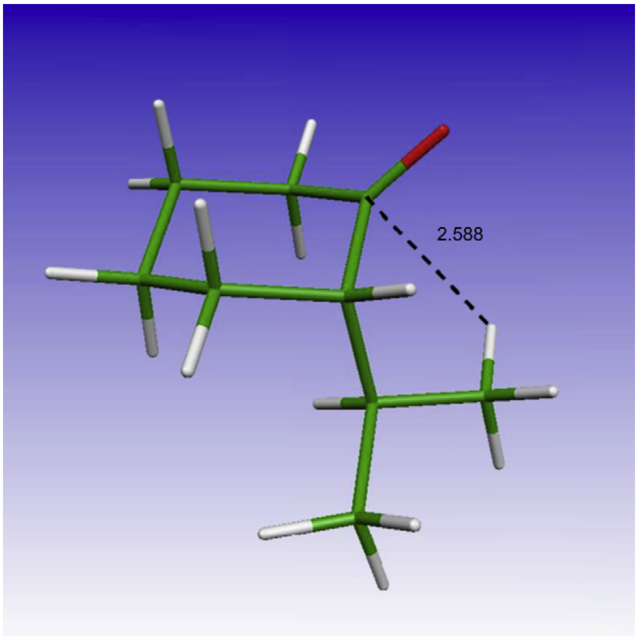


Figure 2. Calculated conformation of 2-isopropyl cyclohexanone **2** (ax1).

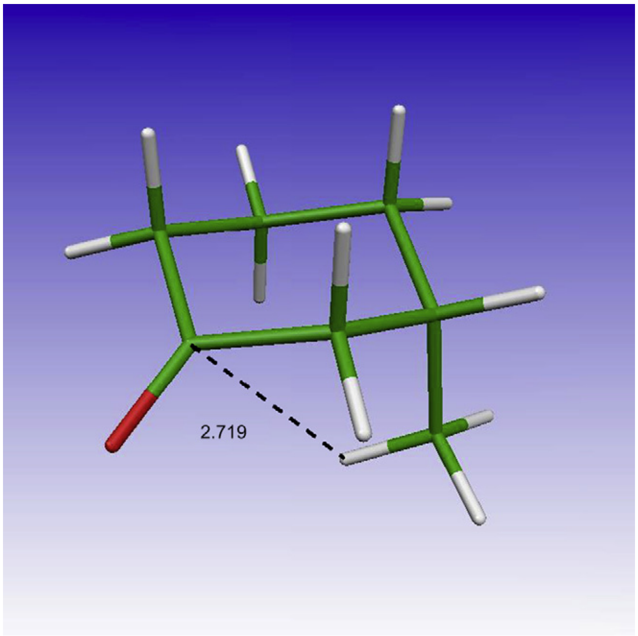
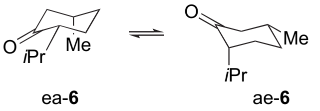


Figure 3. Calculated conformation of 3-methyl cyclohexanone **3** (ax1).

3.6. Conformational equilibrium of isomenthone

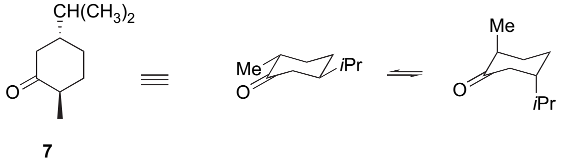
For isomenthone (*cis*-2-isopropyl-5-methylcyclohexanone) **6**, Rickborn suggested that the axial-isopropyl conformation (ae-**6** in Scheme 6) is an important contributor in the equilibrium.[6] Djerassi substantiated this conclusion by CD measurements.[10,15]



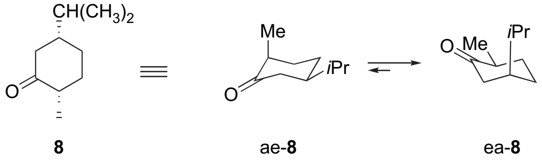
Scheme 6. Conformational equilibrium of isomenthone **6**.

3.7. Conformational equilibrium of isocarvomenthone

Cotterill and Robinson studied the equilibration, by strong alkali treatment, of carvomenthone **7** (*trans*-2-methyl-5-isopropylcyclohexanone) and isocarvomenthone (*cis*-2-methyl-5-isopropylcyclohexanone) **8** (Scheme 7). They reported that **8** prevails in the equilibrium mixture, irrespective of whether **7** or **8** was used as the starting material.[7] The result is remarkable in view of the severe 'steric constraint' expected in the axial-isopropyl conformer of isocarvomenthone ea-**8** (Scheme 8).

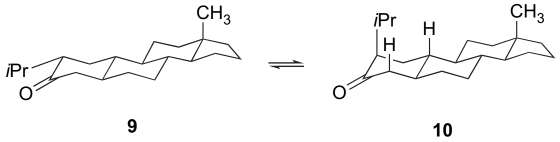


Scheme 7.



Scheme 8.

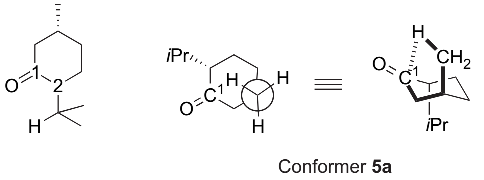
To cite an example from steroid chemistry, Djerassi and co-workers studied the equilibrium of 2α-**9** and 2-β-isopropyl-19-nor-5α-androstan-3-one **10**.[16] Alkali treatment of either **9** or **10** gave a mixture of both the isomers in ca. 5:1 ratio; this also is remarkable in view of the unfavorable 1,3-diaxial interactions involved in **10**. The reason for the above phenomena has remained unexplained, however.



3.8. Ab initio MO calculations of terpenic ketones

In order to explore the genesis of the above noteworthy effects in the conformational equilibrium of terpenic and steroidal ketones, we carried out ab initio MO calculations, at the same level of the approximation, of menthone **5**, isomenthone **6**, and isocarvomenthone **7**. Table 6 summarizes the

Table 6
Conformational Gibbs energies and relevant geometrical parameters of menthone **5**

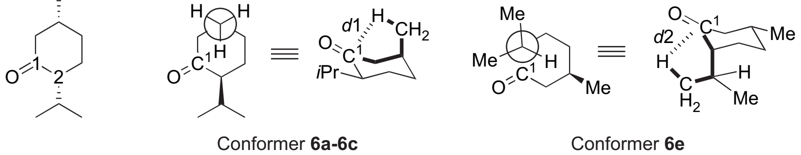


Conformer **5a**

	G^{a}	Ratio[b]	τ^{c}	dH/C^{1} [d]
Me^{ax}*i*-Pr^{ax} **5a**	1.28	4.79	−55	2.75
Me^{ax}*i*-Pr^{ax} **5b**	4.72	0.01	−75	2.90
Me^{ax}*i*-Pr^{ax} **5c**	4.43	0.02	−52	2.58
Me^{eq}*i*-Pr^{eq} **5d**	0.61	14.84	−8	
Me^{eq}*i*-Pr^{eq} **5e**	0.05	38.42	11	
Me^{eq}*i*-Pr^{eq} **5f**	0.00	41.91	3	

[a] Relative conformational energy (kcal mol^{-1}).
[b] Population of the conformer (%).
[c] H–C$^{i\text{-Pr}}$–C^{2}–C^{1} torsional angle (°).
[d] Nonbonded distance between H (ax-CH$_3$) and C^{1} (Å).

Table 7
Conformational Gibbs free energies and relevant geometrical parameters of isomenthone **6**



Conformer **6a-6c** Conformer **6e**

	G^{a}	Ratio[b]	τ^{c}	$d1^{d}$	$d2^{e}$
Me^{ax}*i*-Pr^{eq} **6a**	0.63	18.7	173	2.73	
Me^{ax}*i*-Pr^{eq} **6b**	1.23	6.9	177	2.72	
Me^{ax}*i*-Pr^{eq} **6c**	0.61	19.6	−49	2.70	
Me^{eq}*i*-Pr^{ax} **6d**	3.55	0.1	−44		
Me^{eq}*i*-Pr^{ax} **6e**	0.00	54.5	64		2.59
Me^{eq}*i*-Pr^{ax} **6f**	3.31	0.2	−171		

[a] Relative conformational energy (kcal mol^{-1}).
[b] Population of the conformer (%).
[c] H–C$^{i\text{-Pr}}$–C^{2}–C^{1} torsional angle (°).
[d] Distance between H (ax-CH$_3$) and C^{1} (Å).
[e] Nonbonded distance between H (*i*-Pr–CH$_3$) and C^{1} (Å).

conformational Gibbs energies and relevant geometrical parameters of menthone **5**.

The calculation has shown that **5** exists almost exclusively in the diequatorial conformer. This agrees with the experimental evidence, however, one of the diaxial conformers has been suggested to populate in a not negligible amount, ca. 5%. A short interatomic H/C distance (2.75 Å) was noted in conformer **5a** ($Me^{ax}i\text{-}Pr^{ax}$), between one of the hydrogen atoms of the methyl group and C=O.

Table 7 summarizes the conformational Gibbs free energies and relevant geometrical parameters of isomenthone **6**. For isomenthone, 55% has been suggested to be in the axial-isopropyl conformation in the equilibrium. In the most populated conformer **6e**, a short H/C distance, 2.59 Å, has been noted. Figure 4 shows the conformation of **6e**.

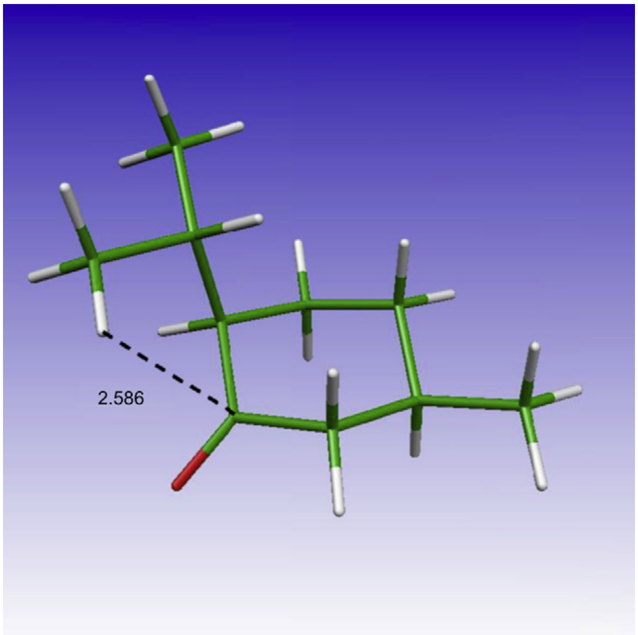
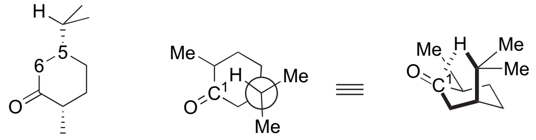


Figure 4. Conformation of isopropyl-axial conformer **6e** of isomenthone.

Table 8
Conformational Gibbs free energies and relevant geometrical parameters of isocarvomenthone **8**



Conformer **8b**

	G^a	Ratio[b]	τ^c	dH/C^1 [d]
$Me^{eq}i\text{-}Pr^{ax}$ **8a**	2.78	0.7	−54	
$Me^{eq}i\text{-}Pr^{ax}$ **8b**	0.00	76.9	61	2.64
$Me^{eq}i\text{-}Pr^{ax}$ **8c**	3.09	0.4	161	
$Me^{ax}i\text{-}Pr^{eq}$ **8d**	1.31	8.4	−179	
$Me^{ax}i\text{-}Pr^{eq}$ **8e**	1.39	7.4	−62	
$Me^{ax}i\text{-}Pr^{eq}$ **8f**	1.49	6.2	175	

[a] Relative conformational energy (kcal mol^{-1}).
[b] Population of the conformer (%).
[c] H–$C^{i\text{-}Pr}$–C^5–C^6 torsional angle (°).
[d] Nonbonded distance between H (ax-i-Pr) and C^1 (Å).

Table 8 summarizes the conformational Gibbs free energies and relevant geometrical parameters of isocarvomenthone **8**. Of note is that one of the isopropyl-axial conformers, **8b**, prevails (ca. 77%) in the equilibrium. This is consistent with the result reported by Cotterill and Robinson.[7] The H/C^1 distance in the most stable conformer **8b** is short, 2.64 Å. Figure 5 shows the conformation of **8b**.

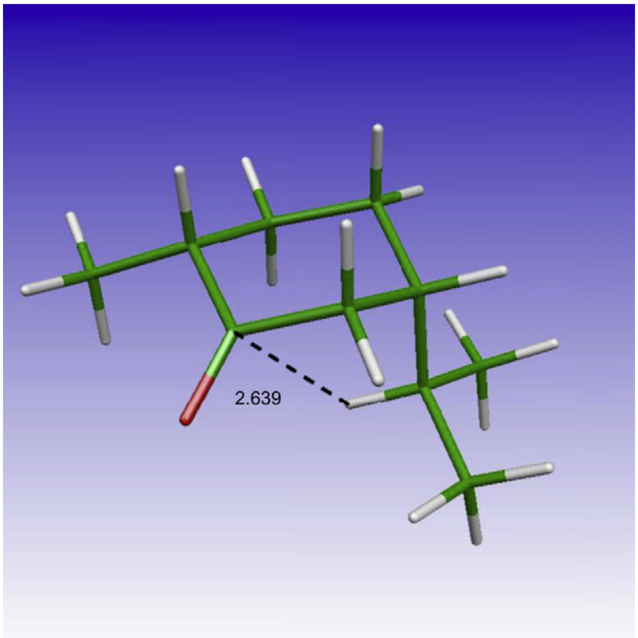


Figure 5. Conformation of isopropyl-axial conformer **8b** of isocarvomenthone.

3.9. Database study

To examine whether short CH/π(C=O) distances are found in crystallographic data, a database search was carried out by using the Cambridge Structural Database (CSD).[17] The structure of cyclohexanone derivatives bearing a methyl group at the β position to the carbonyl group has been surveyed (Fig. 6). Every carbon atom, except the carbonyl carbon, was sp^3-hybridized.

The number of hits was 45 (61 fragments). In Figure 7, the H/C^1 distance is plotted against the C^1–C^2–C^3–C^4 torsional angle ϕ. The circles at ϕ 40–80° are attributed to hydrogens in the β-methyl alkyl group of cyclohexanones, while those with $\phi > 150°$ are in equatorial isomers. Figure 8 demonstrates that a CH/π distance shorter than the sum of the van der Waals radii[18] (1.2 Å for H and 1.7 Å for C ≥2.9 Å[19,20]) is often found in the crystallographic data of β-axial methyl cyclohexanones (27 observations in 22 entries: 2.71±0.12 Å). To ensure that the short nonbonded distances are not the result

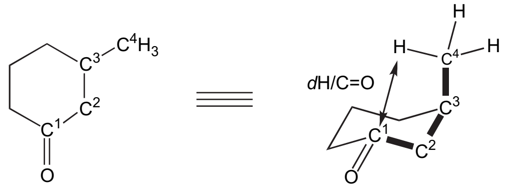


Figure 6. Structure of β-alkyl cyclohexanones to be surveyed.

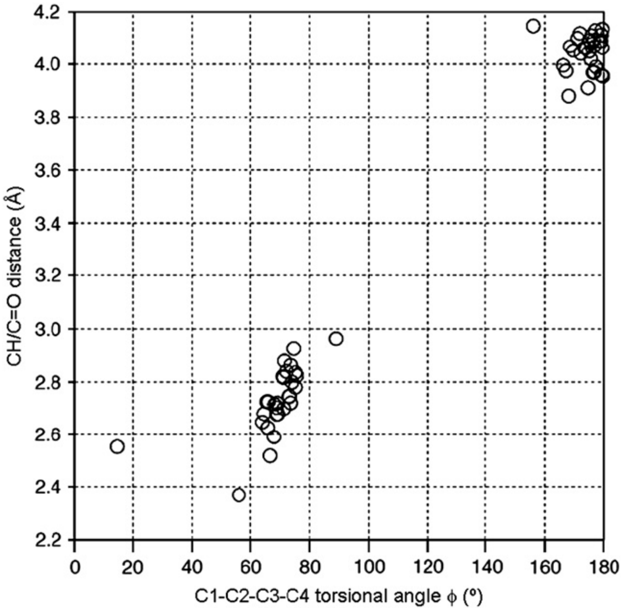


Figure 7. Scattergram showing the distribution of CH/C=O distance.

of unfavorable steric interactions, the crystal structures [CSD refcode: BAYTEA, COJBIM, CUPDEW (2), DAXMHO, EMIHUD, EVOWIV (2), FUJVUB, JEGTUK, JIGFOU (2), IJENIU, IFIDOQ, NABJEF (2), NALDIN (2), NAMZEH, PEQDOE, PEJHAN, ROHCOG, SOQCOQ, TUGWUN, UFECAJ, WOCXOB, YAGTUW] were inspected, manually. In Figures 9 and 10 are shown illustrative examples.

The computational results refer to the conformation in the vapor phase, while the CSD data were obtained in the solid state. Allen and co-workers compared the conformer distribution in the CSD and the calculated energies, and concluded that the so-called crystal-packing effects rarely have a strong systematic effect on molecular conformations.[21] We also found, by a combined database and computational study, that the molecular structure in the crystal reflects the influence from the CH/π hydrogen bond;[22] these suggestion have been substantiated by crystallographic database studies.[23,24]

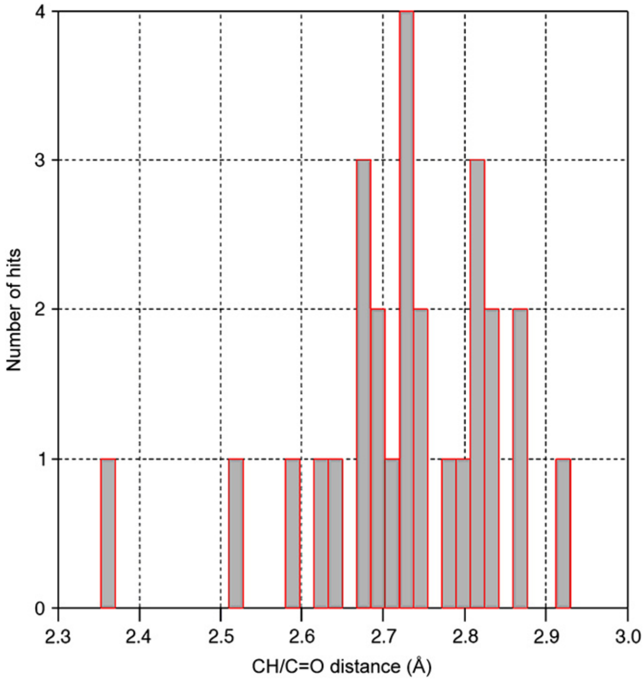


Figure 8. Histogram showing the distribution of short CH/C=O distance.

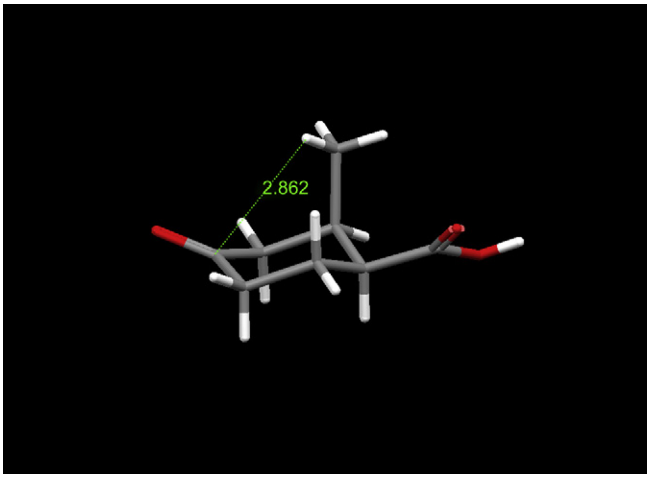


Figure 9. (±)-*cis*-2-Methyl-4-oxocyclohexanecarboxylic acid (EMIHUD),[25] ϕ 73.7°.

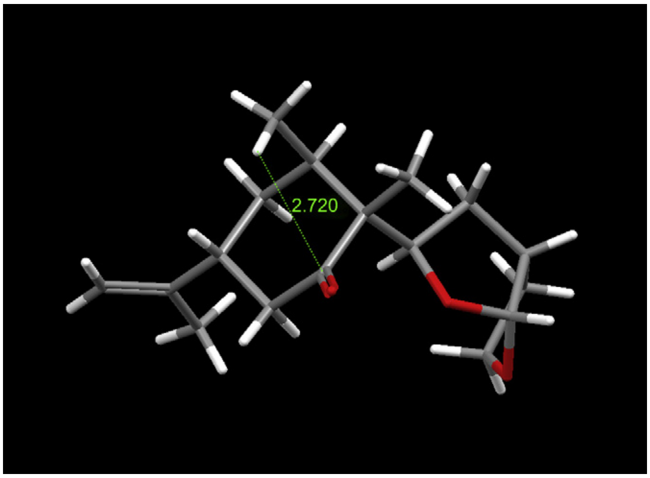


Figure 10. (2*R*,3*R*,5*R*)-2-((2*R*,3α*S*,6α*R*)-2,3,3α,4,5,6α-hexahydrofuro(2,3-β)-furan-2-yl)-5-isopropenyl-2,3-dimethylcyclohexanone (WOCXOB),[26] ϕ 73.7°.

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 free energy of conformational isomers of 2-alkyl cyclohexanones, 3-alkyl cyclohexanones, menthone, isomenthone, and isocarvomenthone. The genesis of the stability (as compared to the corresponding alkyl cyclohexanes) of the axial conformers of these compounds has been sought in the context of a stabilizing CH/π(C=O) hydrogen bond. A short nonbonded distance between CHs in the alkyl group and the carbonyl carbon atom has in fact been noted in the stable axial isomers. A crystallographic database search has provided data, in support of this suggestion. We conclude that the axial preference of an isopropyl group in cyclohexanone derivatives such as isomenthone and isocarvomenthone is rationalized in terms of the CH/π(C=O) hydrogen bond.

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