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DYNAMIC NUCLEAR MAGNETIC RESONANCE AND EMPIRICAL FORCE FIELD STUDIES OF CANNABIDIOL†

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Abstract—Internal rotation of cannabidiol (**1**), its mono-(**2**) and dimethyl (**3**) derivatives has been studied by ^1H and ^{13}C dynamic NMR spectroscopy. The free energy of activation for the rotation of C_3–C_2, bond that we have observed for cannabidiol of 14.7 kcal/mol at 22° in $CDCl_3$ is in contrast with values previously reported in the literature. Molecular mechanics simulation of the rotation of C_3–C_2, bond of a model structure (**4**) well reproduced the presently determined barrier height. Analysis of the calculated rotational transition state structure revealed severe nonbonded C_2H/O and C_2/O interactions as the source of barrier. Calculations of other model structures indicate general occurrence of restricted rotation about the pivot bond of phenylcyclohexanes appropriately substituted at β-carbon of cyclohexane ring and at *ortho* position of phenyl ring. The fully substituted 2,6-dimethyl-1-(*o*,*o*′-dimethylphenyl) cyclohexane (**10**) is predicted to show atropisomerism.

The natural products of *Cannabis sativa* L. have been the subjects of intensive chemical, pharmacological, and clinical studies for the past twenty years.[2,3] One of the major principles, cannabidiol (**1**) has been shown to be potential anticonvulsant agent[4] devoid of psychoactivity. Despite many pharmacological and biochemical investigations, the mechanisms and sites of action of **1** (and of cannabinoids in general) remain obscure.[4] Following our structure-activity relationship studies of analogues,[5,6] we started structural studies of the conformational features of the molecule. Brief mention of the conformational properties of **1** as investigated by ^1H NMR and supported by PCILO calculations has appeared first in a review[2] and later in more detail in a communication,[7] but only a few experimental details have been reported.[13]C NMR chemical shift assignment for all the carbons in **1** has been reported.[8,9]

This paper first describes the dynamic ^1H and ^{13}C NMR investigation of the conformational behavior of **1**. We noticed that values associated with rotation about C_3–C_2, bond of this molecule quoted in the literature[7] differ markedly from our own, and therefore studied the analogs **2** and **3** as well.[10] It was possible to reproduce the observed, considerably high barrier by molecular mechanics simulation of the rotational process of a model of **1**. Inspection of the calculated structure at the saddle point revealed two kinds of severe 1,6-nonbonded repulsions as the major sources of barrier. This finding prompted us to conduct systematic calculations of other model structures, which gave general picture on the internal rotation of phenylcyclohexanes. These computational studies will be described in the latter part of this paper.

RESULTS

Dynamic NMR

Cannabidiol (**1**) is a substituted cyclohexene, where the 3-aryl and 4-isopropenyl groups are *trans* to each other. X-ray crystallographic studies[11,12] of **1** revealed the existence of two solid state conformations, which differ primarily in the conformation of the *n*-amyl side chain. The cyclohexene ring in both structures is a half-chair with the isopropenyl group in an *equatorial* and the aryl group in a *quasi-equatorial* position. This conformation apparently also predominates in solution, since the coupling constant for the vicinal C_3 and C_4 protons of 9.8 Hz (consistent with a *trans-diaxial* orientation) is invariant with temperature down to −90°. Furthermore, the C_3–H resonance does not exhibit coalescence behavior as the temperature is lowered.

On the other hand, dramatic changes are observed in various aromatic ring nuclei in both ^1H and ^{13}C NMR spectra of **1** as a function of the temperature. In ^1H NMR, for example, at ambient probe temperature of 18°, the protons at C_4, and C_6, appear as a sharp singlet at δ 6.16 in acetone-d_6. As the temperature is lowered, the peak gradually broadens and eventually separates into two singlets at δ 6.12 and 6.29. The coalescence temperature (T_c) for this process, which results from hindered rotation about C_3–C_2, bond, is −27°. Similar rotational nonequivalence as a function of the temperature was observed in the ^{13}C NMR spectrum of **1** in acetone-d_6. Thus both $C_{1'}$, $C_{3'}$ and $C_{4'}$, $C_{6'}$ carbon pairs exhibited nonequivalence as the temperature was lowered. At 18°, both carbon resonances ($C_{1'}$, $C_{3'}$ and $C_{4'}$, $C_{6'}$) appear as broad singlet at δ156.8 and 107.9. Alternatively, at −30°, these resonances each exist as equally intense doublets (one for each pair) at δ157.6, 156.4 ($C_{1'}$, $C_{3'}$) and 108.0, 107.0 ($C_{4'}$, $C_{6'}$), respectively. The T_c and the chemical shift separations ($\Delta\delta$) for $C_{1'}$, $C_{3'}$ and $C_{4'}$, $C_{6'}$ are 0°, 76.4 Hz and −5°, 66.6 Hz respectively. Similar experiments were carried out using compounds **2** and **3** in both solvents, the results being recorded in Table 1.[13]C NMR spectra for **3** in chloroform-*d* obtained at different temperatures (Fig. 1) are representative of the observed behavior.

†This work is dedicated to Professor Sukh Dev on the occasion of his sixtieth birthday.

Table 1. Determination of aryl ring rotational barriers in cannbidiol (1) and its derivatives (2 and 3)

	Nuclei	Solvent	$\Delta\delta$[a] Hz	T_c[b] °C	$\Delta G^{\ddagger}$ kcal/mol
1	$H_{4'}, H_{6'}$	chloroform-d	39.0	22	14.6
	$H_{4'}, H_{6'}$	acetone-d_6	15.1	-27	12.5
	$C_{1'}, C_3$	chloroform-d	77.7	35	14.8
	$C_{4'}, C_6$	chloroform-d	77.7	35	14.8
	$C_{1'}, C_3$	acetone-d_6	76.4	0	13.1
	$C_{4'}, C_6$	acetone-d_6	66.6	-5	12.9
2	OCH_3	acetone-d_6	6.2	-30	12.8
	$C_{4'}$	acetone-d_6	70.3	2	13.2
3	OCH_3	acetone-d_6	5.5	-23	13.2
	$C_{1'}, C_3$	chloroform-d	96.2	11	13.5
	$C_{4'}, C_6$	chloroform-d	88.8	9	13.5
	OCH_3	acetone-d_6	9.2	-11	13.7
	$C_{1'}, C_3$	acetone-d_6	82.5	11	13.6
	$C_{4'}, C_6$	acetone-d_6	72.1	11	13.7

[a] Chemical shift separation. [b] Coalescence temperature.

The free energies of activation for the rotation of the C_3–C_2 bond in **1** to **3**, calculated using appropriate equation[13] from ^1H and ^{13}C NMR spectra in acetone-d_6, are all close to 13 kcal/mol (Table 1).

The rotational barrier of **1** was slightly but significantly higher in chloroform-*d* than in acetone-d_6. Thus, $\Delta G^{\ddagger}$ values of 14.6 and 14.8 kcal/mol were obtained from the ^1H and ^{13}C NMR spectra in chloroform-*d*, respectively. Although it might be anticipated that H-bonding of the phenolic proton in **1** with the CO oxygen of acetone-d_6 might contribute to this change, the rotational barriers for the dimethyl ether **3** were found to be in the same range, i.e. 13.2 to 13.7 kcal/mol in acetone-d_6, suggesting that the absence of H-bonding of **1** with solvent chloroform-*d* alone cannot be responsible for the observed increase in the barrier. In the biphenyl series, a negligible solvent effect on the magnitude of rotational barrier was observed.[14] The monomethyl ether **2** also showed temperature dependent spectra in both ^1H and ^{13}C NMR in acetone-d_6.[15] The $\Delta G^{\ddagger}$'s of **2** obtained from the ^{13}C and ^1H NMR agreed well.

Molecular mechanics calculations

Dynamic behaviors of molecules of the size of **1** are most advantageously calculated by molecular mechanics with full geometry optimization.[16] Our modified version of MM2[17] is well suited for the present study, since this version faithfully reproduces barrier heights of internal rotation.[18] Parameters necessary for handling hydroxy and vinyl groups were transferred from MM2.[19] The phenyl group was treated as consisting of sp^2 C atoms having a special stretch force constant and natural bond length.[20] Since molecular mechanics perform best for molecules in the vapor phase, the computational results should be considered as corresponding to the barriers measured in the less polar solvent, chloroform-*d*.

Among two possible rotational axes in **1**, namely C_4–C_8 and C_3–C_2 bonds, Tamir *et al.*[7] have ruled out the significance of the former by rigid rotation calculations using PCILO. Our dynamic NMR study confirmed their conclusion. Hence, before starting the energy minimization, the isopropenyl group was oriented to the position found by X-ray analysis, namely the C_8–C_9 double bond eclipsing with the *axial* proton at C_4, which also turned out to be the least hindering orientation at the barrier of rotation about C_3–C_2 bond. Both OH bonds were oriented away from the pivot bond.

The calculated energy minimum conformation (**M**) of **4**, a side-chain homologue of **1**, was almost identical with the crystal conformation of **1** (Table 2),[11,12] with the plane of the *equatorial* phenyl group parallel to the *axial* C_3–H bond. Upon incrementally rotating the C_3–C_2, bond of **4** (Fig. 2), the energy increased until a saddle point (**T**) was arrived at when the two rings are almost "coplanar" (Fig. 3). The calculated height of **4T** relative to **4M** (16.0 kcal/mol) agreed reasonably well with the observed value (14.7 kcal/mol) of **1** in chloroform-*d* (Table 2).[21]

In the saddle point, the cyclohexene ring has been transformed from the initial half-chair form[12] into a c_s conformation (see ω_r's of **4T** in Table 2) whereas the 4-isopropenyl group still occupies the *pseudo-equatorial* position. Inspection of the structure re-

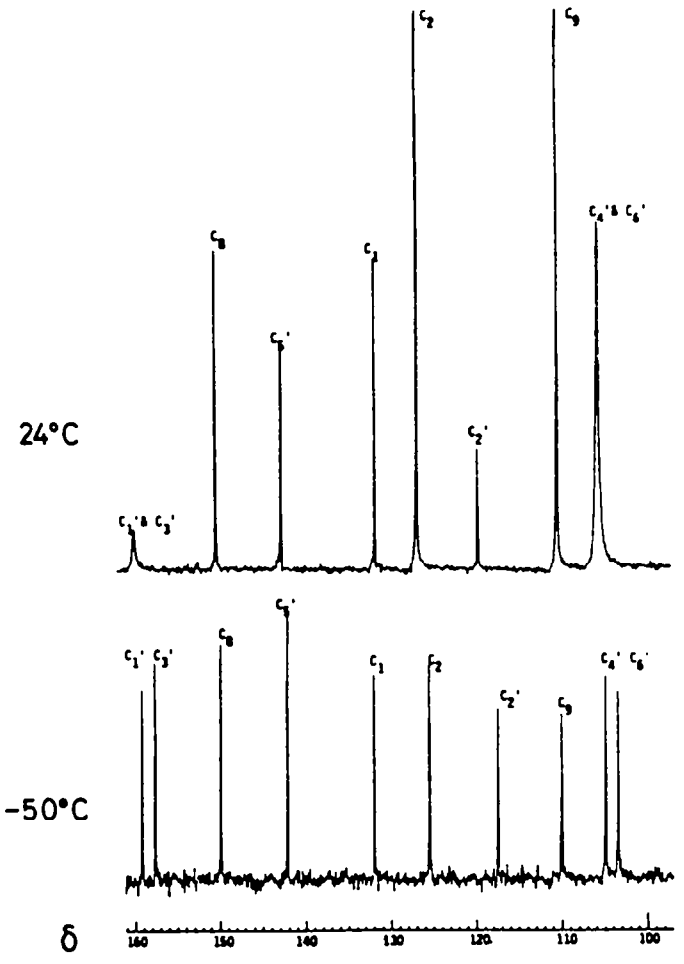
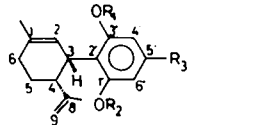


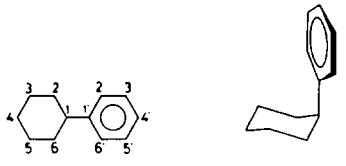
Fig. 1. Partial ^{13}C NMR spectrum of **3** in chloroform-*d*.

vealed two sets of close intramolecular contacts that can be considered as the principal sources of the observed high barrier. They exist between H at C_2 of cyclohexene ring and one of the O atoms and between C_8 and the other O atom. Small nonbonded distances between these atoms as well as unusual valence angles around C_2, C_3 and C_4 are remarkable (Fig. 3). The close contact between C_8 and O atom in **4T** can be readily understood by manipulation of a framework model: they simply come too close to each other. However, the congestion on the other side of the pivot bond, between C_2 methine and other O atom is hardly obvious. Will the rotation of pivot bond be still restricted if this latter OH group is absent?

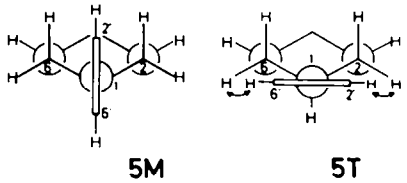
We answer this question by simulating the rotation of pivot bond of a series of substituted phenylcyclohexanes by molecular mechanics (Table 2). Like **4**, phenylcyclohexane (**5**) has the phenyl group in the "*equatorial*-parallel"[22] orientation in the energy minimum (**5M**) and in the "*equatorial*-perpendicular" position at the top of the barrier (**5T**).[23] In the latter (**5T**), which is 2 kcal/mol higher in energy than **5M**, the strain comes mainly from a pair of nonbonded repulsion across the C_1–$C_{1'}$ bond (H_{2e}/H_{ortho} and H_{6e}/H_{ortho}).[23,24] This interaction is weak, 1.0 to 1.2 kcal/mol for each interacting atom pair, but can be strengthened by replacing the end H atom with a larger atom or a group of atoms as in **4**.[25]



1 $R_1=R_2=H$, $R_3=n\text{-}C_5H_{11}$
2 $R_1=H$, $R_2=CH_3$, $R_3=n\text{-}C_5H_{11}$
3 $R_1=R_2=CH_3$, $R_3=n\text{-}C_5H_{11}$
4 $R_1=R_2=H$, $R_3=CH_3$



5 **5A**



5M **5T**

Table 2. Calculated structural features and relative energies of stationary conformations of a cannabidiol homologue (4), phenylcyclohexane (5) and derivatives

Conformation[a]	E_{rel}[b] kcal/mol	Dihedral angle, deg ω_1[c]	ω_2[d]	(ω_r)[e]	T-type[f]
4M	0.00	50.4	-130.5	(0.6,-14.4,44.3,-62.2,48.3,-17.8)[g]	
4T	16.00	-30.7	1.1	(-2.6,1.5,28.4,-58.1,55.4,-26.1)	po/gpo
5M	0.00	62.1	-118.0	(-56.1,56.5,-56.6,56.6,-56.5,56.1)	
5T	2.44[h]	-28.2	28.2	(-53.2,56.7,-57.3,57.3,-56.7,53.2)	p/p
6M[i]	0.00	-118.0	-62.6	(-56.0,56.5,-56.6,56.6,-56.4,56.0)	
$6M_1$[i]	0.43	65.0	117.6	(-55.2,55.9,-56.9,56.9,-56.1,55.4)	
6T	5.75	-24.0	32.2	(-51.4,56.8,-57.6,57.8,-57.3,51.8)	p/po
7M	0.00	-117.1	-64.8	(-54.7,55.9,-57.2,57.2,-55.6,54.6)	
7T	10.68	-27.0	30.0	(-50.1,57.5,-58.0,58.0,-57.6,50.1)	po/po
8M	0.00	-118.0	-66.1	(-54.2,55.6,-57.6,57.4,-55.8,54.7)	
8T	20.95	-25.0	34.9	(7.5,-56.3,42.6,13.6,-64.8,5.2)	po/gpo
9M[i]	0.00	-117.4	-62.8	(-55.3,56.0,-57.0,56.9,-56.6,56.0)	
$9M_1$[i]	0.49	63.5	115.8	(-54.9,55.7,-57.3,57.1,-56.2,55.6)	
9T	14.89	149.5	-174.0	(-47.6,55.3,-59.7,58.3,-56.0,49.4)	p/gpo
$9T_1$	17.11	-35.9	-5.5	(-50.3,56.0,-58.6,57.2,-55.5,51.1)	po/po
10M	0.00	-116.7	-65.1	(-54.3,55.7,-57.8,57.8,-55.6,54.2)	
$10T_1$	27.2	-36.0	-8.6	(66.4,-30.0,-31.2,61.1,-24.9,-37.6)	popo + 1,3-Me...Me[j]

[a] M = energy minimum. T = rotational transition point. [b] Relative to M for each compound. [c] C_2-C_3-$C_{2'}$-$C_{1'}$ for 4, and C_2-C_1-$C_{1'}$-$C_{2'}$ for all other compounds. [d] C_4-C_3-$C_{2'}$-$C_{3'}$ for 4, and C_6-C_1-$C_{1'}$-$C_{6'}$ for all other compounds. [e] Endocyclic C-C-C-C dihedral angles in the order C_6-C_1-C_2-C_3, C_1-C_2-C_3-C_4,...C_5-C_6-C_1-C_2. [f] Classification of rotational transition geometry according to the type of nonbonded interaction: p (progauche), po (progauche + ortho), and gpo (gauche + progauche + ortho). See Discussion. [g] X-Ray results: -2.0, 18.1, -48.4, 65.3, -49.2, 17.6°. Ref.12. [h] Experimental value by NMR = 2.0±0.3 kcal: Schaefer, T.; Niemczura, W.; Danchura, W. Canad. J. Chem. 1979, 57, 355. [i] 6M, 9M: R_1=H, R_2=OH. $6M_1$, $9M_1$: R_1=OH, R_2=H. See structure 5M for the relative positions of R_1 and R_2. [j] 1,3 pseudo-axial, isoclinal Me...Me interaction over a twist-boat cyclohexane.

Introduction of one *ortho*-OH group into **5** to give **6** produces a severe contact between $H_{2'}$ and O atom in the rotational transition state, raising the barrier height by 3.3 kcal/mol compared to the unsubstituted **5**. In the transition state, cyclohexane ring is a somewhat flattened chair (see ω_r's of **6T** in Table 2). Introduction of one more *ortho* OH group produces an additional $H_{6'}$/O interaction (7) which boosts the barrier to 10.7 kcal/mol. In this barrier, the cyclohexane ring is more flattened than that of **6T** (see ω_r's of **7T** in Table 2).

Compound **8** is the model structure closest to **1** (or **4**) carrying a substituent at C_2 as **1** carries the 4-isopropenyl group. Whereas conventional one-bond driver calculations have so far been sufficient to locate the barriers of **4** to **7** (the steric energy vs drive angle curves were all continuous), this technique failed for **8**, giving a discontinuity in the torsional energy curve. Hence, the two-bond driver technique[26] was used. when dihedral angles C_2-C_1-$C_{1'}$-$C_{2'}$ and C_6-C_1-$C_{1'}$-$C_{6'}$ were driven, a smooth energy surface was obtained (Fig. 4). At the saddle point of rotation,

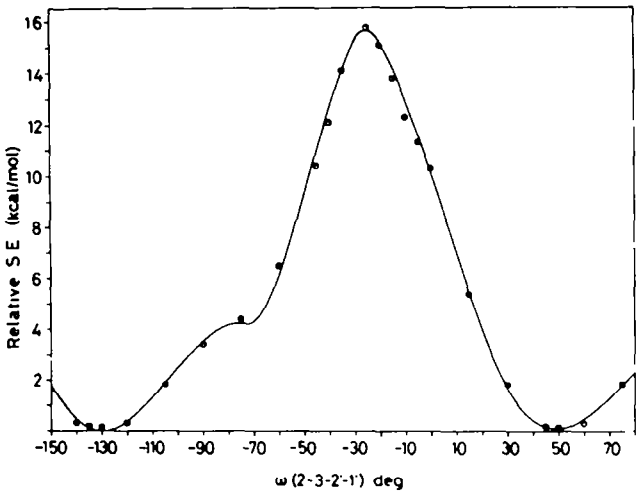
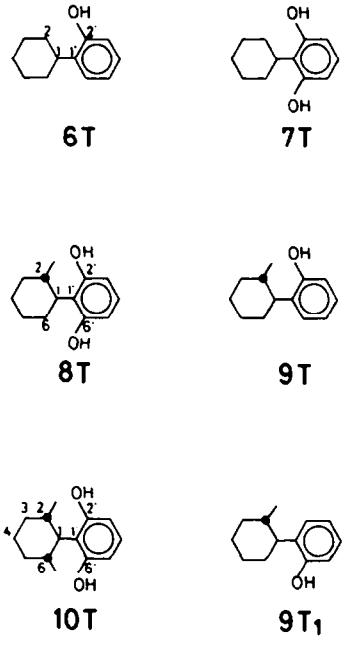


Fig. 2. Calculated torsional energy profile during the rotation of C_3–$C_{2'}$ bond of **4**, a side-chain homologue of **1**.

the cyclohexane ring had been transformed into a twist boat with the Me group in *quasi-equatorial* disposition (see ω_i's of **8T** in Table 2). The rotational barrier of **8** (20.9 kcal/mol) along this pathway (Fig. 4) is significantly higher than those of **1** and **4**. Two reasons may be advanced to interpret this difference. One is the larger steric size of C–H bond of Me in **8** than that of sp^2 C atom with p_z orbital in **4**. The other reason is that the $C_6(sp^3)$–H . . . O interaction in **8** is stronger than the $C_2(sp^2)$–H . . . O interaction in **4** due to different C–C–H angles.[27]

Removal of OH group at $C_{6'}$ of **8** gives **9**, which produces two different rotational transition conformations, **9T** and **9T$_1$**. The former involves the same 1,6-interaction between Me and OH as in **8T**, but the barrier height is 3.8 kcal/mol lower. Clearly, **9T** has dissipated some of the strain by deforming to the side of C_6–C_1–$C_{6'}$, and this observation justifies the assertion of the role of C_2/O interaction in the restricted rotation about the pivot bond of **1**.

The other transition conformation **9T$_1$** has a pair of 1,5-interactions on both sides of pivot bond and in this regard resembles **7T**. The higher calculated barrier of **9T$_1$** compared to **7T** indicate that the



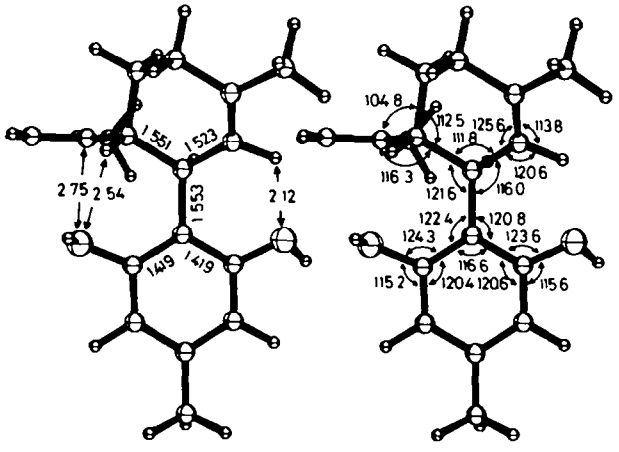


Fig. 3. ORTEP stereodrawing of calculated barrier structure of **4** appeared in the rotation of C_3–$C_{2'}$ bond. Lengths are in Å and angles in degrees.

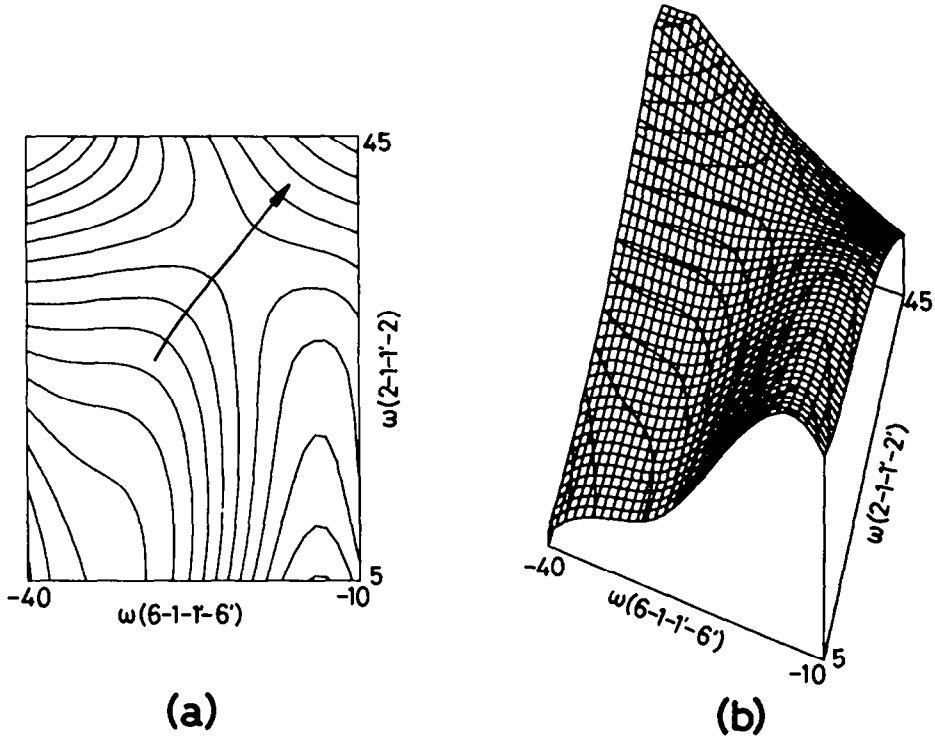


Fig. 4. Torsional energy surface of **8** obtained by driving C_6–C_1–$C_{1'}$–$C_{6'}$ and C_2–C_1–$C_{1'}$–$C_{2'}$ dihedral angles from $-40°$ to $-10°$ and from 5° to 45°, respectively. (a) Contour map with a line separation of 0.5 kcal/mol. (b) Perspective view with contour lines every 0.5 kcal/mol.

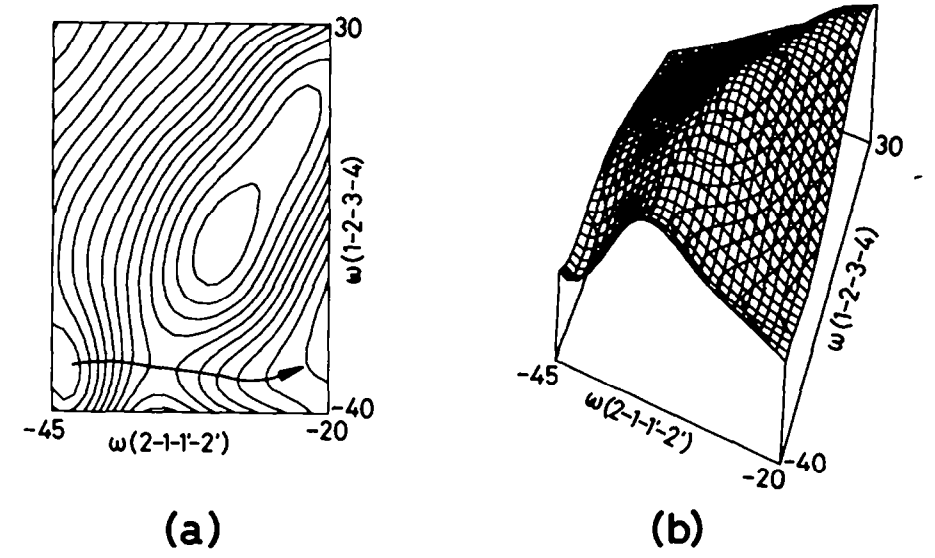


Fig. 5. Torsional energy surface of **10** obtained by driving C_1–C_2–C_3–C_4 and C_2–C_1–$C_{1'}$–$C_{2'}$ dihedral angles from $-40°$ to 30°, and from $-45°$ to $-20°$, respectively. (a) Contour map with a line separation of 0.5 kcal/mol. (b) Perspective view with contour lines every 0.5 kcal/mol.

$CH_3 \ldots CH_2$ interaction is stronger than the $OH \ldots CH_2$ interaction.

Structure **10** is the extreme case in this series, with two Me groups attached to the cyclohexane ring, which would simultaneously produce two sets of severe 1,6-Me/O interactions in the transition state of rotation of the pivot bond, if the chair cyclohexane conformation were maintained. Two-bond driver calculations using the same set of dihedral angles that were used for **8** failed to give continuous energy surface. This failure indicates that the initially expected transition state **10T** with chair cyclohexane ring was very probably too strained to exist. Hence possibilities of nonchair mechanism were sought. A smooth surface was obtained when C_1–C_2–C_3–C_4 dihedral angle was driven in addition to the pivot bond (Fig. 5). At the saddle point (**10T**$_1$, Fig. 6), the cyclohexane ring is an almost perfect twist-boat

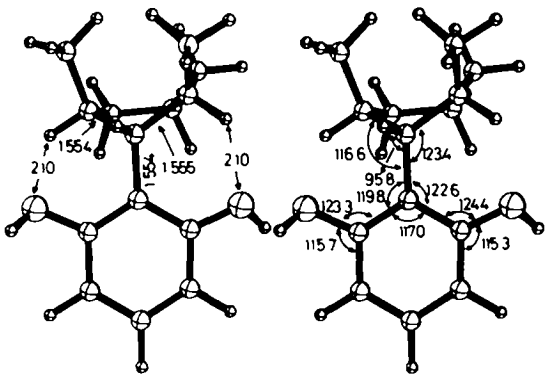


Fig. 6. ORTEP stereodrawing of calculated barrier structure of **10** in the rotation of C_1–$C_{1'}$ bond. Lengths in Å and angles in degrees.

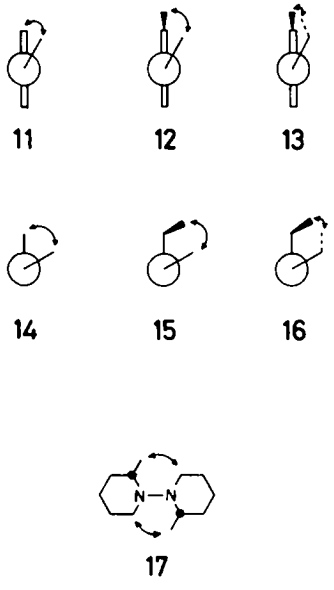
(point group D_2, see ω_i's of **10T**$_1$ in Table 2). This barrier, which is 27.2 kcal/mol higher than the chair/parallel energy minimum (**10M**), contains a pair of 1,5-CH_2/O interactions across the pivot bond and a 1,3 *quasi-axial* Me/*isoclinal* Me interaction over the twist-boat cyclohexane ring as the two main sources of strain. If the pathway shown in Fig. 5 represents the most favorable one for the internal rotation of pivot bond in **10**, which appears likely, molecules having the essential structural feature of **10** should exhibit atropisomerism.

DISCUSSION

First let us propose a new term "*pro-gauche*" to define the conformation of four-atom sequence C_2–C_1–$C_{1'}$–$C_{2'}$ of **5T** (see also **11** for a simplified illustration).[28] Since **5T** is 2 kcal/mol less stable than **5M**, where there are two sets of *gauche*-like interactions across the pivot bond (C_2–C_1–$C_{1'}$–$C_{2'}$, and C_6–C_1–$C_{1'}$–$C_{2'}$), one *pro-gauche* is at least 1 kcal/mol less stable than one *gauche* interaction.[29] The 1,5-interaction occurring in **6T** between OH group and C_2-methylene group may be called as "*po*" (*progauche* at C_2–C_1–$C_{1'}$–$C_{2'}$ + *ortho* at C_1–$C_{1'}$–$C_{2'}$–OH, **12**). Finally, the 1,6-interaction involving Me–C_2–C_1–$C_{1'}$–$C_{2'}$–OH of **8T** may be named *gpo* (*gauche* + *progauche* + *ortho*, **13**).

Attempted dissection of the calculated barriers for **5**–**10** into the sum of *p*, *po* and *gpo* terms failed, because the strain in other parts of molecule, especially in the cyclohexane ring, changes with substituents and also because the strain intensifies in a non-additive way as the number and size of substituents increase.[30] The breakdown of the additivity in steric energy terms is not surprising, as it has been repeatedly proven in a number of stereochemical problems by molecular mechanics method.[16]

It is pertinent to mention here the formal similarity of *p* (**11**), *po* (**12**), and *gpo* (**13**) interactions with *g* (**14**), g^+g^- (**15**), and $g^+g^-g^+$ (**16**) interactions,[31] respectively, in the alkane conformation. The latter two are "forbidden" in the alkane conformation because the end atoms approach and strongly repel each other. Note that *g* and *p* in the *gpo* sequence of **8T** and **9T** have opposite signs as in the *g*'s of **16**. The *po* sequence produces almost planar circumstance. Hence in these 1,5-*po* and 1,6-*gpo* interactions, end atoms are also brought close to each other to produce



strong repulsion. These interactions always arise simultaneously in a pair in the phenylcyclohexane derivatives studied here at the conformational transition point, intensifying each other to increase the barrier beyond the additivity rule would have predicted. The rotational barrier of **1** and **4** can be interpreted similarly: one *po* interaction involving C_2–C_3–$C_{2'}$–$C_{3'}$–O sequence and one *gpo* involving C_8–C_4–C_3–$C_{2'}$–$C_{1'}$–O sequence arise simultaneously at the barrier (Fig. 3).

Thus we recognize here another example of the "staggered" barrier in the internal rotation. Previously, we have realized that the barrier of rotation in *meso*-2,2′-dimethyl-1,1′-bipiperidine (**17**)[32] arises from a pair of equivalent g^+g^- nonbonded interactions involving the end atoms of CH_3–CH–N–N–CH_2 sequence. In all the transition conformations studied here, **4T** to **10T**$_1$, the arrangement of bonds about the pivot bond is more or less staggered (see ω_1 and ω_2 of Table 2), and contrasts against the conventional "eclipsed" barrier in the internal rotation of ethane derivatives.[33]

The right end column of Table 2 classifies the transition conformer type according to the *p*, *po* and *gpo* terminology. The correspondence between **4T** and **8T** is now clearer (both *po*/*gpo*). It was impossible to achieve the energy minimization of a transition state corresponding to the highest energy combination, *gpo*/*gpo*, in the present study.

Another characteristic feature of the internal rotation of phenylcyclohexane derivatives is the frequently observed deformation of cyclohexane ring from chair into nonchair conformation, and in the case of cyclohexene ring of **1** from half-chair into a C_s form. As our molecular mechanics results indicate, such ring deformation takes place when the barrier exceeds the chair–chair inversion barrier of cyclohexane (12.1 kcal/mol).[34, 35]

CONCLUSIONS

The surprisingly high barrier of the pivot bond rotation observed for **1** was rationalized by molecular mechanics simulation of the torsional process of a

homologue **4**. Hence the previously reported[7] low rotational barrier of **1** appears wrong.[36] Analysis of our computational results of **4** and appropriately substituted phenylcyclohexanes suggested a new and systematic interpretation of the restricted rotation about the pivot bond of these molecules. The principal source of barrier is the two sets of nonbonded 1,5- and/or 1,6-van der Waals repulsion occurring simultaneously on both sides of the rotating bond at the transition state.[37]

EXPERIMENTAL

Materials. Cannabidiol (**1**) was supplied from the National Institute on Drug Abuse (Makor Batch 7657, RTI 2167-14-2), m.p. 67-69°. Published procedures were used to prepare ethers **2** and **3**.[38] These compounds were purified by column chromatography over silica gel and were characterized by spectral methods including mass and IR spectroscopy.

NMR analysis. The ^1H (250 MHz) and ^{13}C (62.9 MHz) NMR spectra were recorded on a Bruker WM-250 Fourier transform NMR spectrometer equipped with a Bruker ASPECT-2000 computer and a Diablo Model 44b disk accessory. TMS was used as the internal standard. The temperature stability was ±1°.

Computation. As a check for the adaption of "mechanical" treatment of phenyl group as a collection of special sp^2 C atoms (stretch force constant 8.066 mdyne/Å and natural bond length 1.399 Å) in MM2′, the energy difference between the global energy minimum "*equatorial*-parallel"[22] conformation (**5M**) and "*axial*-perpendicular" conformation (**5A**) was calculated. The result, 3.13 kcal/mol, agreed well with the known A value of phenyl group.[39] Oxygen[40] and vinyl parameters have been transferred from MM2.[19] The barrier heights were estimated based on the smoothed torsional energy surface.[26b]

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[15]In the ^1H NMR spectrum, only the OMe resonance became nonequivalent as the temp was lowered.
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[21]Whereas the calculated barrier heights correspond to enthalpies (ΔH^*), these are usually compared directly with the observed free energies ΔG^* because of the generally small ΔS^* values in the intramolecular process. The calculated ΔH^* is considerably higher than the observed ΔG^*'s of ethers, **2** and **3**.
[22]The terms, parallel and perpendicular, refer to the relative disposition of phenyl plane with regard to the C-H bond at the phenyl-bearing C atom.[23]
[23]N. L. Allinger and M. T. Tribble, *Tetrahedron Letters* 3259 (1971).
[24]Strictly speaking, **4T** cannot be classified as "*equatorial*-perpendicular", since the bond C_3–C_4 is eclipsed with phenyl plane (Table 2). Actually, the eclipsing is an incidental result of minimizing the congestion at the C_4/O contact.
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[26a]U. Burkert and N. L. Allinger, *J. Comput. Chem.* **3**, 40 (1982);[b]E. Ōsawa *Ibid.* **3**, 400 (1982).
[27]We used different effective dielectric constants for **4**(10) and **8**(1.5), implying that the calculated results with **4** refer to chloroform-*d* solution and those with **8** to the gas phase. In this case, however, the effect of medium upon the barrier height is small due to the internal compensation of bond dipole interactions.
[28]*Pro-gauche* differs from *gauche* in two aspects. First, the dihedral angle is about 30° in the former, and about 60° in the latter. Second, two carbon atoms in the former are sp^2-hybridized and hence have different valence angles and bond lengths from those of the latter.
[29]*Pro-gauche* × 2 − *gauche* × 2 = 2 kcal/mol.
[30]For example, additivity leads to 1.2 kcal/mol/*p* and 4.55 kcal/mol/*po* hence predicted 4.55 × 2 = 9.1 kcal/mol of barrier for **7T**, whose MM2′ barrier is actually 10.7 kcal/mol. Similarly, additivity gives 13.6 kcal/mol for a *gpo* interaction, and hence predicted 4.5 + 13.6 = 18.1 kcal/mol for **8T**. The MM2′ barrier of **8T** is 21 kcal/mol.
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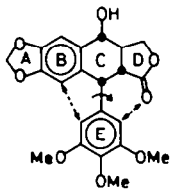
[35]Further studies on variously methylated phenylcyclohexanes support this reasoning. Results of these studies will be described elsewhere.

[36]Prof. Mechoulam recalculated $\Delta G^{\ddagger}$ of **1** from the coalescence temp of 288 K and the chemical shift difference of 10 Hz which they observed in chloroform-*d* at 60 MHz on a Bruker WP–60 spectrometer and obtained a value of 15 kcal/mol in close agreement with us. Furthermore, he obtained the following activation parameters based on the temperature dependence of the rate constants:

$$\Delta H^{\ddagger} = 14.3 \pm 1.9 \text{ kcal/mol}$$
$$\Delta S^{\ddagger} = 7.88 \pm 6.6 \text{ e.u.}$$
$$\Delta G^{\ddagger} = 12.03 \pm 3.8 \text{ kcal/mol}$$

(private communications). This activation enthalpy agrees with the $\Delta H^{\ddagger}$ value calculated for **4** within experimental error.

[37]Recently Bushweller *et al.* (C. D. Rithner, C. H. Bushweller W. J. Gensler and S. Hoogasian, *J. Org. Chem.* **48**, 1491 (1983)) observed restricted rotation about the pivot bond of a 3-phenylcyclohexane, podophyllotoxin (**18**). The low $\Delta G^{\ddagger}$ value at 156 K (7.0 ± 0.2 kcal/mol) determined



18

for **18** may appear surprising since **18** seems to involve the same 1,6-nonbonded interactions across the pivot bond as we have seen for **1**. However, the E ring of **18** is in the *quasi-axial* position on the *C* ring which is in half-chair conformation. In this orientation, the 1,6-distances across the pivot bond are large. Note that the phenyl group of **1** is also attached at C_3 atom of a half-chair cyclohexene ring but in *quasi-equatorial* position. It is necessary for the high rotational barrier to appear that the nonbonded interaction across the pivot bond be in a near plane, namely phenyl group be in *equatorial* position.

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