

Structural Determination of Menthol and Isomenthol, a Minty Compound and Its Nonminty Isomer, by Means of Gas Electron Diffraction Augmented by Theoretical Calculations

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The molecular structures of menthol and isomenthol were determined by means of gas electron diffraction. The nozzle temperatures were 90 °C and 137 °C, for menthol and isomenthol, respectively. The results of RHF and DFT calculations were used as supporting information. FTIR spectra were measured and used to refine the theoretical force constants. It was found that the electron diffraction data of menthol can be reproduced by assuming essentially one conformer in which all the substituents of the cyclohexane ring, isopropyl, methyl, and hydroxyl groups are in the equatorial position. On the other hand, isomenthol has two stable conformers in the gas phase with comparable abundance. One conformer has its isopropyl and hydroxyl groups in the equatorial position, and the other conformer has them in the axial position. The abundance of the former is $63 \pm 30\%$ and that of the latter is 37%. The determined structural parameters (r_g and \angle_α) of menthol are as follows: $\langle r(\text{C}-\text{C}) \rangle = 1.534(2) \text{ \AA}$, $r(\text{C}-\text{O}) = 1.408(10) \text{ \AA}$, $\langle r(\text{C}-\text{H}) \rangle = 1.117(3) \text{ \AA}$, $\langle \angle \text{C}-\text{C}-\text{C}_{\text{ring}} \rangle = 112.2(5)^\circ$, $\langle \angle \text{C}-\text{C}-\text{C}_{\text{exo}} \rangle = 111.6(6)^\circ$, $\langle \angle \text{C}-\text{C}-\text{O} \rangle = 110.0(11)^\circ$, $\langle \angle \text{C}-\text{C}-\text{H} \rangle = 109.2(11)^\circ$, $\phi = 57(7)^\circ$. Angle brackets denote average values; parenthesized values are the estimated limits of error (3σ) referring to the last significant digit. Angles $\text{C}-\text{C}-\text{C}_{\text{exo}}$ are the $\text{C}-\text{C}-\text{C}$ angles other than the six $\text{C}-\text{C}-\text{C}$ angles in the cyclohexane ring. Angle ϕ is the torsional angle around the $\text{C}_{i-\text{pr}}-\text{C}_{\text{ring}}$ bond. Those of the main conformer of isomenthol whose isopropyl and hydroxyl groups are in the equatorial position are as follows: $\langle r(\text{C}-\text{C}) \rangle = 1.538(1) \text{ \AA}$, $r(\text{C}-\text{O}) = 1.427(13) \text{ \AA}$, $\langle r(\text{C}-\text{H}) \rangle = 1.112(3) \text{ \AA}$, $\langle \angle \text{C}-\text{C}-\text{C}_{\text{ring}} \rangle = 112.6(25)^\circ$, $\langle \angle \text{C}-\text{C}-\text{C}_{\text{exo}} \rangle = 111.5(9)^\circ$, $\langle \angle \text{C}-\text{C}-\text{O} \rangle = 109.0(17)^\circ$, $\langle \angle \text{C}-\text{C}-\text{H} \rangle = 108.9(15)^\circ$, $\phi = -63(17)^\circ$. The relationships between the minty odor and conformations are briefly discussed.

Introduction

As the first targets of our new project, electron diffraction studies of odorous molecules, menthol (Figure 1) and one of its isomers, isomenthol (Figure 2), have been chosen. This project is on the line of our recent theme, structural and conformational investigation of bioactive compounds, the first target of which was nicotine.¹ Despite the structural resemblance between menthol and isomenthol, the former has the odor of mint and the latter has quite a different one. The relationship between the molecular structure and the minty odor has been studied extensively for various compounds including menthol and isomenthol by Chastrette and Rallet.² Their investigations were not based on the experimentally determined structures and conformational properties but on the computationally obtained ones by using molecular mechanics method with the Sybyl³ force field. No experimental molecular structure of menthol is available except for that determined by Bombicz et al. by means of single-crystal X-ray diffraction.⁴ On the other hand, it has been becoming practical to apply gas electron diffraction method aided by today's sophisticated theoretical calculations to rather complicated molecules, such as some mesogens.^{5,6} Compared with the mesogens MBBA⁶ and PAA,⁵ which had been investigated successfully by means of gas electron diffraction, it can be said that investigations of menthol and isomenthol are well within our reach. In this study, the geometrical structures and conformational properties have been determined

by gas electron diffraction supported by ab initio and DFT calculations and infrared spectroscopy.

Experimental Section

The samples of (1R,2S,5R)-(–)-menthol and (1S,2R,5R)-(+)-isomenthol with purity of 99% were purchased from Aldrich Chemical Co. and were used without further purification. Electron diffraction patterns were recorded on 8 in. \times 8 in. Kodak projector slide plates with an apparatus equipped with an r^3 -sector.⁷ The camera distance was about 244 mm to cover the s -range sufficient for the molecule of this size. To generate enough sample pressure, a nozzle that can heat the sample up to about 200 °C (ref 5) was used. The accelerating voltage of incident electrons was about 37 kV. Other experimental conditions are summarized in Table 1. The photographic plates were developed for 4.5 min in a Dektol developer diluted 1:1. The photometry process was described in details elsewhere.⁶ The molecular scattering intensity $M(s)$ was calculated as $M(s) = (I_T(s) - I_B(s))/I_B(s)$. The experimental intensities and backgrounds are available as Supporting Information (Table S1). The electron wavelength was calibrated to the $r_a(\text{C}=\text{S})$ distance of CS_2 (1.5570 Å).⁸

Elastic atomic scattering factors were calculated as described in ref 9, and inelastic ones were taken from ref 10. The experimental molecular scattering intensities are shown in Figure 3 with the final calculated ones. A diagonal weight matrix was used in the least-squares analysis on the molecular scattering intensities. The weight function was set to unity in the medium s region while it was reduced in the small and large s regions by using two Gaussian functions.¹¹

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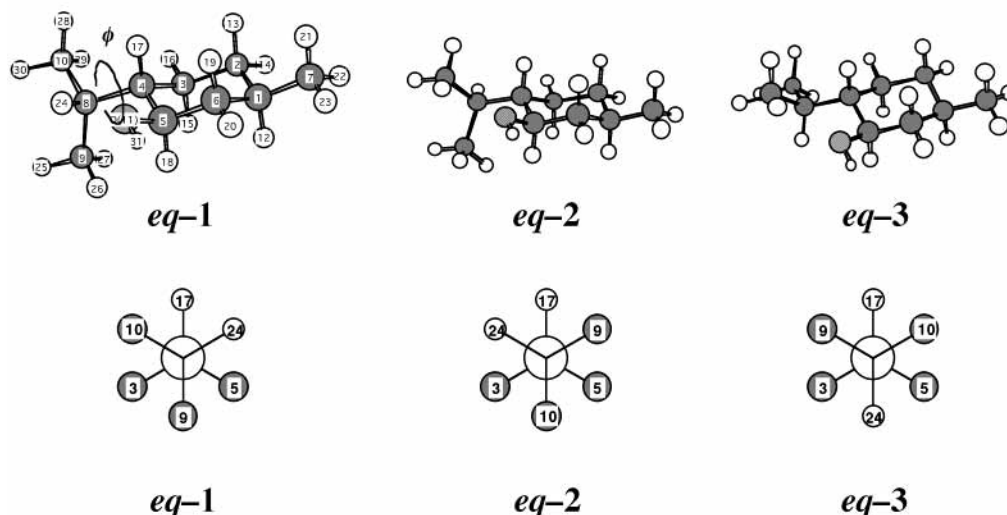
(-)-Menthol

Figure 1. Molecular models and atom numbering for some possible conformers of menthol. Angle ϕ is the dihedral angle C₃–C₄–C₈–C₉. Newman projections are viewed from the direction of C₈ to C₄.

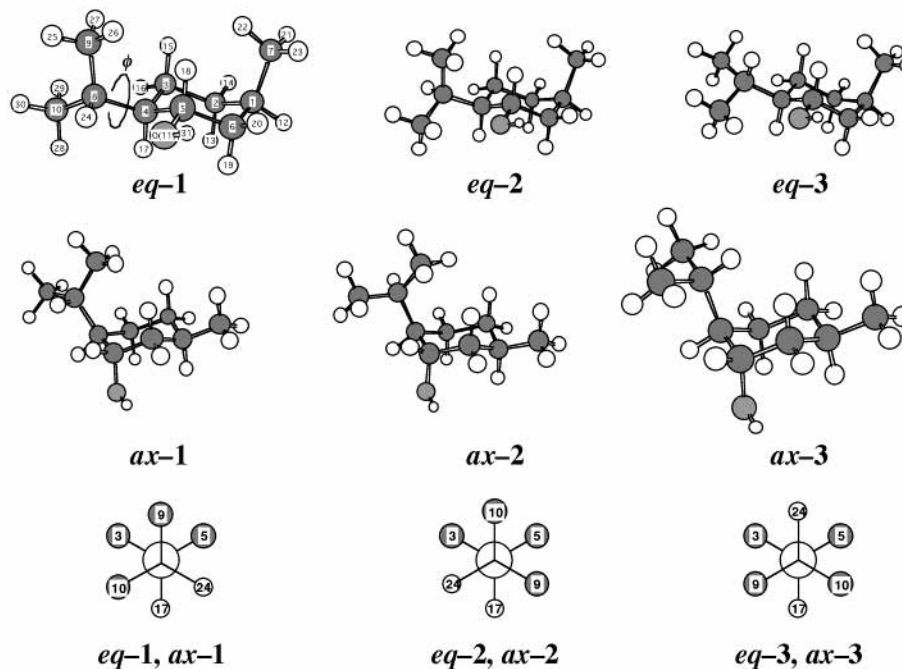
(+)-Isomenthol

Figure 2. Molecular models and atom numbering for some possible conformers of isomenthol. Angle ϕ is the dihedral angle C₃–C₄–C₈–C₉. Newman projections are viewed from the direction of C₈ to C₄.

Gas-phase FTIR spectra of menthol and isomenthol were measured at room temperature on a Bomem DA3.16 spectrometer with a resolution of 0.5 cm⁻¹. An absorption cell with a path length of 10 m was used. The sample pressures were 150 and 75 mTorr for menthol and isomenthol, respectively. The obtained spectra are shown in Supporting Information. Observed frequencies for both molecules are available as Supporting Information (Table S3).

Theoretical Calculations

Possible Conformers. When the cyclohexane ring of menthol takes a chair form, all the substituents (isopropyl, methyl, and hydroxyl groups) will take the equatorial or axial positions simultaneously, and it is expected that the former has a much

TABLE 1: Experimental Conditions for Gas Electron Diffraction Experiments of Menthol and Isomenthol

	menthol	isomenthol
camera distance/mm	244.3	244.2
nozzle temperature/K	363	410
electron wavelength/Å	0.06336	0.06334
uncertainty in the scale factor/%	0.04	0.03
background pressure during exposure/ 10 ⁻⁶ Torr	4.6–4.8	5.4–5.9
beam current/μA	1.7	1.2
exposure time/s	63–84	72–90
number of plates used	4	4
range of <i>s</i> value/Å ⁻¹	5.1–33.8	4.5–33.8

lower energy than that of the latter.¹² This was confirmed by a preliminary ab initio calculation in which the RHF/6-31G*

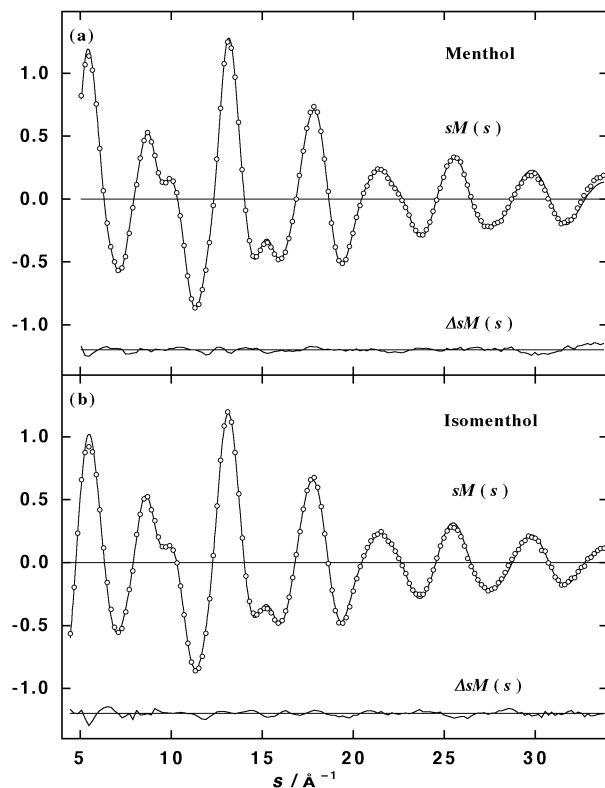


Figure 3. Experimental (open circles) and theoretical (solid curves) molecular scattering intensities of (a) menthol and (b) isomenthol; $\Delta sM(s) = sM(s)^{\text{obs}} - sM(s)^{\text{calc}}$. The theoretical curves were calculated from the best-fit parameters.

energy of the all-axial form of the menthol is a few kcal mol⁻¹ higher than that of the all-equatorial form. Therefore, it was concluded to assume that all the substituents of menthol are in the equatorial position,² and hence, only the internal rotations of the isopropyl and hydroxyl groups are left as sources of structural flexibility. However, the internal rotation of the hydroxyl group virtually changes the position of the only one hydrogen atom (H₃₁ in Figure 1), and no significant difference in the electron diffraction data is expected by this change. So, it was assumed that the O–H bond takes the trans orientation to the C₄–C₅ bond, which is bonded to the isopropyl group (see Figure 1), and that only the internal rotation of the isopropyl group causes the conformational change. The possible conformers of menthol are labeled as *eq-1*, *eq-2*, and *eq-3* according to the three possible orientations of the isopropyl group as illustrated in Figure 1.

In contrast to menthol, isomenthol has the three substituents oriented differently and there are two possible ring conformations. In one form, the isopropyl and hydroxyl groups take the equatorial position and the methyl group takes the axial position. In another form, i.e., when the ring is inverted from the first position, only the methyl group takes the equatorial position. These two ring conformations are labeled *eq* and *ax*, respectively, according to the position of the isopropyl group. As in the case of menthol, these forms are further classified by the orientation of the isopropyl group such as *eq-1*, *ax-3*, and so on, as illustrated in Figure 2. If the cyclohexane ring of isomenthol takes the boat form, it is tentatively possible for all the substituents to take the equatorial position. However, a preliminary RHF calculation revealed that this boat conformer has very high energy, and hence, it was ruled out.

RHF Calculations. At first, geometrical optimizations for all the conformers shown in Figures 1 and 2 were carried out

TABLE 2: Relative Energies and Estimated Abundance for the Possible Conformers of Menthol and Isomenthol Obtained from the RHF/6-31G* ab Initio Calculations (in kcal mol⁻¹ and %)

conformers ^a	menthol		isomenthol	
	ΔE^b	abundance ^c	ΔE^d	abundance ^e
<i>eq-1</i>	0.00	72.2	0.00	49.9
<i>eq-2</i>	0.76	25.2	0.75	19.9
<i>eq-3</i>	2.40	2.6	2.40	2.6
<i>ax-1</i>			3.36	0.8
<i>ax-2</i>			3.61	0.6
<i>ax-3</i>			0.53	26.0
boat			4.39	0.2

^a See Figures 1 and 2 for the definitions of the conformers. ^b Absolute value of the energy for the *eq-1* conformer is $-465.194630E_h$. ^c Estimated from the ΔE assuming the temperature of 363 K. ^d Absolute value of the energy for the *eq-1* conformer is $-465.190870E_h$. ^e Estimated from the ΔE assuming the temperature of 410 K.

in order to choose the conformers to be assumed in the analyses of the electron diffraction data. The method and basis set used were RHF/6-31G*, and the program GAUSSIAN 94¹³ was used. The obtained relative energies are listed in Table 2. As shown in this table, the *eq-1* and *eq-2* conformers of menthol have significantly lower energies than the *eq-3* conformer, and hence, the *eq-3* of menthol was excluded from the further analysis. On the other hand, the *ax-3* conformer of isomenthol has energy comparable with those of *eq-1* and *eq-2* conformers. Therefore, these three conformers were included into the further analysis.

DFT Calculations. According to the above-mentioned results, the geometries of the *eq-1* and *eq-2* conformers of menthol and the *eq-1*, *eq-2*, and *ax-3* conformers of isomenthol were further optimized by using the B3LYP/DFT method with a 6-31G* basis set in order to obtain more reliable structural parameters. The results of the calculations are listed in Table 3. The vibrational calculations for these conformers were also carried out with the same method and basis set.

Analyses

Normal Vibration Analysis. The Cartesian force constants of menthol and isomenthol by the B3LYP/6-31G* calculations were transformed into the internal force constants f_{ij} . As the *eq-1* conformer was predicted to be the most abundant by the theoretical calculations for the both compounds, f_{ij} 's for the *eq-1* were modified by the scaling method so as to reproduce the experimental vibrational wavenumbers of the FTIR spectra. The linear scaling formula¹⁴ $f_{ij}(\text{scaled}) = (c_i c_j)^{1/2} f_{ij}(\text{unscaled})$ was used where c_i is a scale factor. The definitions of internal coordinates with the resultant scale factors are listed in Table S2 of Supporting Information. The calculated vibrational wavenumbers and scaled force constants are listed in Tables S3 and S4 of Supporting Information, respectively.

Analysis of Electron Diffraction Data. As menthol and isomenthol consist of only four types of single bond, C–C, C–O, C–H, and O–H, and all the bond angles are close to the tetrahedral angle, it is easily understood that the radial distributions of these compounds will show the limited number of peaks with each of which being contributed by many unequal atomic pairs. Therefore, the differences between the following structural parameters were fixed at their B3LYP/6-31G* values in order to reduce the number of adjustable parameters: (1) the C–C bond lengths, (2) the six C–C–C angles of the cyclohexane ring, (3) the seven C–C–C angles to determine the directions of methyl and isopropyl groups, (4) the two C–C–O angles, (5) the C–H bond lengths, (6) the C–C–H angles, (7) the C₄–

TABLE 3: Geometrical Parameters and Relative Energies of Menthol and Isomenthol Obtained from the B3LYP/6-31G* DFT Calculations^a

parameters	menthol					parameters	isomenthol				
	<i>eq-1</i>	<i>eq-2</i>	<i>eq-1</i>	<i>eq-2</i>	<i>ax-3</i>		<i>eq-1</i>	<i>eq-2</i>	<i>eq-1</i>	<i>eq-2</i>	<i>ax-3</i>
bond lengths (in Å)						bond angles (in deg)					
C ₁ –C ₂	1.538	1.537	1.543	1.542	1.539	C ₄ –C ₃ –H ₁₆	109.9	109.0	109.9	109.0	107.7
C ₂ –C ₃	1.536	1.535	1.538	1.536	1.537	C ₃ –C ₄ –H ₁₇	107.5	107.4	107.5	107.3	107.6
C ₃ –C ₄	1.543	1.545	1.543	1.545	1.546	C ₅ –C ₄ –H ₁₇	105.7	106.5	105.6	106.5	106.1
C ₄ –C ₅	1.538	1.538	1.538	1.537	1.545	C ₈ –C ₄ –H ₁₇	106.3	107.2	106.2	107.2	106.7
C ₅ –C ₆	1.535	1.535	1.537	1.538	1.538	C ₄ –C ₅ –H ₁₈	108.8	108.3	108.9	108.4	109.8
C ₆ –C ₁	1.538	1.538	1.542	1.543	1.539	C ₆ –C ₅ –H ₁₈	108.4	108.2	109.2	109.0	108.7
C ₁ –C ₇	1.533	1.533	1.538	1.538	1.532	O ₁₁ –C ₅ –H ₁₈	109.6	109.4	109.3	109.1	108.6
C ₄ –C ₈	1.554	1.559	1.554	1.559	1.557	C ₁ –C ₆ –H ₁₉	109.7	109.8	109.6	109.6	110.0
C ₈ –C ₉	1.538	1.538	1.538	1.538	1.539	C ₅ –C ₆ –H ₁₉	108.1	108.3	107.2	107.4	109.1
C ₈ –C ₁₀	1.537	1.538	1.537	1.538	1.540	C ₁ –C ₆ –H ₂₀	109.9	109.9	110.0	109.9	109.6
C ₅ –O ₁₁	1.431	1.432	1.432	1.432	1.436	C ₅ –C ₆ –H ₂₀	109.4	109.2	109.3	109.2	108.9
C ₁ –H ₁₂	1.102	1.102	1.099	1.099	1.099	C ₁ –C ₇ –H ₂₁	110.9	111.0	110.7	110.7	111.2
C ₂ –H ₁₃	1.101	1.101	1.099	1.099	1.098	C ₁ –C ₇ –H ₂₂	111.2	111.2	112.6	112.6	111.1
C ₂ –H ₁₄	1.098	1.098	1.098	1.098	1.101	C ₁ –C ₇ –H ₂₃	111.4	111.4	110.8	110.9	111.5
C ₃ –H ₁₅	1.099	1.100	1.098	1.099	1.095	H ₂₁ –C ₇ –H ₂₂	107.7	107.7	107.4	107.4	107.6
C ₃ –H ₁₆	1.096	1.097	1.096	1.097	1.096	H ₂₁ –C ₇ –H ₂₃	107.7	107.7	107.6	107.7	107.7
C ₄ –H ₁₇	1.102	1.101	1.102	1.101	1.100	H ₂₂ –C ₇ –H ₂₃	107.8	107.8	107.4	107.4	107.6
C ₅ –H ₁₈	1.104	1.104	1.102	1.102	1.099	C ₄ –C ₈ –H ₂₄	105.6	105.5	105.5	105.5	108.9
C ₆ –H ₁₉	1.100	1.100	1.099	1.099	1.101	C ₉ –C ₈ –H ₂₄	107.3	106.7	107.3	106.7	107.2
C ₆ –H ₂₀	1.101	1.101	1.101	1.101	1.100	C ₁₀ –C ₈ –H ₂₄	107.3	107.0	107.3	107.0	107.6
C ₇ –H ₂₁	1.097	1.098	1.097	1.097	1.097	C ₈ –C ₉ –H ₂₅	110.2	110.5	110.2	110.5	110.4
C ₇ –H ₂₂	1.097	1.097	1.095	1.096	1.098	C ₈ –C ₉ –H ₂₆	112.0	111.0	112.1	111.1	112.6
C ₇ –H ₂₃	1.097	1.097	1.097	1.097	1.097	C ₈ –C ₉ –H ₂₇	111.9	111.0	112.0	111.1	111.0
C ₈ –H ₂₄	1.096	1.101	1.096	1.101	1.100	H ₂₅ –C ₉ –H ₂₆	107.3	107.6	107.2	107.6	107.3
C ₉ –H ₂₅	1.097	1.097	1.097	1.097	1.096	H ₂₅ –C ₉ –H ₂₇	107.2	108.6	107.2	108.6	107.5
C ₉ –H ₂₆	1.096	1.097	1.096	1.097	1.094	H ₂₆ –C ₉ –H ₂₇	107.9	107.9	107.9	107.9	107.8
C ₉ –H ₂₇	1.097	1.093	1.097	1.093	1.098	C ₈ –C ₁₀ –H ₂₈	111.4	112.3	111.4	112.3	113.0
C ₁₀ –H ₂₈	1.097	1.097	1.097	1.097	1.094	C ₈ –C ₁₀ –H ₂₉	112.1	110.9	112.1	110.9	110.7
C ₁₀ –H ₂₉	1.097	1.096	1.097	1.096	1.098	C ₈ –C ₁₀ –H ₃₀	110.6	110.3	110.6	110.3	110.5
C ₁₀ –H ₃₀	1.097	1.096	1.097	1.096	1.096	H ₂₈ –C ₁₀ –H ₂₉	107.8	108.2	107.8	108.2	107.6
O ₁₁ –H ₃₁	0.970	0.970	0.970	0.970	0.970	H ₂₈ –C ₁₀ –H ₃₀	107.6	107.4	107.6	107.3	107.2
bond angles (in deg)						dihedral angles (in deg)					
C ₂ –C ₁ –C ₆	109.5	109.3	109.3	109.0	110.1	C ₆ –C ₁ –C ₂ –C ₃	–54.1	–53.6	52.5	51.8	–53.5
C ₁ –C ₂ –C ₃	112.0	112.1	112.7	112.9	111.7	C ₁ –C ₂ –C ₃ –C ₄	56.4	55.6	–56.2	–55.7	57.4
C ₂ –C ₃ –C ₄	112.3	113.0	112.1	112.7	112.8	C ₂ –C ₃ –C ₄ –C ₅	–55.6	–54.8	56.1	56.0	–56.3
C ₃ –C ₄ –C ₅	109.3	108.9	109.4	108.8	108.3	C ₃ –C ₄ –C ₅ –C ₆	55.1	55.1	–55.2	–55.6	54.5
C ₄ –C ₅ –C ₆	111.5	111.7	111.4	111.5	112.5	C ₄ –C ₅ –C ₆ –C ₁	–56.4	–57.3	55.6	56.5	–54.7
C ₅ –C ₆ –C ₁	112.9	112.8	113.9	113.9	113.2	C ₅ –C ₆ –C ₁ –C ₂	54.5	55.0	–52.7	–52.7	52.6
C ₂ –C ₁ –C ₇	112.1	112.1	112.7	112.6	112.1	C ₃ –C ₂ –C ₁ –C ₇	–178.7	–178.2	–73.7	–74.2	–178.2
C ₆ –C ₁ –C ₇	111.7	111.8	112.8	112.8	111.5	C ₂ –C ₃ –C ₄ –C ₈	176.5	177.1	–176.0	–175.8	70.9
C ₃ –C ₄ –C ₈	114.5	111.3	114.6	111.4	114.6	C ₃ –C ₄ –C ₈ –C ₉	58.6	–151.3	–58.8	151.6	50.0
C ₅ –C ₄ –C ₈	112.9	115.2	112.9	115.4	113.1	C ₃ –C ₄ –C ₈ –C ₁₀	–67.5	81.9	67.5	–81.5	172.7
C ₄ –C ₈ –C ₉	114.1	112.7	114.2	112.8	112.0	C ₃ –C ₄ –C ₅ –O ₁₁	176.9	177.3	–176.4	–177.1	–67.2
C ₄ –C ₈ –C ₁₀	111.6	113.7	111.6	113.7	111.9	C ₂ –C ₁ –C ₇ –H ₂₁	61.7	61.7	–59.2	–59.8	–57.9
C ₉ –C ₈ –C ₁₀	110.5	110.6	110.5	110.5	108.9	C ₂ –C ₁ –C ₇ –H ₂₂	–58.1	–58.1	61.0	60.3	61.9
C ₄ –C ₅ –O ₁₁	107.7	108.6	107.6	108.6	105.9	C ₂ –C ₁ –C ₇ –H ₂₃	–178.4	–178.4	–178.6	–179.2	–178.2
C ₆ –C ₅ –O ₁₁	110.8	110.6	110.4	110.2	111.1	C ₄ –C ₈ –C ₉ –H ₂₅	175.3	175.3	–175.3	–174.7	175.1
C ₂ –C ₁ –H ₁₂	107.5	107.6	107.8	107.9	107.4	C ₄ –C ₈ –C ₉ –H ₂₆	55.9	55.9	–56.0	–55.3	–65.0
C ₆ –C ₁ –H ₁₂	107.8	107.8	107.3	107.4	107.3	C ₄ –C ₈ –C ₉ –H ₂₇	–65.5	–64.1	65.4	64.7	55.9
C ₇ –C ₁ –H ₁₂	107.9	107.9	106.8	106.8	108.3	C ₄ –C ₈ –C ₁₀ –H ₂₈	–53.0	–52.3	52.7	52.1	62.6
C ₁ –C ₂ –H ₁₃	108.9	108.8	108.7	108.7	109.6	C ₄ –C ₈ –C ₁₀ –H ₂₉	67.8	68.9	–68.1	–69.2	–58.2
C ₃ –C ₂ –H ₁₃	109.4	109.3	108.7	108.5	109.8	C ₄ –C ₈ –C ₁₀ –H ₃₀	–172.7	–172.0	172.3	171.7	–177.2
C ₁ –C ₂ –H ₁₄	109.9	110.0	109.9	110.0	109.2	C ₄ –C ₅ –O ₁₁ –H ₃₁	–178.9	–178.9	178.9	178.4	178.0
C ₃ –C ₂ –H ₁₄	110.0	110.0	110.1	110.1	110.3	Δ <i>E</i> /kcal mol ^{–1} ^b	0.0	0.50	0.0	0.52	0.41
C ₂ –C ₃ –H ₁₅	108.8	109.2	109.7	110.1	110.4	abundance/%	86.5 ^c	13.5 ^c	56.5 ^d	10.0 ^d	33.5 ^d
C ₄ –C ₃ –H ₁₅	109.7	109.5	109.8	109.6	110.6						
C ₂ –C ₃ –H ₁₆	109.6	109.8	109.2	109.4	108.7						

^a See Figures 1 and 2 for the atom numberings and the definitions of the conformers. ^b The absolute energy of the *eq-1* conformer of menthol and that of isomenthol are $-468.343467E_h$ and $-468.339976E_h$, respectively. ^c Estimated from the theoretical values for ΔE , vibrational frequencies, and rotational constants assuming the temperature of 363 K. ^d Estimated from the theoretical values for ΔE , vibrational frequencies, and rotational constants assuming the temperature of 410 K.

C₅–O–H dihedral angles. In addition, the O–H bond length was fixed to that of methanol (0.975 Å).¹⁵ The independent parameters and the constraints are summarized in Table S5 of Supporting Information.

Mean amplitudes l and shrinkage corrections¹⁶ $r_a - r_\alpha$ were calculated from the above-mentioned scaled force constants.

Those of the minor conformers (*eq-2* of menthol and *eq-2* and *ax-3* of isomenthol) were obtained from the results of the B3LYP/6-31G* calculations and were scaled with the same scale factor c_i as that of the most stable conformer, *eq-1*. The model of small amplitude vibrations was adopted. The mean amplitudes of the C–H and O–H bonds were adjusted in a group and those

of the C–C and C–O bonds were adjusted in another group. In addition, those of the geminal nonbonded pairs such as $C_1 \cdots C_3$ were adjusted as the third group. The differences among mean amplitudes in each group were fixed at the calculated values. The mean amplitudes of other pairs were not varied and were fixed at their calculated values. Table S6 of Supporting Information lists the mean amplitudes with the corresponding r_a distances. The anharmonicity parameters¹⁷ κ for bonded atom pairs were estimated in a diatomic approximation,¹⁸ $\kappa = (a/6)l^4$, where the Morse parameter a was assumed to be 2.0 \AA^{-1} . Those for nonbonded atom pairs were assumed to be zero.

Results and Discussion

First, preliminary analyses were carried out by assuming various conformational composition in which the dihedral angle $C_3-C_4-C_8-C_9$ was fixed at its B3LYP value. For menthol, the mixture model with the *eq*-1 and *eq*-2 conformers was tried first, and it resulted in the relative abundance of 99% and 1% for the *eq*-1 and *eq*-2, respectively. The obtained standard deviation for the abundance was as much as 11%. Therefore, it was assumed that the existence of the *eq*-2 conformer is not significant. The final analysis was carried out by assuming the *eq*-1 conformer only and by varying the dihedral angle $C_3-C_4-C_8-C_9$ as an independent parameter.

On the other hand, three models were tried for isomenthol. The mixture model with the *eq*-1, *eq*-2, and *ax*-3 conformers resulted in the negative abundance (–41%) of the *eq*-2. The second model with the *eq*-1 and *eq*-2 conformers did not result in the significant abundance for the *eq*-2 conformer (12% with the standard deviation of 10%). The *R*-factor¹⁹ of this analysis was 0.056. The third model with the *eq*-1 and *ax*-3 conformers provided the significant abundance for the both conformers (69 \pm 27 and 31% for the *eq*-1 and *ax*-3, respectively), although the fitting quality improved only slightly (the *R*-factor was 0.055). Therefore, this model was adopted in the final analysis in which the dihedral angle, $C_3-C_4-C_8-C_9$, of the *eq*-1 was varied and that of the *ax*-3 was fixed at its B3LYP value.

Table 4 lists the obtained structural parameters for the *eq*-1 conformer of menthol and isomenthol. Experimental radial distribution curves with residuals are shown in Figure 4. The *R*-factor of the analysis is 0.045 for menthol, and it is 0.055 for isomenthol. The final conformational composition of isomenthol has been determined to be 63 \pm 30% vs 37% for the *eq*-1 and *ax*-3 conformers, respectively. These values correspond to the ratio of the conformers at 410 K (nozzle temperature). The ratio at room temperature (298 K) was calculated to be 68 (+30/–40%) vs 32% for the *eq*-1 and *ax*-3 conformers, respectively.

The *eq*-2 conformer has been found with a significant amount for neither menthol nor isomenthol, contrary to the prediction by the DFT calculations. Of course these results do not necessarily rule out the existence of a small amount of this conformer.

The dihedral angle $C_3-C_4-C_8-C_9$ has been determined with rather large error limits ($\pm 7^\circ$ for menthol and $\pm 17^\circ$ for isomenthol as three times standard deviations). However, there is no strong correlation between this dihedral angle and other independent parameters of the least-squares fitting with the exception of the angle $C-C-C_{\text{ring}}$ of isomenthol (correlation matrix element is 0.92). Therefore, it has been concluded to leave this dihedral angle as an independent parameter. The obtained values, 57° and -63° for menthol and isomenthol, respectively, are close to their theoretical values (58.6° and -58.8°). The correlation matrix is listed in Table S7 of Supporting Information.

TABLE 4: Molecular Structures of Menthol and Isomenthol^a

parameters ^b	menthol (<i>eq</i> -1)		isomenthol (<i>eq</i> -1)	
	ED (r_g and \angle_α)	DFT ^c	ED (r_g and \angle_α)	DFT ^c
bond lengths (in \AA)				
C_1-C_2	1.533	1.538	1.540	1.543
C_2-C_3	1.531	1.536	1.535	1.538
C_3-C_4	1.538	1.543	1.541	1.543
C_4-C_5	1.533	1.538	1.536	1.538
C_5-C_6	1.530	1.535	1.534	1.537
C_6-C_1	1.533	(2) 1.538	(1) 1.540	1.542
C_1-C_7	1.528	1.533	1.536	1.538
C_4-C_8	1.550	1.554	1.552	1.554
C_8-C_9	1.533	1.538	1.535	1.538
C_8-C_{10}	1.532	1.537	1.535	1.537
$\langle C-C \rangle$	1.534	1.539	1.538	1.541
C_5-O_{11}	1.408 (10)	1.431	1.427 (13)	1.432
$\langle C-H \rangle$	1.117 (3)	1.098	1.112 (3)	1.098
O–H	0.975 ^d	0.970	0.975 ^d	0.970
bond angles and dihedral angles (in deg)				
$C_2-C_1-C_6$	110.4	109.5	110.4	109.3
$C_1-C_2-C_3$	112.9	112.0	113.8	112.7
$C_2-C_3-C_4$	113.2	112.3	113.2	112.1
$C_3-C_4-C_5$	110.3	(5) 109.3	110.5	(25) 109.4
$C_4-C_5-C_6$	112.5	111.5	112.5	111.4
$C_5-C_6-C_1$	113.9	112.9	115.0	113.9
$\langle C-C-C_{\text{ring}} \rangle$	112.2	111.3	112.6	111.5
$C_2-C_1-C_7$	111.2	112.1	111.4	112.7
$C_6-C_1-C_7$	110.9	111.7	111.6	112.8
$C_3-C_4-C_8$	113.6	114.5	113.4	114.6
$C_5-C_4-C_8$	112.0	112.9	111.6	112.9
$C_4-C_8-C_9$	113.2	(6) 114.1	113.0	(9) 114.2
$C_4-C_8-C_{10}$	110.7	111.6	110.4	111.6
$C_9-C_8-C_{10}$	109.6	110.5	109.3	110.5
$\langle C-C-C_{\text{exo}} \rangle$	111.6	112.5	111.5	112.7
$C_4-C_5-O_{11}$	108.4	107.7	107.6	107.6
$C_6-C_5-O_{11}$	111.6	(11) 110.8	110.5	(17) 110.4
$\langle C-C-O \rangle$	110.0	109.3	109.0	109.0
$\langle C-C-H \rangle$	109.2 (11)	109.2	108.9 (15)	109.2
$C_3-C_4-C_8-C_9$	57 (7)	58.6	–63 (17)	–58.8
puckering amplitude (in \AA)				
Q^e	0.533 (16)	0.570	0.522 (90)	0.564
abundance (%)				
C_{eq-1}	100 ^f	86.5	63 (30)	56.5

^a Values in parentheses are estimated error limits (3σ) referring to the last significant digit. The indices of resolution are 0.93(2) and 0.87(2) for menthol and isomenthol, respectively. ^b See Figures 1 and 2 for the atom numberings. Angle brackets denote average values. ^c Obtained from the B3LYP/6-31G* calculations in the present study. ^d Assumed as r_a distance. ^e Dependent parameter. See ref 20 for the definition. ^f Assumed.

The average C–C bond length of isomenthol has been found to be slightly longer than that of menthol ($1.538 \pm 0.001 \text{ \AA}$ for isomenthol, and $1.534 \pm 0.002 \text{ \AA}$ for menthol). This tendency is reproduced qualitatively in the B3LYP theoretical structure (1.541 \AA for isomenthol, and 1.539 \AA for menthol). On the other hand, the C–O bond length shows a larger isomer dependence ($1.408 \pm 0.010 \text{ \AA}$ for menthol, and $1.427 \pm 0.013 \text{ \AA}$ for isomenthol). However, as this parameter could be determined only with large error limits, no definite conclusion can be derived from the present results. As for the bond angles, there are no significant differences between menthol and isomenthol.

Bombicz et al. revealed that menthol crystal contains three independent molecules with the *eq*-1 conformation in the asymmetric unit cell.⁴ The average C–C distances of these molecules were determined to be 1.514 ± 0.005 , 1.516 ± 0.005 , and $1.516 \pm 0.005 \text{ \AA}$. These values are significantly shorter than the gas-phase value, $1.534 \pm 0.002 \text{ \AA}$. Although Bombicz

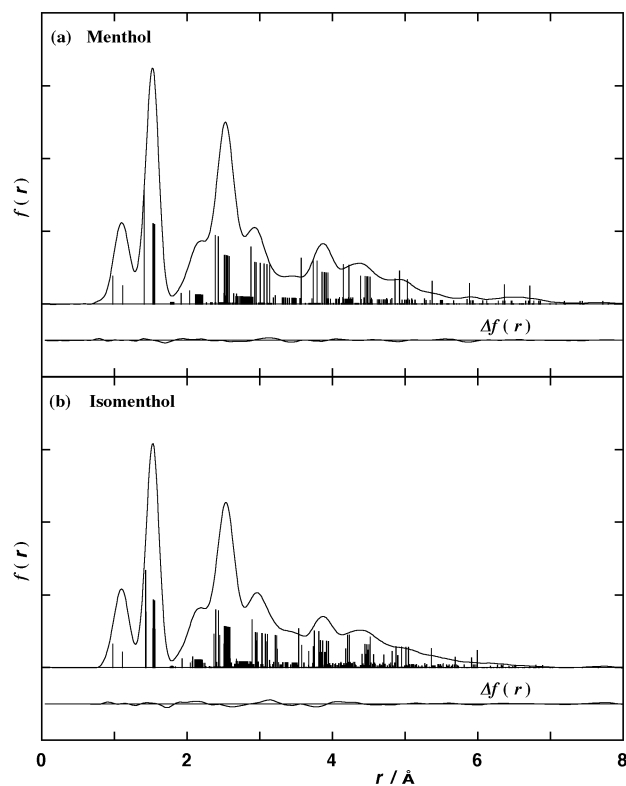


Figure 4. Experimental radial distribution curves of (a) menthol and (b) isomenthol (63% *eq*-1 and 37% *ax*-3); $\Delta f(r) = f(r)^{\text{obs}} - f(r)^{\text{calc}}$. Distance distributions are indicated by vertical bars.

et al. did not report the bond angles, they reported the puckering amplitudes Q (ref 20) for the cyclohexane ring of these three independent molecules of menthol to be 0.554 ± 0.004 , 0.565 ± 0.004 , and 0.559 ± 0.004 Å, corresponding to the molecules with the above-listed C–C distances. From the result of the present gas-phase structures, the Q values were determined to be 0.533 ± 0.016 and 0.522 ± 0.090 Å for the *eq*-1 conformers of menthol and isomenthol, respectively. The amplitude Q represents the “thickness” of the puckered ring and should be proportional to the average C–C distance of the ring if all the C–C–C angles are unchanged. On the other hand, the smaller C–C–C angles should provide the larger Q value for the given C–C distances. Despite the shorter C–C distances, the puckering amplitudes Q in the crystal structure are larger than that of the gas-phase state. Therefore, this suggests that menthol has smaller C–C–C angles in the crystalline state than those in the gas, indicating the packing effect.

Finally, relationships between the minty odor and conformation of the menthol and its isomers are briefly discussed. Among the eight isomers of (–)-menthol including the optical isomers, only (–)-menthol, (+)-menthol, and (–)-neomenthol are reported to be minty.² From the result of the present study, isomenthol, which is not minty, has two stable conformers, *eq*-1 and *ax*-3, with significant abundance. As for the *eq*-1 conformer,

the methyl group in the axial position seems to be hindering the minty odor. On the other hand, the *ax*-3 conformer is not minty presumably because of the isopropyl group in the axial position although its axial hydroxyl group does not seem to prevent the minty odor because (–)-neomenthol has an axial hydroxyl group and is minty.

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Supporting Information Available: Tables of the leveled total intensities and the backgrounds, definitions of the internal coordinates and the corresponding scale factors, vibrational wavenumbers, the scaled harmonic force constants, structural constraints, mean amplitudes, the correlation matrix, and the gas-phase FTIR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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