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Structural determination of vanillin, isovanillin and ethylvanillin by means of gas electron diffraction and theoretical calculations

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Abstract

The molecular structures of vanillin (4-hydroxy-3-methoxybenzaldehyde), isovanillin (3-hydroxy-4-methoxybenzaldehyde) and ethylvanillin (3-ethoxy-4-hydroxybenzaldehyde) were determined by means of gas electron diffraction. Among them, vanillin and ethylvanillin have a vanilla odor but isovanillin smells differently. The nozzle temperatures were 125, 173 and 146 °C, for vanillin, isovanillin and ethylvanillin, respectively. The results of MP2 and B3LYP calculations with the 6-31G** basis set were used as supporting information. The MP2 calculations predicted that vanillin and isovanillin have two stable conformers and ethylvanillin has four stable conformers. The electron diffraction data were found to be consistent with these conformational compositions. The determined structural parameters (r_g and $\angle_\alpha$) of vanillin are as follows: $<r(\mathrm{C–C})_{ring}> = 1.397(4)$ Å; $r(\mathrm{C_1–C_{aldehyde}}) = 1.471(\leftarrow)$ Å; $r(\mathrm{C_3–O_{Me}}) = 1.374(9)$ Å; $r(\mathrm{C_4–O_H}) = 1.361(\leftarrow)$ Å; $r(\mathrm{O–C_{Me}}) = 1.428(\leftarrow)$ Å; $r(\mathrm{C{=}O}) = 1.214(8)$ Å; $<r(\mathrm{C–H})> = 1.110(11)$ Å; $r(\mathrm{O–H}) = 0.991(\leftarrow)$ Å; $\angle \mathrm{C_6–C_1–C_2} = 120.6(2)°$; $\angle \mathrm{C_1–C_2–C_3} = 118.8(\leftarrow)°$; $\angle \mathrm{C_1–C_6–C_5} = 120.1(\leftarrow)°$; $\angle \mathrm{C_2–C_1–C_{aldehyde}} = 122.7(18)°$; $\angle \mathrm{C_1–C{=}O} = 119.4(16)°$; $\angle \mathrm{C_4–C_3–O_{Me}} = 112.2(12)°$; $\angle \mathrm{C_3–C_4–O_H} = 119.1(\leftarrow)°$; $\angle \mathrm{C_3–O–C} = 121.7(29)°$. Those of isovanillin are as follows: $<r(\mathrm{C–C})_{ring}> = 1.402(4)$ Å; $r(\mathrm{C_1–C_{aldehyde}}) = 1.479(\leftarrow)$ Å; $r(\mathrm{C_4–O_{Me}}) = 1.369(9)$ Å; $r(\mathrm{C_3–O_H}) = 1.357(\leftarrow)$ Å; $r(\mathrm{O–C_{Me}}) = 1.422(\leftarrow)$ Å; $r(\mathrm{C{=}O}) = 1.221(9)$ Å; $<r(\mathrm{C–H})> = 1.114(14)$ Å; $r(\mathrm{O–H}) = 0.995(\leftarrow)$ Å; $\angle \mathrm{C_6–C_1–C_2} = 120.2(3)°$; $\angle \mathrm{C_1–C_2–C_3} = 119.0(\leftarrow)°$; $\angle \mathrm{C_1–C_6–C_5} = 119.9(\leftarrow)°$; $\angle \mathrm{C_2–C_1–C_{aldehyde}} = 124.6(25)°$; $\angle \mathrm{C_1–C{=}O} = 121.3(24)°$; $\angle \mathrm{C_3–C_4–O_{Me}} = 114.4(12)°$; $\angle \mathrm{C_4–C_3–O_H} = 121.2(\leftarrow)°$; $\angle \mathrm{C_4–O–C} = 123.8(26)°$. Those of ethylvanillin are as follows: $\langle r(\mathrm{C–C})_{ring}\rangle = 1.397(6)$ Å; $r(\mathrm{C_1–C_{aldehyde}}) = 1.471(\leftarrow)$ Å; $r(\mathrm{C_3–O_{Et}}) = 1.365(13)$ Å; $r(\mathrm{C_4–O_H}) = 1.352(\leftarrow)$ Å; $r(\mathrm{O–C_{Et}}) = 1.427(\leftarrow)$ Å; $r(\mathrm{C–C_{Et}}) = 1.494(21)$ Å; $r(\mathrm{C{=}O}) = 1.206(9)$ Å; $<r(\mathrm{C–H})> = 1.109(10)$ Å; $r(\mathrm{O–H}) = 0.990(\leftarrow)$ Å; $\angle \mathrm{C_6–C_1–C_2} = 120.2(3)°$; $\angle \mathrm{C_1–C_2–C_3} = 118.4(\leftarrow)°$; $\angle \mathrm{C_1–C_6–C_5} = 119.7(\leftarrow)°$; $\angle \mathrm{C_2–C_1–C_{aldehyde}} = 121.7(21)°$; $\angle \mathrm{C_1–C{=}O} = 128.8(22)°$; $\angle \mathrm{C_4–C_3–O_{Et}} = 112.8(14)°$; $\angle \mathrm{C_3–C_4–O_H} = 119.6(\leftarrow)°$; $\angle \mathrm{C_3–O–C} = 115.1(27)°$; $\angle \mathrm{O–C–C_{Et}} = 102.7(28)°$. Angle brackets denote average values; parenthesized values are the estimated limits of error (3σ) referring to the last significant digit; left arrows in the parentheses mean that these parameters are bound to the preceding one.

Keywords: Vanillin; Isovanillin; Ethylvanillin; Molecular structure; Gas electron diffraction; MP2 calculations; DFT calculations

1. Introduction

Recently, we have been focusing on the structure determination of some bioactive compounds including odorant molecules and have investigated the geometrical structures and conformational properties of minty compounds, menthol and carvone, as well as isomenthol, that is the non-minty isomer of menthol, by means of gas electron diffraction [1,2]. The conformation of carvone has been further studied by laser-jet spectroscopy [3]. Vanillin (4-hydroxy-3-methoxybenzaldehyde) and related molecules, isovanillin (3-hydroxy-4-methoxybenzaldehyde) and ethylvanillin (3-ethoxy-4-hydroxybenzaldehyde), have been chosen as the second group of targets of this project in the present study (see Fig. 1). Vanillin is included in the vanilla bean extract and has a characteristic vanilla odor and ethylvanillin has a stronger vanilla odor than vanillin. On the other hand, isovanillin has almost no, if any, odor of vanilla.

The recognition of vanillin and ethylvanillin by their olfactory receptors has been investigated by Touhara and co-workers recently [4]. They identified the receptor of eugenol (a compound with a odor of clove), mOR-EG, and that of ethylvanillin, mOR-EV, and measured the sensitivity of various odorant molecules that have the structural resemblance to ethylvanillin and eugenol, to these receptors. Their results showed that vanillin and isovanillin are recognized by mOR-EG and mOR-EV differently. Vanillin is more sensitive than ethylvanillin to mOR-EG, but the order is reversed for their

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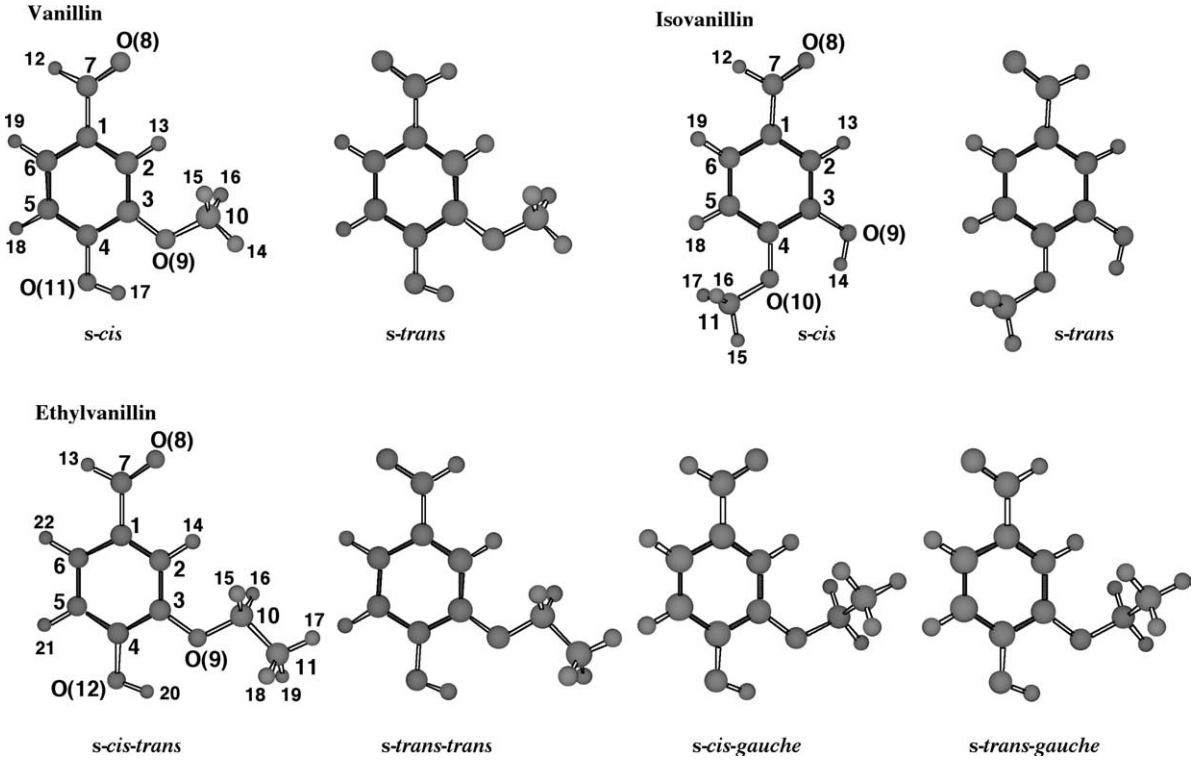

Fig. 1. Molecular models and atom numberings for the possible conformers of vanillin, isovanillin and ethylvanillin.

sensitivity with mOR-EV. No other compound than vanillin and ethylvanillin was recognized by the ethylvanillin receptor, mOR-EV [4].

Although it has been pointed out that the stereochemical structure of odorant molecule is the essential factor in the molecular recognition by olfactory receptors, most of the discussions are not based on the experimentally determined geometrical structures of the odorant molecules, and it is expected that the reliable molecular structures of them will contribute to the investigation of the molecular recognition by the receptors.

As for vanillin and isovanillin, X-ray diffraction studies of crystal have been reported [5,6]. However, the solid-phase structures are not suitable for the study of the structure–function relationship of bioactive molecules because they are subject to the distortion caused by the packing effect. In the present study, the molecular structures and conformation of the title compounds have been investigated by means of gas electron diffraction and theoretical calculations in order to provide the 'distortion-free' structural parameters.

2. Experimental

The samples of vanillin, isovanillin and ethylvanillin with purity of 99% were purchased from Aldrich Chemical Co. and were used without further purification. Electron diffraction patterns were recorded on 8 in.×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 molecules of this size. These samples have insufficient vapor pressure for the electron diffraction experiment at room temperature, in spite of their distinct smells. Therefore, the samples were heated by using the nozzle reported in Ref. [8]. The acceleration voltage of incident electrons was about 37 kV and the electron wavelength was calibrated to the r_a (C=S) distance of CS_2 (1.5570 Å) [9]. 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 detail elsewhere [10]. The experimental intensities and backgrounds are available as Supplementary Information (Table S1).

Elastic atomic scattering factors were calculated as described in Ref. [11], and inelastic ones were taken from Ref. [12]. The experimental molecular scattering intensities are

Table 1
Experimental conditions of gas electron diffraction experiments for vanillin, isovanillin and ethylvanillin

	Vanillin	Isovanillin	Ethylvanillin
Camera distance (mm)	244.18	244.35	244.37
Nozzle temperature (K)	398	446	419
Electron wavelength (Å)	0.06334	0.06326	0.06326
Uncertainty in the scale factor (%)	0.05	0.04	0.10
Background pressure during exposure (10^{-6} Torr)	5.0–6.0	4.1–4.8	2.6–3.0
Beam current (μA)	1.24–1.27	1.41–1.48	1.38–1.39
Exposure time (s)	65–74	68–96	65–70
Number of plates used	3	4	4
Range of s value ($Å^{-1}$)	4.7–33.8	4.7–33.8	4.5–33.5