

## CONFORMATIONAL ANALYSIS OF WHISKY LACTONE USING FOURIER TRANSFORM MICROWAVE SPECTROSCOPY AND QUANTUM CHEMICAL CALCULATIONS

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Whisky lactone (WL), which is known as an important aroma ingredient of whisky, is named as 3-methyl-4-octanolide, shown in Fig. 1, according to an IUPAC convention; it consists of a lactone ring with a methyl group and a *normal*-butane chain substituted at C(3) and C(4), respectively. The molecule takes two configurations as to the CH<sub>3</sub> with respect to the butyl group: *trans*-3S4R (or -3R4S) and *cis*-3R4R (or -3S4S). A sample obtained from Aldrich Co. was subjected to molecular beam Fourier transform microwave spectroscopy, combined with quantum chemical calculations, to observe and to identify the rotational spectra in the frequency region from 5 to 15 GHz. Internal rotation about each of the three C–C bonds: C(4)–C(5), C(5)–C(6), and C(6)–C(7) leads to three stable conformations, the *gauche*(*G*) at the internal-rotation angle  $\tau$  of about 60°, the *trans*(*T*) at  $\tau$  of about 180°, the *gauche*(*G'*) at  $\tau$  of about -60°, and hence there will exist 27 rotational isomers with three different torsional angles of  $\tau_1$ [C(3)-C(4)-C(5)-C(6)],  $\tau_2$ [C(4)-C(5)-C(6)-C(7)], and  $\tau_3$ [C(5)-C(6)-C(7)-C(8)]. Some of the rotational isomers will not be stable because of steric repulsion between the butyl and methyl groups. The *TTT* form of the *trans*-3S4R is calculated to be the most stable, in which both the butyl and methyl groups are located at the equatorial position of the lactone ring. We have so far detected three isomers: the *TTT* of the *trans*-3S4R with 115 *b*-type and 54 *a*-type transitions assigned, the *GTT* of the *cis*-3R4R with 156 *a*-type and 8 *b*-type transitions, and the *TTT* of the *cis*-3R4R with 82 *a*-type, 82 *b*-type, and 6 *c*-type transitions. These results are in good agreement with the predictions made by quantum chemical calculations, MP2/6-311++G(d,p).

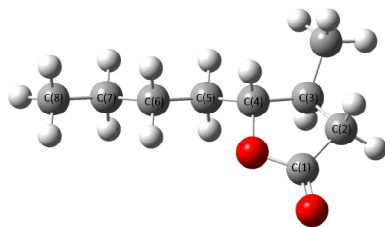


Fig.1 Molecular structure of the *trans*-3S4R *TTT* form of WL

## ROTATIONAL SPECTRA OF SUGARS: RING-PUCKERING IN RIBOFURANOSE

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Sugars are polymorphic species exhibiting both constitutional and conformational isomerism. The intramolecular reaction between the carbonyl and hydroxy groups gives rise to cyclic hemiacetal/ketals, particularly stable for five- or six-membered ring forms (furanoses or pyranoses). Internal rotation of the multiple hydroxyl groups additionally produces a very rich conformational landscape. A previous microwave spectroscopy study on ribose proved that this five-carbon aldose is a pyranose in gas-phase, with several coexisting ( $\alpha/\beta$   $^1C_4/{}^4C_1$ ) low-energy conformers [1]. Other rotational studies of sugars also revealed that the six-membered ring form is dominant [2].

However, the pyranose form starkly contrasts with the five-membered ring exhibited by ribose in biological compounds, like RNA. In order to explore the molecular structure of the five-membered ring in sugars we studied  $\beta$ -methyl-ribofuranose using Fourier-transform microwave spectroscopy in a supersonic jet expansion. The rotational spectrum revealed two conformers sharing the same puckered structure, but differing in the orientation of the three free hydroxyl groups. Similar to other sugars the hydroxyl groups form O-H...O hydrogen bond networks stabilizing the molecule. In both conformers the internal rotation of the methyl group split the rotational transitions, yielding an accurate value for the barrier height. A comparison with computational results (MP2/M06-2X/B3LYP) and a discussion of the conformational landscape will be also presented.

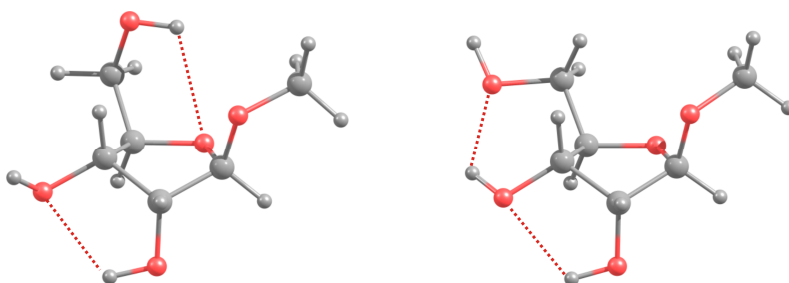


Figure 1. The two most stable conformers of  $\beta$ -methyl-ribofuranose.

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## SECOND (PLANAR) MOMENTS AND THEIR APPLICATION IN SPECTROSCOPY

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Microwave rotational spectra are universally analyzed in terms of the rotational constants A, B, and C. Each rotational constant is related to a principal moment of inertia according to  $A = (h/8\pi^2 I_a)$  where  $I_a = \sum m_i (b_i^2 + c_i^2)$ , and similarly for  $I_b$  and  $I_c$ . Interpreting a molecular structure from its rotational constants is challenging because a rotational constant is proportional to the inverse of a principal moment of inertia, a sum of terms of two variables for each atom  $i$ ,  $b_i^2 + c_i^2$  in the case of  $I_a$  and similarly for  $I_b$  and  $I_c$ . The second moment,  $P_{aa} = \sum m_i a_i^2$  (and similarly for  $P_{bb}$  and  $P_{cc}$ ), measures the extension of masses along the molecule's  $a$  axis (or out of the  $bc$  plane). Interpreting a molecular structure in terms of its second moments is easier since a second moment is a function of only one coordinate per atom and no reciprocal is involved. They are calculated from the moments of inertia according to  $P_{aa} = (I_b + I_c - I_a)/2$ , etc. A second moment commonly used is the inertial defect,  $\Delta = (I_c - I_a - I_b = -2P_{cc})$ , examining molecular planarity. If spectra of isotopologs have been measured, second moments are used to determine Kraitchman's substitution ( $r_s$ ) structure[1].

Another application of second moments not commonly used is to adjust an approximate molecular model to one which exactly reproduces the observed rotational spectrum. Choose a model for the molecule and generate its principal axis coordinates. Multiply each atom's  $a$  coordinate by the square root of the ratio of  $(P_{aa}(\text{obs'd})/P_{aa}(\text{model}))$ . Repeat for  $b$  and  $c$  coordinates. This scaled model exactly reproduces the observed rotational constants without moving the center of mass nor the direction of the principal axes [2]. This result is rigorously exact for a rigid molecule and still very accurate for ground states of real molecules.

Second moments are also useful for discussing other molecular structure properties. Just as bond lengths and angles are transferable among similar molecules, second moments of many common groups are also transferable. This paper discusses applications of second moments to compounds containing  $\text{CH}_2/\text{CH}_3$  groups,  $\text{CF}_2/\text{CF}_3$  groups, isopropyl/tert-butyl groups, phenyl groups, combinations of any of them, and planarity of molecules.

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**A BROAD VIEW RESOLVING THE DETAILS: IMPACT-FT-MW INVESTIGATION OF MOLECULES WITH CONFORMATIONAL FREEDOM**

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Since the advent of wideband Fourier transform microwave spectroscopy techniques [1] the complexity of studied molecular systems has increased [2]. Due to the ability to record broad ranges of the rotational spectra at once without loss of precision and resolution in comparison with Fabry-Pérot-type spectrometers [3,4] it becomes possible to rapidly determine gasphase structures and hyperfine constants of quite flexible molecules with more than a single conformation.

Organic rings are common building blocks in biologically active molecules. In contrast to six membered rings molecules with five or a larger number of ring atoms have a less rigid structure which allows for conformational diversity connected by internal dynamics. The broadband in-phase/quadrature-phase-modulation passage-acquired-coherence technique (IMPACT) FT-microwave spectroscopy [5] is the ideal experimental method to gain insight into the conformational freedom and structure of this molecular motive.

The combination of high spectral resolution and accuracy with a 1 GHz wide acquisition range per experiment (over the entire 2 to 26.5 GHz range) make the IMPACT spectrometer a time-saving tool when it comes to the investigation of fine structure and wide tunnelling splittings at the same time.

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## HALOGEN SUBSTITUTION EFFECTS ON THE TAUTOMERIC AND CONFORMATIONAL EQUILIBRIA OF MOLECULES AND MOLECULAR COMPLEXES: A ROTATIONAL STUDY

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Halogen substitution in molecules is a common practice to modulate physicochemical properties of bio-organic molecules and functional materials [1,2]. The effects of halogenation are related to the high electronegativity of the atoms and their different polarizabilities. The presence of a halogen atom greatly alters lipophilicity, dipole moment, reactivity, chemical stability and interactions with other functional groups present in the molecule. Above all, the introduction of a fluorine atom becomes particularly interesting because it can activate or increase the molecule capability of creating hydrogen bonds or non-covalent bonds. For this reason we also investigate clusters where a molecule of water is used as a probe to reveal the changes on the electrostatic potential on the halogenated compounds.

The experimental conditions are achieved in supersonic expansions using Molecular Beam Fourier Transform Microwave Spectroscopy (MBFTMW) [3] or Free Jet Absorption Microwave Spectroscopy (FJAMW) [4] techniques. The high resolution and sensitivity of rotational spectroscopy give direct access to the structural arrangement of the compounds, allowing the measurement of bond length and angles. Moreover this gas phase technique can help to unveil subtle structural and dynamical effects usually related to changes in non-covalent interactions.

Regarding chlorination we present results on model compounds such as 5- and 6-chlorohydroxypyridine in which we investigate the effects of halogenations on the tautomeric equilibrium. Regarding fluorination we first present a study on the changes in the conformational potential energy surface of 2-fluorobenzylamine with respect to the un-substituted molecule. The conformational space of such molecules is shaped by non bonding interactions which can be changed drastically through substitution of even a single atom. We have also studied a series of clusters between different fluorinated pyridines and a molecule of water: 2-fluoropyridine, 3-fluoropyridine and penta-fluoropyridine. The results clearly show that the introduction of a single fluorine atom into a molecule already induces significant effects, but as the number of fluorine atoms increases, such as in the case of penta-fluoropyridine, the material starts to behave as a completely novel species [5]. The perfluorination effect is clearly observable: and in the penta-fluoropyridine-water adduct the water oxygen lone pairs point towards the aromatic ring.

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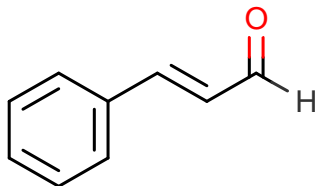
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**STRUCTURE DETERMINATION OF CINNAMALDEHYDE USING BROADBAND MICROWAVE SPECTROSCOPY**

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The high-resolution rotational spectrum of gas-phase trans-cinnamaldehyde ((2E)-3-phenylprop-2-enal) has been obtained with chirped-pulse microwave spectroscopy in the frequency range of 2 - 8.5 GHz. The odorant molecule is the essential component in cinnamon oil and causes the characteristic smell. Studying the structure of odorant molecules to learn more about the structure-odor relationship can give insights into molecular recognition by olfactory receptors.



trans-cinnamaldehyde

In the measured high-resolution spectrum, we were able to assign the rotational spectra of cinnamaldehyde as well as all  $^{13}\text{C}$ -substituted species of the molecule. The change in mass, caused by carbon atom substitution in natural abundance, leads to a change of the molecular moments of inertia and thus of the rotational constants. From these additionally obtained parameters, the molecular structure can be determined by using Kraitchman's equations.

## ROTATIONAL SPECTRUM OF ZINGERONE: CHECKING THE AB INITIO AND DFT CALCULATION METHODS

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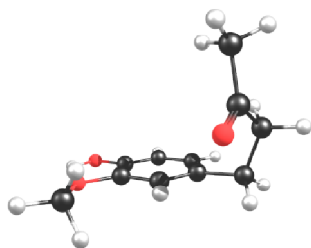
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Following previous studies on vanillin [1] and its derivatives (ethyl vanillin [1], o-vanillin [2], acetovanillone [3] and 6-hydroxy-3-methoxyacetophenone [3]) we analyzed here the conformational properties and structure of zingerone (vanillylacetone) using rotational spectroscopy.

Zingerone is a methoxyphenol with a butanone side chain. The methoxyphenol group is locked by an intramolecular O-H...O hydrogen bond. Conversely, the side chain can bend above the ring, eventually forming either a CH... $\pi$  weak hydrogen bond between the terminal methyl group and the aromatic ring or a vicinal interaction between the ketone and adjacent hydrogen atoms. The MP2 and M06-2X methods gave conflicting results for these structures, so in order to solve this question we conducted a microwave study on zingerone. The rotational spectrum unambiguously revealed a single conformer, which thus allowed distinguishing between the two different calculation methods. The M06-2X DFT method turned out to be more accurate than MP2, as the last method predicted the CH- $\pi$  bond conformer as the most stable, contrary to observations. The role of dispersion forces is probably at the origin of the different predictions in the two methods.

(a)



(b)

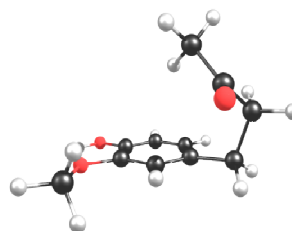


Fig. 1 Most stable conformers of zingerone; (a) M06-2X DFT (b) MP2 method.

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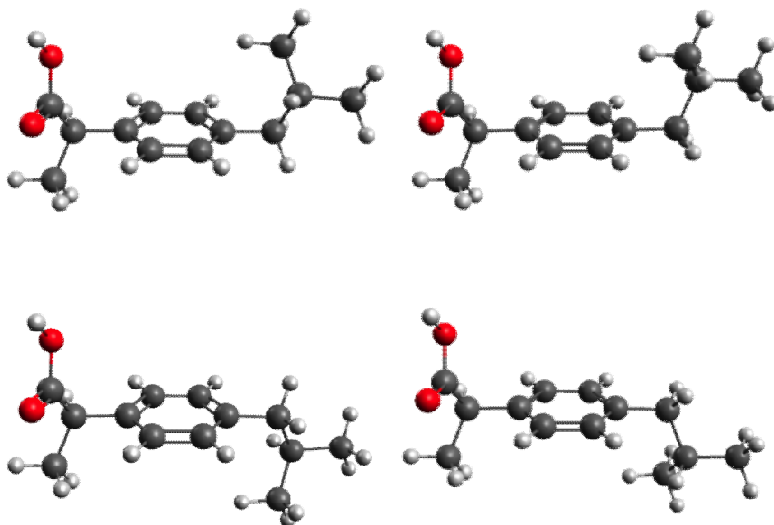
**IBUPROFEN: CONFORMERS AND THERMAL DECOMPOSITION PRODUCTS**

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Ibuprofen acts in biological systems as an anti-inflammatory drug and is today one of the most important pain-relievers used in modern pharmacy. Interestingly, only one enantiomer of this molecule shows this medical effect and thus the function of this molecule is highly correlated to its structure.

In this contribution, the results of a broadband rotational spectroscopy study of ibuprofen in the range of 2 to 8 GHz under supersonically expanded conditions are presented. The four lowest energy gas-phase conformers of ibuprofen, differing in the orientation of the isopropyl group, were identified. Based on these results the conformational properties and the stabilizing, intra-molecular interactions of ibuprofen are clarified. In addition the rotational spectra of two thermal decomposition products of ibuprofen were observed. Their line splitting, probably due to internal rotation, and challenging identification are discussed as well.





## THE STRUCTURE OF THE ANESTHETIC FLUOROXYNE BY BROADBAND ROTATIONAL SPECTROSCOPY

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There is a wide structural variety among substances inducing anesthesia. Molecules apparently unrelated (ethers, di or triatomic gases, alcohols or haloalkanes) produce anesthetic effects. The molecular mechanism of anaesthesia is not fully understood, but points to an interaction between these drugs and ligand/voltage-gate ion channel proteins inhibiting neuronal synapses [1]. High resolution structural studies of anesthetics and related intermolecular complexes in the gas phase may provide insight into the intermolecular forces that govern these biological processes. Anesthetics based on halogenated ethers such as isoflurane [2] and sevoflurane [3] have been previously studied by supersonic-jet microwave spectroscopy, as well as intermolecular complexes such as isoflurane-water [4] and sevoflurane-benzene [5].

We hereby present the structural determination of the anesthetic fluoroxene (2,2,2 trifluoroethyl vinyl ether) which has been carried out in the CP-FTMW (Chirped Pulse Fourier Transform Microwave) spectrometer recently built at the University of the Basque Country. The rotational spectrum revealed a dominant conformer of  $C_s$  symmetry with the heavy atoms in the symmetry plane. All the monosubstituted isotopologues ( $^{13}\text{C}$  and  $^{18}\text{O}$ ) were observed in natural abundance. This has allowed the accurate determination of the substitution ( $r_s$ ) and effective ( $r_0$ ) structures of fluoroxene. The experimental work was supported by DFT and ab initio calculations.

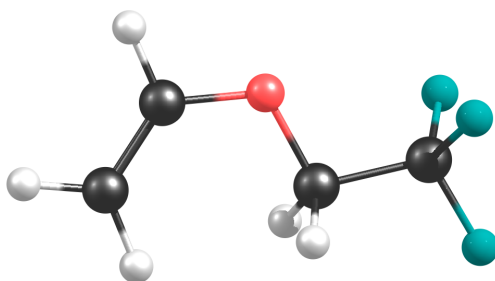


Fig. 1 Effective structure of fluoroxene

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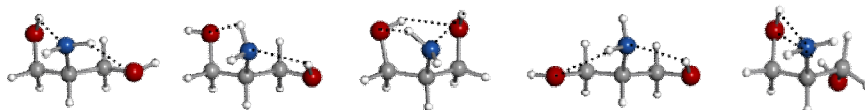
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## INTRAMOLECULAR INTERACTIONS IN THE POLAR HEAD OF SPHINGOSINE

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The rotational spectrum of the amino alcohol serinol, CH<sub>2</sub>OH-CH(NH<sub>2</sub>)-CH<sub>2</sub>OH, which constitutes the hydrophilic head of the lipid sphingosine, has been investigated using chirped-pulsed Fourier transform microwave spectroscopy in combination with laser ablation<sup>1</sup>. Five different forms of serinol have been observed and conclusively identified by the comparison between the experimental values of their rotational and <sup>14</sup>N quadrupole coupling constant and those predicted by *ab initio* calculations. In all observed conformers several hydrogen bonds are established between the two hydroxyl groups and the amino group in a chain or circular arrangement. The most abundant conformer is stabilised by O-H···N and N-H···O hydrogen bonds forming a chain rather than a cycle. One of the detected conformers presents a tunneling motion of the hydrogen atoms of the functional groups similar to that observed in glycerol<sup>2</sup>.

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## CONFORMATIONAL LANDSCAPE OF AROMATIC MOLECULES: A ROTATIONAL STUDY OF MEPHENESIN AND ISOBUTAMBEN

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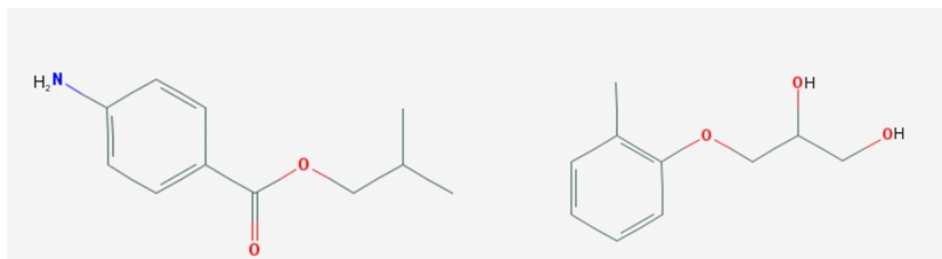
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Previous studies have examined the vibronic [1] and rotational spectra [2] of aromatic local anesthetics such as benzocaine or butamben. We report here on the conformational properties and structure of two molecules with anaesthetic and muscle relaxant properties, i.e., isobutamben and mephenesin. Both molecules share an aromatic ring linked to a ramified lateral side-chain containing carbonyl, ether or alcohol groups, which can establish several competing intramolecular hydrogen bonds within the side chain, with the ring or with both. All possible species can be analysed separately by their rotational spectrum, providing information on their conformational landscape.

Two different conformations were detected in the rotational spectrum of isobutamben, while three isomers were observed in the case of mephenesin [3] using Fourier-transform microwave spectroscopy in a supersonic jet expansion. Different fine and hyperfine effects appeared in both molecules. In mephenesin we observed tunnelling splittings due to the internal rotation of the methyl group, which yielded the  $V_3$  barrier height hindering this internal motion. In isobutamben the presence of the  $^{14}\text{N}$  nucleus produced hyperfine splittings due to nuclear quadrupole coupling interactions. Accurate rotational constants and quartic centrifugal distortion terms were calculated for the two compounds. Theoretical calculations using MP2 and M06-2X methods supplemented the experimental work. Conformational preferences will be discussed in the presentation.



**Figure 1.-** Isobutamben (left) and mephenesin (right)..

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