

Vibrational and computational study on maltol (3-hydroxy-2-methyl-4h-pyran-4-one) polymorphism

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Abstract

In this work, we present solid-state IR and Raman spectra of 3-hydroxy-2-methyl-4H-pyran-4-one, so-called maltol. Maltol is a natural, non-toxic compound used as a food additive. In coordination chemistry, maltol is widely known as a potent monoanionic, bidentate metal chelator. Various maltol complexes are studied extensively because of their catalytic and biochemical properties. Theoretical vibrational spectra of maltol polymorphs have been predicted by quantum chemical calculations at the HF/6-31G^{*} level and compared with experimental data. Spectra of deuterated maltol have been also taken into account. A comparison of theoretical and experimental vibrational data clearly show the presence of a polymorph built from maltol dimers. This conclusion is also supported by the lack of changes in the contour shape of the O–H stretching band after deuteration.

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1. Introduction

The polymorphism phenomenon of chemical compounds is a very intriguing topic. It is important in pharmaceutical industry, where polymorphism of a drug can strongly affect its bioavailability and stability [1]. It has been also shown that antibacterial activity of a compound can depend on its crystallinity [2]. Therefore, a rapid development in the prediction, screening and analysis of orally administered drug polymorphs is expected in the future [3]. On the other hand, non-linear optical activity of a compound may be also induced by polymorphism [4].

Computational studies seem to constitute a valuable tool in pharmaceutical solid-state research. Theoretical calculations can assist in polymorph identification, and may be also

helpful in predicting their properties. Determination of all possible polymorphic forms of organic molecules by computer modeling only is very difficult [5]. Thus, the theory has to be supported by different spectroscopic and diffraction methods. Among them, vibrational spectroscopy is one of the most common tool used for the molecular structure determination. A standard protocol that involves experimental-theoretical technique is based on a comparison of the experimental vibrational spectra with the harmonic frequencies calculated *ab initio* and scaled by an appropriate factor [6].

The aim of this work is to study possible polymorphic forms of maltol (3-hydroxy-2-methyl-4H-pyran-4-one, Hma). Maltol has many applications, especially in the bioinorganic chemistry, where it serves as a chelator for many metal ions. Its complexes with oxovanadium(IV) and iron(III) ions can be potentially used in the treatment of diabetes [7,8] and iron deficiency anaemia [9], respectively.

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Among others, maltol complexes with indium(III) [10] and gadolinium(III) [11] ions have been tested as new radio-pharmaceuticals. On the other hand, maltol has been suggested as an oral agent that can be used to remove the excess of iron ions in thalassaemia or haemochromatosis [12]. It has been also shown that it can also reduce the aluminium level in the body, possibly slowing down the progress of different dementias [12]. Because of these potential applications of maltol as an orally administered drug, investigating of its polymorphism seems to be important.

2. Experimental

2.1. Materials

Maltol of 99% purity was purchased from Aldrich Chemical Co. (Poznań, Poland) and used without further purification. Deuterated maltol was prepared by consecutive recrystallizations of the ligand from D₂O. In order to obtain its different polymorphic forms, maltol and deuterated maltol samples were recrystallized from many solvents, namely: CCl₄, CHCl₃, benzene, ethanol, water/ethanol mixture and ethanol solution equilibrated with heptane.

2.2. Spectroscopic measurements

FT-MIR data were measured from standard KBr discs using a Bruker spectrometer model IFS 48. For the FT-Raman measurements, a Bio-Rad step-scan spectrometer model FTS 6000 combined with a Bio-Rad model FTS 40 Raman Accessory was used. A few milligrams of maltol were placed in a capillary tube and excited by a Spectra-Physics model Topaz T10-106c cw Nd:Yag laser at 1064 nm. The power at the sample was maintained at 200 mW. A spectral resolution for FT-IR and FT-Raman was set at 2 cm⁻¹.

2.3. Computational details

The quantum mechanical calculations used in this work are based on the Hartree–Fock (HF) approximation [13,14] combined with the standard 6-31G* basis set [15]. The geometries of the different clusters, consisting of four maltol molecules, were taken from crystallographic data or proposed using the Molden program [16]. For these clusters, full geometry optimization was performed followed by calculations of vibrational frequencies: IR intensities and Raman activities. The vibrational frequencies calculated were scaled by a factor of 0.90. This is the standard accepted procedure because of the usual frequency overestimating due to neglecting electron correlation and anharmonicity in the HF method [17]. In the next step, labile protons of the OH groups were replaced by deuterons and the theoretical spectra were recalculated. All of these calculations were

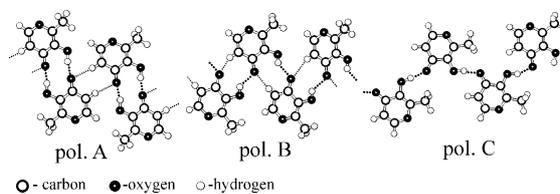


Fig. 1. Hydrogen-bonded structures of investigated maltol clusters.

executed using the Gaussian 98 package [18]. The Raman intensities were calculated from Raman activities using the RAIN program [19]. Theoretical width was obtained for every single vibrational band to fit the experimental data.

3. Results and discussion

Two different maltol polymorphs were reported in the literature [20,21]. Polymorph A was crystallized from ethanol solution equilibrated with heptane, while the polymorph B was obtained from the ethanol/water mixture. Polymorph A is built from symmetric maltol dimers in which single maltol units form two intermolecular O–H...O hydrogen bonds. In this structure, weaker C–H...O interactions link the dimeric maltol units into a ribbon chain. Polymorph B consisted of monomeric maltol molecules arranged alternately into a chain. In both cases, maltol chains were nearly planar. The structures of both polymorphs are presented in Fig. 1.

Despite numerous recrystallizations of maltol from several solvents (see Section 2), we were able to obtain only one polymorphic form. The vibrational spectra of recrystallized maltol are the same as those measured for commercially available samples. Thus, our data do not support existence of two polymorphic forms of maltol, which depend upon the crystallization conditions.

In order to determine the structure of the obtained maltol sample, theoretical calculations on different suggested models of maltol clusters were performed. First of all, clusters derived from structures reported in the literature (polymorphs A and B) were used. Additionally, a third polymorphic structure (polymorph C) was taken into account. Polymorph C differs from polymorph B in conformation of the hydroxyl group, which influences the hydrogen bonding structure. This group in polymorph B is directed towards the keto group from the same molecule. In polymorph C, it is pointed in the opposite direction.

Complete geometry optimizations of all clusters were performed. However, during optimization, polymorph C transforms into polymorph B. This shows that polymorph C is unstable. What is responsible for this transformation? In polymorph B, distances between maltol molecules are shorter than those in form C. In the case of polymorph C, maltol molecules are connected by the O–H...O hydrogen bonds only. Additional C–H...O interactions that exist in polymorph B, stabilize its structure (see Fig. 1). Such weak

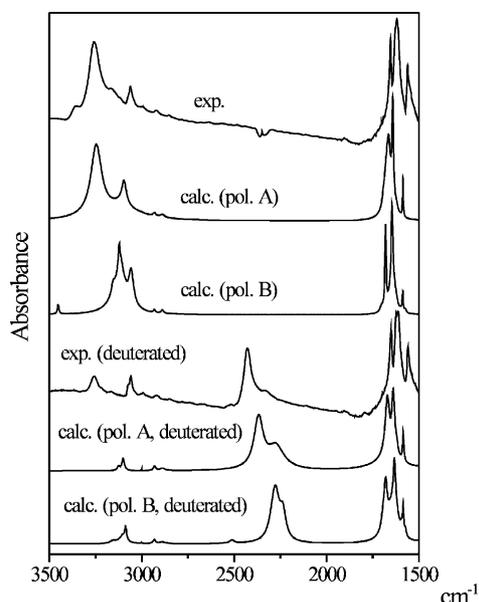


Fig. 2. Theoretical (HF/6-31G*) and experimental (solid state, KBr disc) IR spectra of maltol in the range of 1500–3500 cm⁻¹.

hydrogen bonding were studied by quantum-mechanical calculations in the case of the crystalline inclusion complex of β -cyclodextrin with but-2-yne-1,4-diol [22]. The interaction energies of the C–H...O contacts were estimated in the range from 0.7 to 1.1 kcal/mol. The energies of the O–H...O hydrogen bonds were estimated to range from 4 to 6 kcal/mol. This shows that the role of the C–H...O interactions in the building of solid-state structures cannot be neglected. Thus, the lack of such bonding is probably responsible for the instability of polymorph C. The above-mentioned interactions are also important in the case of the polymorphic structure of form A.

The experimental Raman and IR spectra are compared with the results of theoretical calculations obtained for polymorphs A and B, see Figs. 2 (IR) and 3 (Raman). Major differences between theoretical data obtained for polymorphic form A and B are observed in the range of 1500–3500 cm⁻¹. Therefore, this range of spectra is discussed in this work only. In this study, the Raman spectroscopy has one well-known disadvantage in comparison to the IR. This is due to the fact that Raman intensities of the –O–H stretching modes are very weak.

Fig. 2 presents the experimental and theoretical IR spectra of maltol and its deuterated analogue. All maltol spectra calculated in the range of 1500–1750 cm⁻¹ are similar. Hence, it is difficult to decide which polymorph exists in solid state when the range of the C=O and C=C stretching modes frequencies is compared to the experimental data. However, the spectra calculated in the O–H stretching region strongly suggest that polymorph A is experimentally observed. This is clearly seen in non-deuterated and deuterated maltol spectra. It has to be emphasized that the frequencies calculated for polymorph B are always significantly lower than those measured and

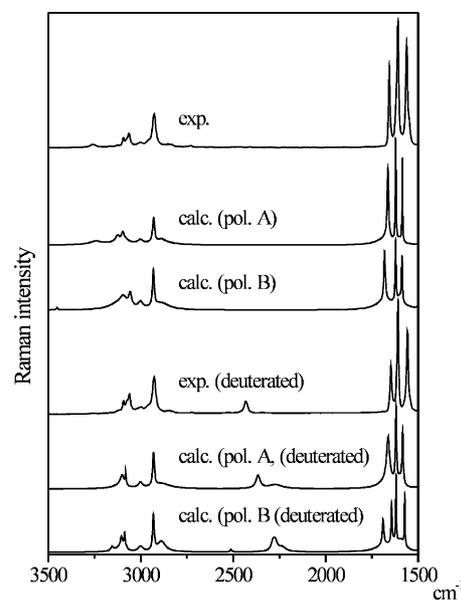


Fig. 3. Theoretical (HF/6-31G*) and experimental (solid state) Raman spectra of maltol in the range of 1500–3500 cm⁻¹.

calculated for polymorph A. The vibrations of both polymorphs were visualized using the Molden program. In the case of polymorph B, a strong coupling of the O–H and C–H stretching modes is observed and is responsible for the decreasing frequency in this polymorph.

In the Raman spectra of neat maltol, both experimental and calculated intensities of the O–H modes are low and inadequate for analysis, see Fig. 3. However, the frequency-decreasing effect (the same as that observed in the IR spectroscopy) is seen for the O–D stretching modes of polymorph B in the Raman spectra of deuterated maltol. Additionally, a strong difference is observed in the 1500–1700 cm⁻¹ range. For the calculated spectrum of polymorph B, four bands are present. However, only three bands are observed in the experimental spectrum and in the spectrum theoretically predicted for polymorph A, see Fig. 3.

On the basis of the experimental and calculated vibrational spectra presented here, we conclude that despite the consecutive repeated crystallization of maltol from different solvents, only polymorph A is formed. Polymorph B is not observed in our studies contrary to the literature data [20]. This conclusion is supported by the contour of the vibrational spectra after partial deuteration shown in Fig. 4. The replacement of protons by deuterons that form hydrogen bonds should be accompanied by changes in the shape of the stretching O–H bands. Such effect was found in the spectra of alcohol crystals built by open chains of the associated molecules [23]. A different situation was noticed for cyclic dimers, namely those of carboxylic acids [24]. In the latter case, no bands from the HD dimers (one proton and one deuteron in the pair of hydrogen bonds in the same dimer) were observed in the partially deuterated spectrum. This resulted in very small, or even negligible, variations in the spectrum shape of the O–H stretching range. Thus, the

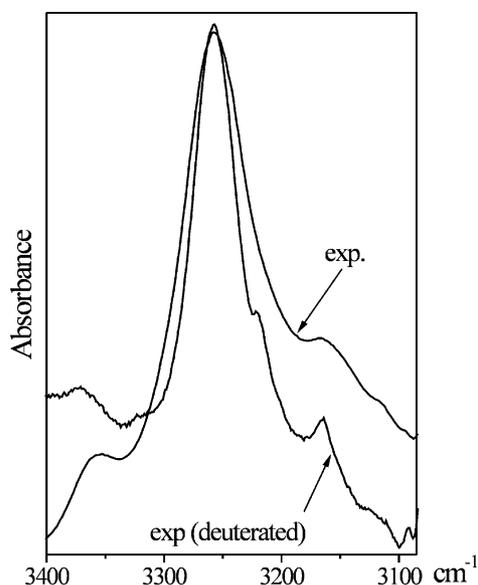


Fig. 4. Comparison of the shape of non-deuterated and deuterated maltol IR spectra in the range of 3100–3400 cm^{-1} .

intensity of this bond strongly decreased, but the shape of the spectrum in this range remains the same. The same effect is observed in the deuterated IR maltol spectrum, see Fig. 4. Negligible changes in the 3100–3350 cm^{-1} range support our suggestion that maltol molecules form cyclic dimers in the solid state forming the structure described as polymorph A. The same effect is expected in the Raman spectrum, however, is not clearly observed due to the very weak intensity of the O–H stretching bands.

4. Conclusions

In order to obtain two polymorphic forms reported in the literature, maltol samples were crystallized from several solvents. Nevertheless, no changes in the vibrational spectra, measured for obtained samples, were observed. Thus, we have to conclude that only one maltol polymorph is formed.

In order to determine polymorphic structure of investigated maltol samples, theoretical calculations have been performed for the model maltol clusters. It was shown that polymorph C was not stable and transformed into polymorph B during geometry optimization. Comparison of the experimental and theoretical data show that only polymorph A, that is the one built up of symmetric maltol dimers, is observed in vibrational spectra presented in this work. This conclusion is supported by the lack of changes in the shape of the O–H stretching band in the IR spectrum after deuteration of maltol molecules.

Additionally, we showed the importance of the C–H...O interactions in the building of polymorphic forms. The

influence of the C–H and O–H stretching modes mixing on the vibrational pattern of polymorph B was also discussed.

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