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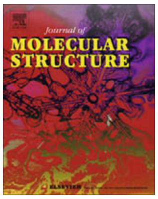

Structure and properties of the sodium, potassium and calcium salts of 2-(2,3-dimethylphenyl)aminobenzoic acid

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ABSTRACT

The mefenamic acid sodium, potassium, and calcium salts with general formulae $[Na(mef)(H_2O)_2]_n \cdot nH_2O$, $[K(mef)(H_2O)]_n$ and $[Ca(mef)_2(H_2O)_2]_n \cdot nH_2O$ have been synthesised, studied by X-ray crystallography, ^1H and ^{13}C NMR and IR spectroscopy. The complex salts are air stable and soluble in water. During heating the Na and K complexes melt in the complexed water and next recrystallise in anhydrous form. In the solid state all salts create one-dimensional coordination polymers. The central atoms are five, six and seven coordinated, respectively, for Na, K and Ca complexes. In all structures exist O—H···O, N—H···O and C—H···O hydrogen bonds. The vibrational analysis has been carried out for mefenamic acid and its three coordination polymer compounds on the basis of experimental results as well as quantum mechanical calculations. The theoretical and experimental vibrational frequencies are similar and reveal characteristic vibrations for all IR active oscillators. In the IR spectra of salts exist strong bands at ca. 1365 and 1600 cm^{-1} typical for carboxylate groups.

1. Introduction

Mefenamic acid (2-(2,3-dimethylphenyl)aminobenzoic acid, Hmef) belongs to the fenamates family and is commonly used as non-steroidal anti-inflammatory, analgesic, and antipyretic agent [1,2]. It has been shown to affect various types of membrane channels [3,4]. The disadvantage of mefenamic acid is its low solubility in aqueous media that influences the bioavailability and pharmacokinetic behaviour [5,6]. Moreover, it can cause the side effects such as nausea, stomach upset, loss of appetite, headache, rash, etc. The variable bioavailability of mefenamic acid is related to pharmaceutical preparation process and in a consequence to variations in dissolution rate. It is known that the particle size distribution, crystal form, crystallinity and surface area of the drug are important parameters that influence its dissolution [7]. Thus it has been suggested that solubility is one of the main factors in determining bioavailability and reducing side effects. The search of mefenamic acid derivatives, possessing enlarged pharmacological activity, lower toxicity and higher solubility is continuously an active area of investigations. It has been shown that the stability and solubility of mefenamic acid can be enhanced, for example, by forming the inclusion complexes with cyclodextrins [8]. On the other hand the development and studying of coordination chemistry of hybrid frameworks and multinuclear assemblies originate from applications of these new functional materials [9,10]. The carboxylic acid anions exhibit a variety modes of binding to metal ions. Their complexes have been extensively studied due to their ability to coordinate in monodentate mode [11,12], form stable chelates [13,14], create di- and multinuclear species [15,16] and polymeric compounds with different topologies and dimensionality [17,18]. In addition, the carboxylate groups are excellent hydrogen bond acceptors and are used to create supramolecular assemblies [19].

In accordance to above mentioned findings, the studies on the coordination compounds of mefenamic acid with biologically important *s* block elements were carried out. It was previously claimed that sodium and calcium salts were obtained, characterised by IR spectroscopy and structurally studied [20,21], but these results are partially questionable and partially seem to be wrong (for detailed discussion see comment). Apart from mentioned *s* block elements, the mefenemates coordination compounds with *p* and *d* block elements were also studied and structurally characterised, namely *bis*(*N*-(2,3-dimethylphenyl)aniline-2-carboxylato)-*bis*(2-pyridylmethanol)-copper(II) [22], *bis*(($_3$-oxo)-*bis*(μ_2-2-(2,3-dimethylphenylamino)benzoato)-tetramethyl-di-tin(IV)) [23], *bis*((μ_3-oxo)-*bis*(μ_2-2-(2,3-dimethylphenylamino)benzoato)-tetra-*n*-butyl-di-tin(IV)) [23], catena-(*bis*(μ_2-3-pyridylmethanol-*N*,*O*)-*bis*(2-(2,3-dimethylanilino)benzoato-*O*)-cadmium(II)) [24], diaqua-*bis*(2-((2,3-dimethylphenyl)amino)benzoato-*O*)-*bis*(*N*′,*N*′-diethylnicotinamide-*N*)-copper(II) [25],

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tetrakis(*N*-xylyl-anthraniloato-*O*,*O*′)-*bis*(dimethylformamide-*O*)-di-copper(II) [26,27], (2-[*bis*(2,3-dimethylphenyl)amino]benzoato)-triphenyl-tin [28], *bis*(*N*-(2,3-dimethylphenyl)aniline-2-carboxylato)-*bis*(methanol)-bis(pyridine)-copper(II) [22,29], tetrakis(μ_2-*N*-(2,3-dimethylphenyl)anthranilato-*O*,*O*′)-*bis*(dimethylsulfoxide)-di-copper(II) [30], catena-((μ_2-2-((2,3-dimethylphenyl)amino)benzoato-*O*,*O*′)-trimethyl-tin(IV)) [31].

2. Experimental

2.1. Synthesis

1.000 g (4.14 mmol) of mefenamic acid (Hmef, obtained from Sigma) was added to 0.226 g (4.18 mmol) of sodium methanolate (>99%, obtained from POCh) dissolved in 12 cm^3 of methanol and to 0.299 g (4.26 mmol) of potassium methanolate (>99%, obtained from POCh) dissolved in 25 cm^3 of methanol. The solutions were stirred and left at room temperature. After a week the crystals of hydrated salts grew from the solutions with 74% and 69% yields, respectively, for $[Na(mef)(H_2O)_2]_n \cdot nH_2O$ (**1**) and $[K(mef)(H_2O)]_n$ (**2**). 0.182 g (4.28 mmol) of calcium hydride (99.9%, obtained from Aldrich) was added slowly to 15 cm^3 of methanol and after reaction completing 1.000 g (4.14 mmol) of mefenamic acid was added. The mixture was stirred on the magnetic stirrer for 2 weeks, heated to boiling and filtered after cooling. The precipitate was mixed with methanol, the obtained suspension was boiled, cooled and filtered. Combined filtrates were left at room temperature. After a week the crystals of $[Ca(mef)_2(H_2O)_2]_n \cdot nH_2O$ (**3**) salt grew from solution with 51% yield. Elemental analysis (calculated/found): **1**: C 56.78/56.54, H 6.35/6.42, N 4.41/4.40, O 25.21/25.29, Na 7.2/

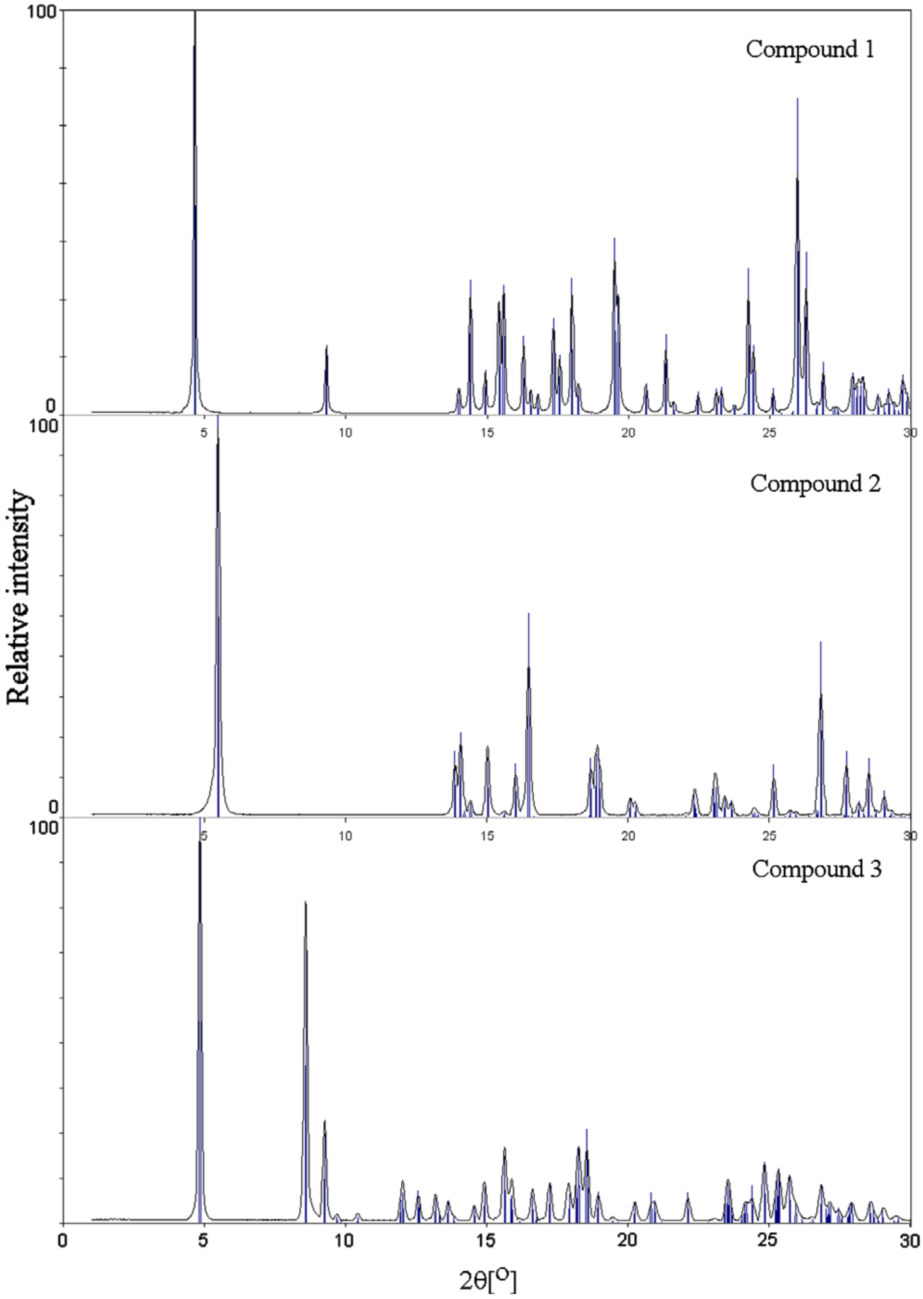

Fig. 1. The comparison of recorded XRPD patterns (curves) and these ones calculated on the basis of single crystal measurements (bars) for compounds **1–3**. Reflections of the standard were subtracted from the recorded XRPD patterns.