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Infrared studies of the polymorphic states of the fenamates

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Abstract

Infrared spectroscopy has been used to characterize the polymorphic purity as well as to study the thermal conversion of three of the more common fenamates between their different crystalline forms via measuring changes in the NH stretch region that occur between 3300 and 3350 wavenumbers. Shifts in band frequency for mefenamic acid result from differences in internal hydrogen bonding between the NH group and either the carbonyl or hydroxyl groups of the acid moiety. Due to out-of-plane rotations about the central N–C_{ring2} bond additional polymorphic states have been suggested for flufenamic and tolfenamic acids. Rates of conversion are given for flufenamic, mefenamic, and tolfenamic acids at temperatures between 85 and 160 °C depending on the polymorphic transition for a particular analyte. Subsequently, these rates are used to calculate the activation energy for the observed polymorphic transition. Values of 71.6, 49.0, and 50.8 kcal/mol are obtained respectively for (1) the polymorph I to II transition of mefenamic acid, (2) the polymorph I to II transition of tolfenamic acid, and (3) the polymorph III to I transition of flufenamic acid.

Keywords: Infrared spectroscopy; Polymorph; Thermal conversion; Fenamates; Flufenamic acid; Mefenamic acid; Tolfenamic acid

1. Introduction

Fenamates are an important group of pharmaceutical compounds with anti-inflammatory and analgesic–antipyretic activity that are *N*-arylated derivatives of anthranilic acid. Their mode of interaction is as potent prostaglandin synthetase inhibitors [1–5]. Since their introduction many manuscripts have appeared that discuss various structural and physical properties of fenamates [6–12] as well as numerous individual analytical methods for quantifying them [1–4,13–22].

A common physical property of the fenamates is their general lack of solubility in water and other common organic solvents which is influenced by their polymorphic form [6,12]. As such, a typical dosage of the fenamates may require several liters of fluid [6]. For example, the solubility of mefenamic acid is only about 40 and 80 μg/ml at 25 and 37 °C, respectively, in water at pH 7.1 [11]. Because of this, it has been suggested that solubility is a key factor in determining bioavailability.

Crystallographic measurements of the fenamates and their metal complexes have shown that they share a common and invariant structural feature [23–30]. The carboxyl group, the ring containing it, and the bridging amino group are all coplanar resulting from resonance interactions and internal hydrogen bonding between the NH and the carboxyl group on ring 1. This is illustrated in Fig. 1 where the positional substituents on ring 2 are given in Table 1 for three of the more common fenamates. In the case of mefenamic acid, its two reported polymorphic states are illustrated by conformations a and b in Fig. 1. Whereas in other cases, additional polymorphic states have been suggested as the result of out-of-plane rotational differences between the central NH group and ring 2 containing the different substituents (i.e., rotations about the N–C bond) [9].

Mefenamic acid has been reported to have only two crystalline modifications: a white form, polymorph I, and a green form, polymorph II [6,9,31–34]. However, flufenamic acid has suggested to have as many as seven possible forms

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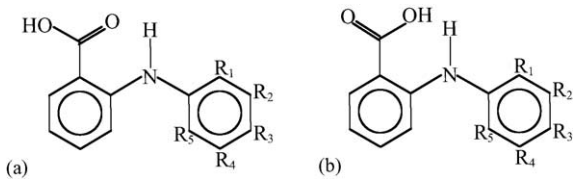

Fig. 1. Conformational changes in fenamates between different polymorphs that also include possible out-of-plane rotational differences at the central N—C_{ring2} bond.

[1,34–39], but of these, only forms I and III are stable under typical conditions and can be obtained respectively by recrystallization from either xylene or methanol [37]. Intermediate between these polymorphic extremes are the other fenamates. In the case of tolfenamic acid, it has two thermally stable forms and a third possible form that is only stable at lower temperatures [40].

Most studies of the polymorphs of the fenamates have employed either X-ray or differential scanning calorimetric methods to characterize the different crystallographic states. However, in a few cases infrared spectroscopy has been used, but in most instances only as a qualitative tool to characterize the differences in the spectral features. Although in one study of mefenamic acid it was noted that the NH stretching band in the infrared shifted from 3313 cm^{-1} for polymorph I (i.e., the initially crystallized form) to 3347 cm^{-1} for polymorph II (i.e., produced via heating) little additional information was provided in terms of discussing these spectral differences as they relate to structural changes [6]. Infrared spectroscopy also has been used to study the Fe(III) complexes [29] and the sodium and calcium complexes [30] of mefenamic acid. In the latter instance, it was noted that the NH bands did not change, which is inconsistent with the spectra that appear in the manuscript. Moreover, these drugs are not stable and products of its decomposition can enhance undesirable effects [41]. However, in formulations, cyclodextrins can be used to increase both the stability and solubility of mefenamic acid [42] and tolfenamic acid [43].

Based on the observations discussed above, an infrared study was carried out to examine the feasibility of using changes in the infrared band frequency and shape to elucidate structural differences between the different polymorphs of three of the more common fenamates, flufenamic, mefenamic, and tolfenamic acids. The rates of thermal conversion for flufenamic from polymorph III to I, mefenamic acid from polymorph I to II, and tolfenamic acid from polymorph I to II were studied at temperatures between 85 and 160 °C depending on the polymorphic transition and particular analyte. Subsequently, the resulting kinetic data were used to calculate the activation energy for the individual polymorphic transitions.

Table 1
Positional substitutions for the different fenamates

Compound	R_1	R_2	R_3	R_4	R_5
Mefenamic acid	CH_3	CH_3	H	H	H
Tolfenamic acid	CH_3	Cl	H	H	H
Flufenamic acid	H	CF_3	H	H	H

2. Experimental

2.1. Chemical and reagents

The HPLC grade methanol and the IR grade potassium bromide for preparing the infrared pellets were from Fisher Scientific (Pittsburgh, PA). The ACS grade 95% ethanol was purchased from McCormick Distilling Co., Inc. (Weston, MO). The flufenamic, mefenamic, and tolfenamic acid samples were obtained from Sigma (St. Louis, MO).

2.2. Infrared equipment and procedures

All infrared measurements were carried out on a Bomem (Quebec City, Que., Canada) model DA-8 high resolution FT-IR spectrometer, equipped with a globar source, KBr beam splitter and a MCT detector. Samples of mefenamic acid were ground with IR grade potassium bromide at weight ratios of 1:50, pressed at 6000 psi into pellets and mounted between two 13 mm × 2 mm KBr windows (ThermoSpectra-Tech, Madison, WI). Spectra were an average of either 64 or 256 scans and were collected in the vacuum mode. Interferograms were collected at a 5.0 cm aperture, 1.00 cm/s mirror speed, 0.5 cm^{-1} resolution, and transformed using boxcar appodization. Band shape analysis was carried out using the Bomem-Grams software package which includes baseline correction, spectral smoothing, and curve fitting algorithms.

The thermal conversion studies of mefenamic acid from polymorph I to II were carried out at 150, 155, and 160 °C using the following procedure. Samples of mefenamic acid (300 mg) were weighed into small glass bottles, the openings of the bottles covered loosely with aluminum foil, and then placed into a constant temperature oven (i.e., a GC oven). They were maintained at elevated temperatures for varying periods up to 3 days. During this time, bottles were removed from the oven at specified times, cooled to room temperature, and the mefenamic acid blended with KBr as described above. In addition, the thermal conversion of tolfenamic acid from polymorph I to II, and flufenamic acid from polymorph III to I were studied respectively at 90, 95, and 100 °C and 85, 90, and 95 °C using a similar procedure.

Quantitation of the individual heated samples involved a standard addition approach that was carried out as follows. Pure polymorph II of mefenamic acid was prepared by heating the original as received mefenamic acid for 48 h at 160 °C and then verifying the identity and purity of the product that formed by infrared spectroscopy (i.e., the absence of any traces of an NH stretch band at 3311–3312 cm^{-1} and only a band at 3346–3347 cm^{-1}). Additional details about this process are presented in the Section 3. Subsequently, varying amounts of pure polymorph II and mefenamic acid, as