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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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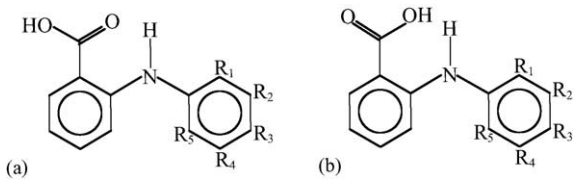

Fig. 1. Conformational changes in fenamates between different polymorphs that also include possible out-of-plane rotational differences at the central N—C_{ring2} bond.

[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

it was received from Sigma (i.e., about 90% polymorph I), were weighed out and blended together with KBr as described above to produce pellets with accurately known standard addition compositions. Polymorph I of tolfenamic acid was prepared by rapidly cooling a boiling 95% ethanol solution of it to 0 °C using an ice bath and allowing the compound to recrystallize [40]. Subsequently, the identity and purity of the product that formed was verified by infrared spectroscopy (i.e., the absence of any traces of an NH stretch band at 3340–3341 cm^{-1} and only a band at 3324–3325 cm^{-1}). Polymorph III of flufenamic acid was obtained by recrystallization using methanol as the solvent 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 3321–3322 cm^{-1} and only a band at 3315–3316 cm^{-1}) [37]. The standard addition experiments for tolfenamic acid and flufenamic acid were carried out using similar procedures to those for mefenamic acid as described above.

In curve fitting the individual bands within a data set, an iterative process was employed that involved initially allowing the instrument's software to pick both the frequency and width of the individual spectral components. Subsequently, the average values for the frequency and width were calculated and these values held constant and new fits calculated across all data within an individual temperature. In most cases the r^2 values of the spectral fits were 0.997 or better and in all cases they were at least 0.993.

3. Results and discussion

Shown in Fig. 2 are representative spectra for samples of flufenamic (a), mefenamic (b), tolfenamic (c), acids as they were received from the supplier. Except for the presence of a small amount of polymorph II (i.e., about 10%), the spectrum for mefenamic acid is consistent with that previously published for the polymorphic I form [6]. Likewise, the spectrum for flufenamic acid is consistent with that reported for polymorph I [38]. In the case of tolfenamic acid, previously reported infrared information could not be found. An important spectral feature that can be used to distinguish the different crystal forms of the fenamates is the NH stretching band that occurs between 3300 and 3350 cm^{-1}. This is illustrated in Figs. 3–5 by the series of partial spectra over this region for mefenamic, tolfenamic, and flufenamic acids as they are thermally converted from one polymorphic form to another polymorphic form.

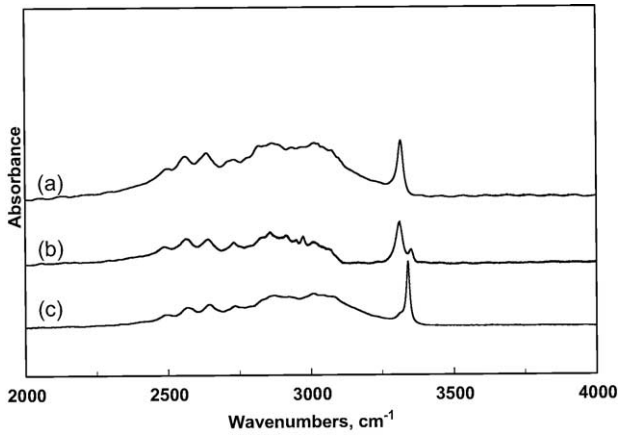

Fig. 2. Infrared spectrum of (a) flufenamic, (b) mefenamic, and (c) tolfenamic acids as received from the supplier.

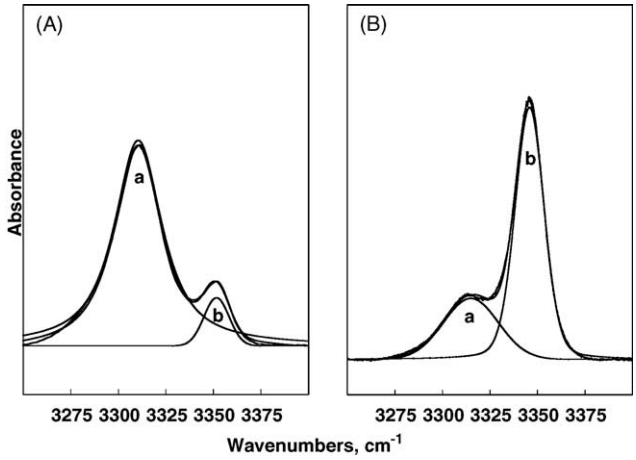

Fig. 3. Infrared spectra of the NH stretch region of mefenamic acid. Samples: (A) as received from the supplier and (B) after heating at 160 °C for 24 h. Bands: (a) polymorph I at 3311–3312 cm^{-1} and (b) polymorph II at 3346–3347 cm^{-1}.

As shown in Fig. 3, mefenamic acid is converted from polymorph I to II when it is heated at temperatures near 160 °C. The band at about 3311–3312 cm^{-1} arises from the amino group internally hydrogen bonding with the carbonyl group and the band at 3346–3347 cm^{-1} is from the NH stretch in the polymorphic II form shown in Fig. 1. Similarly, as shown in Fig. 4, tolfenamic acid is converted from polymorph

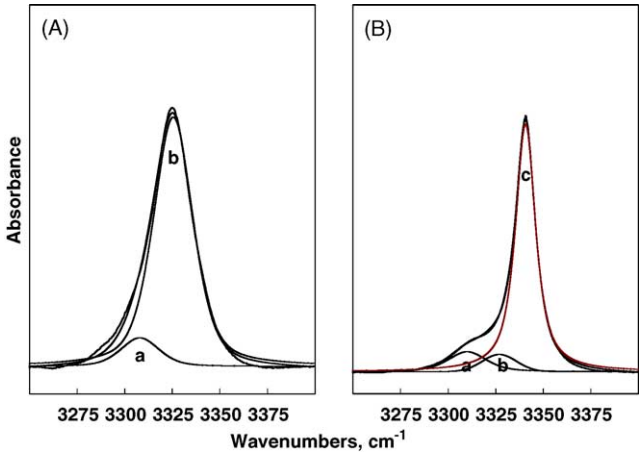

Fig. 4. Infrared spectra of the NH stretch region of tolfenamic acid. Samples: (A) polymorph I obtained by low temperature recrystallization from 95 % ethanol (B) as received from the supplier. Bands: (a) unidentified trace component at 3310 cm^{-1}, (b) polymorph I at 3324–3325 cm^{-1}, and (c) polymorph II at 3340–3341 cm^{-1}.

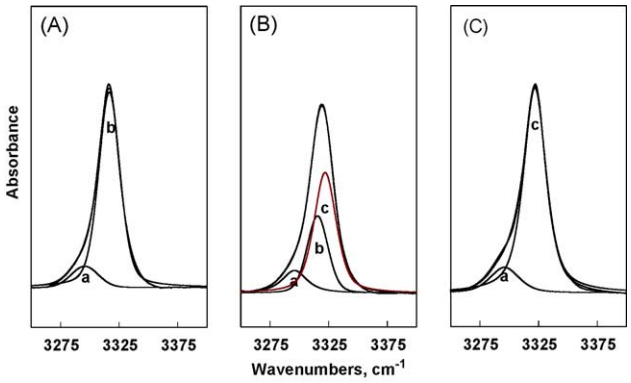

Fig. 5. Infrared spectra of the NH stretch region of flufnamic acid. Samples: (A) polymorph III obtained by recrystallization from methanol, (B) after heating sample A at 85 °C for 48 h, and (C) as received from the supplier. Bands: (a) unidentified trace component at 3295 cm^{-1}, (b) polymorph III at 3315–3316 cm^{-1}, and (c) polymorph I at 3321–3322 cm^{-1}.

I to II by heating it at temperatures near 100 °C. The bands for the two polymorphs are at 3324–3325 and 3340–3341 cm^{-1}, respectively. The third relatively small spectral component appearing at 3310 cm^{-1} remained constant under the conditions used to study the thermal conversion of polymorph I to II and within experimental error, it did not appear to affect the quality of the curve fitting results for the 3324–3325 and 3340–3341 cm^{-1} bands. In the case of flufenamic acid, as many as seven possible polymorphs have been suggested; however, the current study examined only two of these, the conversion of polymorph III to polymorph I, which occurs at 85–95 °C. The NH bands for forms III and I are at 3315–3316 and 3321–3322 cm^{-1}, respectively. As in the case of flufenamic acid, there also was an unidentified trace component at 3295 cm^{-1}, which within experimental error did not affect the quality of the curve fitting results for the 3315–3316 and 3321–3322 cm^{-1} bands. Nevertheless, the origin of this band as well as the 3310 cm^{-1} in tolfenamic acid is interesting and may be due to additional polymorphs, crystal defects, or trace impurities. Of these possible reasons, the presence of additional polymorphic forms seems to be the most plausible explanation based on HPLC analysis of the purity of the compounds and reported minimum-energy conformational calculations that support the possibility of other polymorphs [9].

There are two important spectral features that are shown in Figs. 3–5: (1) shifts in the central band frequency and (2) changes in band $width_{1/2}$ when the fenamates are heated. These changes are summarized in Table 2. The frequency shifts and band $width_{1/2}$ changes were largest for mefenamic acid and smallest for flufenamic acid. In the first instance the NH band shifts from 3311–3312 to 3346–3347 cm^{-1} and its band $width_{1/2}$ changes from about 29–30 wavenumbers to 16–17 wavenumbers. These large spectral differences are reflective of large conformation differences when the NH group is hydrogen bonding with either the carbonyl group or the OH group in the polymorph I and II forms. Both of these spectral changes are consistent with crystallographic data [28] and quantum mechanical considerations of the structure of mefenamic acid and related fenamic compounds [9].

The changes in the central band frequency and $width_{1/2}$ are significantly smaller for both tolfenamic acid and flufenamic acid compared to mefenamic acid. In both cases the polymorphic transitions being studied for these compounds are due to out-of-plane rotational differences at the central $N–C_{ring2}$ bond. These types of conformational changes compared to those observed for mefenamic acid have a smaller effect on the internal hydrogen bonding interactions that influence the NH stretch.

In order to study the rate of conversion between different polymorph forms, changes in the NH stretch region were monitored as a function of time at temperatures of 150, 155, and 160 °C for mefenamic acid. Two additional temperatures, 140 and 180 °C, also were studied; however results from these measurements are not included because of extremely slow conversion kinetics in the case of the lower temperature and analyte degradation at the higher temperature. In the latter case, the mechanisms and kinetics of thermal degradation of mefenamic acid at elevated temperatures is being reported in a separate study. In the 150–160 °C temperature range, mefenamic acid was found to be thermally stable (i.e., no measurable degradation) using a HPLC stability indicating assay over the time period needed to monitor the polymorphic changes. Similar thermal conversion studies also were carried out at 90, 95, and 100 °C for tolfenamic acid, and at 85, 90, and 95 °C for flufenamic acid.

Because the molar absorptivity of the NH stretches are different between the polymorphic forms and only one of them could be obtained in pure form for each of the three compounds, a standard addition method was used to correct for these differences. Shown in Fig. 6 is a plot of the area% of polymorph II compared with the total area of the two bands plotted against the percentage of polymorph II added to the as received mefenamic acid sample. In carrying out the standard addition calibration experiment, multiple measurements were made at the individual data points and their average values used to construct the calibration plot. As in the case of the thermal measurements, the r^2 values for the statistical

Table 2
Shifts in the frequency and changes in the $width_{1/2}$ of N—H band for the more common polymorph forms of mefenamic, tolfenamic, and flufenamic acids

Compound	Polymorphic transition	N—H band frequency (cm^{-1})	N—H band $width_{1/2}$ (cm^{-1})
Mefenamic acid	I → II	3311–3312 → 3346–3347	29–30 → 16–17
Tolfenamic acid	I → II	3324–3325 → 3340–3341	25–26 → 13–14
Flufenamic acid	III → I	3315–3316 → 3321–3322	22–23 → 24–25

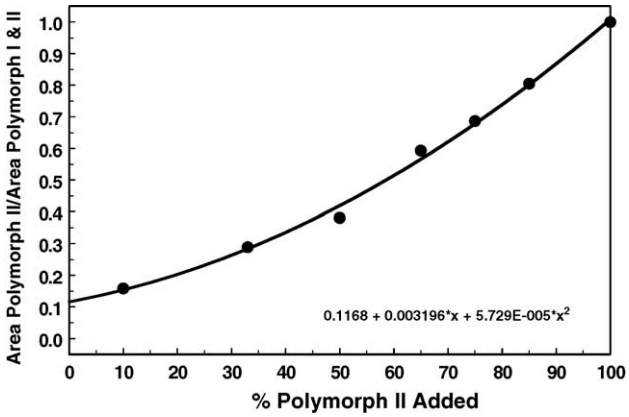

Fig. 6. Standard addition calibration curve for the initial as received mefenamic acid sample (i.e., polymorph I) with varying amounts of pure polymorph II added.

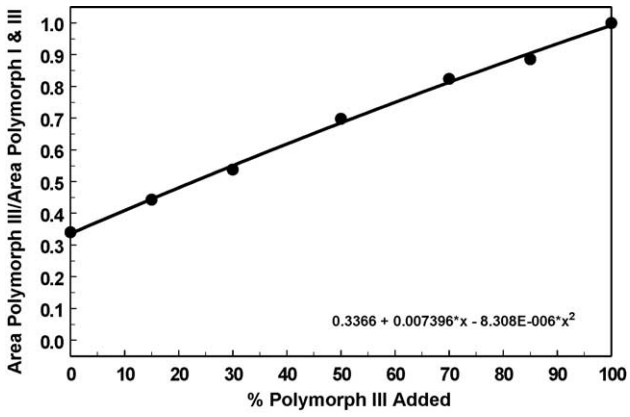

Fig. 8. Standard addition calibration curve for the initial as received flufenamic acid (i.e., polymorph I) with varying amounts of pure polymorph III added.

fits of the infrared bands were in almost all cases better than 0.997. Subsequently, the points shown in Fig. 6 were fitted by a second order polynomial which is the solid line with an intercept value of about 10% (i.e., the amount of polymorph II in the original as received sample of mefenamic acid used to prepare the calibration mixtures). Also, shown in Fig. 6 are the coefficients for the second order regression fit. The standard addition calibration curves for tolfenamic and flufenamic acids are shown in Figs. 7 and 8. These data also were fitted using a second order polynomial. The values of the individual coefficients appear in each of the individual figures.

The individual calibration equations were used to correct the area ratio values (i.e., NH stretch band response differences) for the thermal conversion experiments carried out at temperatures of 150, 155, and 160 °C for mefenamic acid, at 90, 95, and 100 °C for tolfenamic acid, and at 85, 90, and 95 °C for flufenamic acid. The relative rates of thermal conversion from polymorph I to polymorph II for mefenamic acid and tolfenamic acid are shown respectively in Figs. 9 and 10 and polymorph III to polymorph I for flufenamic acid in Fig. 11.

The slopes from plots in Figs. 9–11 were used to determine the activation energy for the crystal to crystal transitions of mefenamic, tolfenamic, and flufenamic acids. This is shown

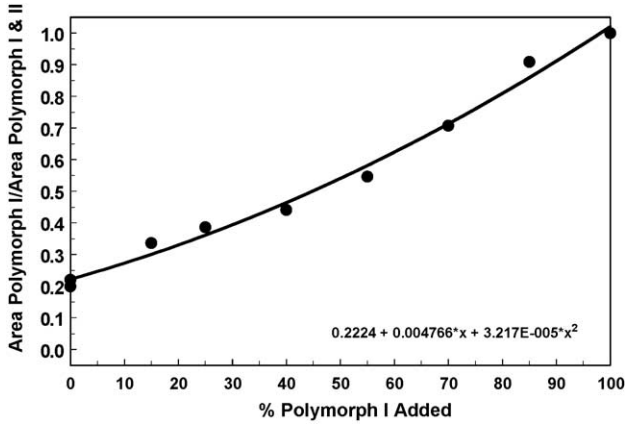

Fig. 7. Standard addition calibration curve for the initial as received tolfenamic acid sample (i.e. polymorph II) with varying amounts of pure polymorph I added.

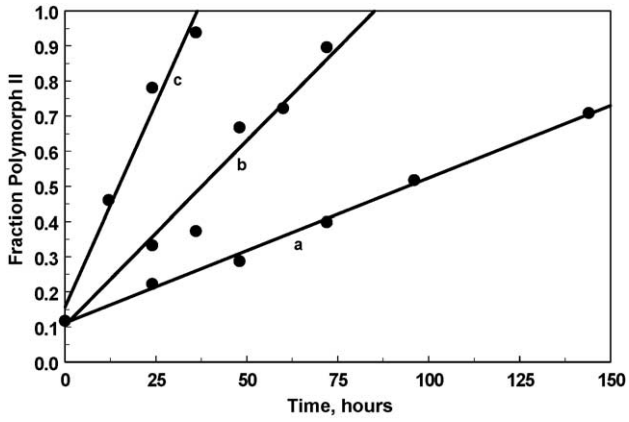

Fig. 9. Thermal conversion of mefenamic acid from polymorph I to polymorph II for temperatures of (a) 150 °C, (b) 155 °C, and (c) 160 °C.

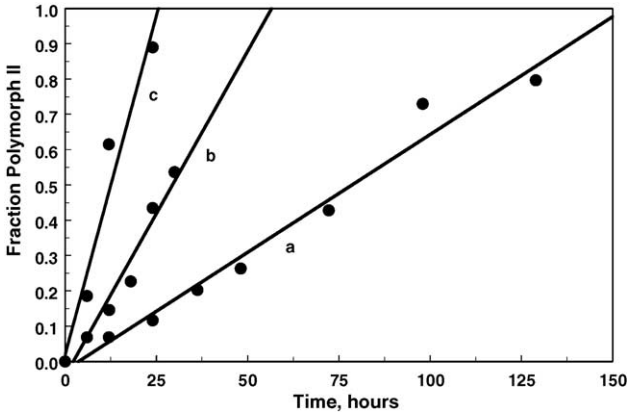

Fig. 10. Thermal conversion of tolfenamic acid from polymorph I to polymorph II for temperatures of (a) 90 °C, (b) 95 °C, and (c) 100 °C.

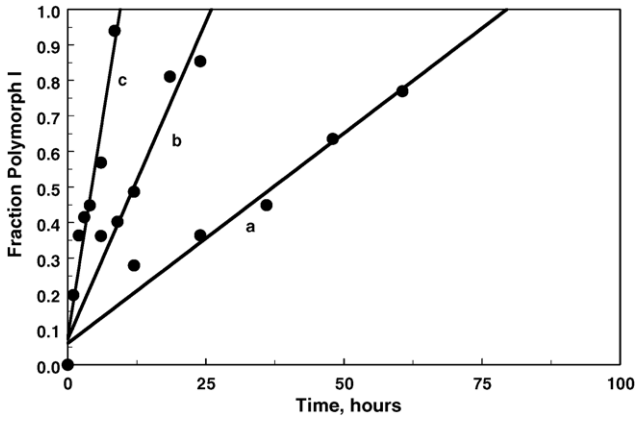

Fig. 11. Thermal conversion of flufenamic acid from polymorph III to polymorph I for temperatures of (a) 85 °C, (b) 90 °C, and (c) 95 °C.

in Fig. 12 where the relative rate of change is plotted against the inverse of the temperature in K. The slopes of these plots yielded activation energies of 71.6, 49.0 and 50.8 kcal/mol for mefenamic, tolfenamic, and flufenamic acids, respectively.

Interestingly, the thermal conversion of mefenamic acid from polymorph I to II has been studied previously by differential scanning calorimetry and reported to have an activation energy of 86.4 kcal/mol [33]. Further in this same study, significantly faster rates of conversion were noted at the individual temperatures. In carrying out the previously reported DSC work, apparently small amounts of sample (1–2 mg) were placed in the sample pans, heated to a given elevated temperature between 140 and 150 °C, and maintained for varying periods of time. Following this, scans were completed through the thermal range where the crystal to crystal transition of mefenamic acid could be observed as an exothermic event. Subsequently, the area of the thermal transition was plotted against time for hold temperatures of 140, 145, and 150 °C and the isothermal conversion rates used to construct a van't Hoff plot that yielded a value of 86.4 kcal/mol for the activation energy which differs from that obtained in the current work and is attributable to possible sublimation of

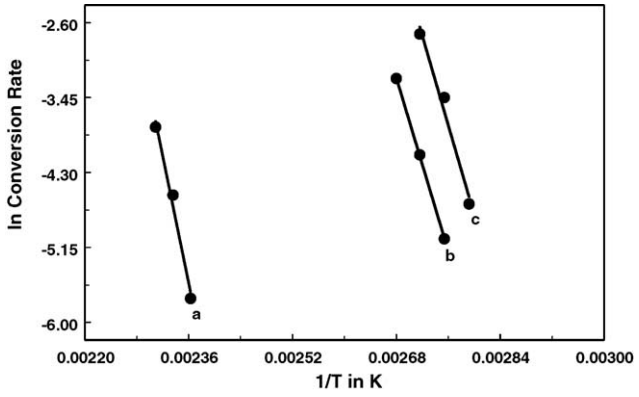

Fig. 12. Plot of the natural logarithm of the rate of conversion vs. reciprocal temperature in K for (a) mefenamic acid, (b) tolfenamic acid, and (c) flufenamic acid.

the compound when small amounts of sample are thermally stressed in the DSC pans and has been discussed elsewhere [31]. To our knowledge, activation energy data for flufenamic acid and tolfenamic acid have not been reported previously.

4. Conclusion

The current work demonstrates that infrared spectroscopy provides a useful alternative procedure for measuring both the polymorphic purity and relative rates of conversion of fenamates between polymorph forms. Additional work is in progress to apply this infrared approach to other structurally similar compounds.

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