

## **INFRARED SPECTROSCOPY AND THE CHARACTERIZATION OF TERFENADINE CRYSTALLIZED FROM SOLVENTS**

*M. L. P. Leitão*<sup>1\*</sup>, *J. Canotilho*<sup>2</sup>, *A. Sousa*<sup>1</sup>, *A. A. C. C. Pais*<sup>1</sup>,  
*A. T. Sousa*<sup>2</sup> and *J. Simões Redinha*<sup>1</sup>

<sup>1</sup>Departamento de Química, Universidade de Coimbra, 3004-535 Coimbra, Portugal

<sup>2</sup>Faculdade de Farmácia, Universidade de Coimbra, 3000-295 Coimbra, Portugal

(Received November 8, 2002; in revised form March 11, 2003)

### **Abstract**

In this paper the structural characterization of terfenadine crystallized from ethanol–water, ethanol and methanol is performed by infrared spectroscopy. The OH stretching vibration, composed of three markedly overlapped bands, is analyzed by peak fitting. The assignment of the hydrogen bonds was conducted making use of band parameters, spectroscopic data for CCl<sub>4</sub> solutions, and molecular dynamics calculations from dimeric systems. Terfenadine just precipitated from solvents is never in the highest crystalline state. This state is reached when the samples are heated at a temperature above 100°C. Some amorphous solid is coprecipitated with the crystalline phase, particularly in methanol.

**Keywords:** crystallization, curve fitting, FT-IR, terfenadine

### **Introduction**

Infrared spectroscopy is an excellent method for structure investigation particularly when hydrogen bonds are present. The interaction between a hydrogen donor group, X–H, and an acceptor, A, giving rise to the hydrogen bonded complex, X–H...A, disturbs the infrared spectra pattern in different regions. The stretching vibration modes are very sensitive to hydrogen bonding and, for this reason, they are often used to characterize molecular structures in different matter states. A decrease in the stretching frequency of the X–H bond and an increase of the width and intensity of the corresponding absorption band are common manifestations of hydrogen bonding.

The first effect is well understood in qualitative terms. Indeed, the attractive interaction between the hydrogen of the donor group and the acceptor leads to a decrease of the absorption constant force for X–H and consequently to a displacement of the band position towards a lower frequency. The difference between the maximum frequency of the bands in absence and presence of the hydrogen bond,

\* Author for correspondence: E-mail: mlleitao@ci.uc.pt

$\Delta\nu_m = \nu_m^0 - \nu_m$ , has been used for establishing correlations with structural parameters such as X...A distance, X-H...A angle and with thermodynamic properties of bond formation. The peak frequency has been related with hydrogen bond geometry, in particular with X...A and X-H distances. Such correlations are very useful both on the theoretical and practical viewpoints as one can infer structural features or estimate the bond strengths simply by determining the band peak position [1-3].

The peak shift of H-X stretching band has been related with the energy of hydrogen bond formation. Since Badger-Bauer's classical rule many authors worked out correlations between the two quantities [3-5]. Difficulties arise when we want to establish correlations comprising a diversity of systems or within wide concentration ranges. Based on data obtained for phenol hydrogen bonded complexes, Iogansen [6] recently proposed the following equation for O-H...O,

$$\Delta H = -1.39(\Delta\nu_m - 40)^{1/2} \quad (1)$$

where  $\Delta H$  is expressed in  $\text{kJ mol}^{-1}$  and  $\Delta\nu_m$  in  $\text{cm}^{-1}$ .

This correlation was later confirmed by data supplied by other systems and proved also to be valid for solids.

It has been observed that hydrogen bonding broadens the X-H stretching vibration band. Values for the half-band width,  $\Delta\nu_{1/2}$ , in the presence and absence of hydrogen bonds were determined and relationships between this parameter and the maximum band shift have been proposed. However,  $\Delta\nu_{1/2}$  has not been much explored in the characterization of hydrogen bonding. The interpretation being advanced for band broadening due to the hydrogen bond are not clearly understood because several factors accounting in varying degrees for the band shape have been referred [5].

Another spectral feature affected by hydrogen bonding is the band intensity,  $A$ . Depending on the width of the absorption range and also on the absorbance, this is a very sensitive parameter. The reasons why the intensity is not as used as the frequency shift results from the difficulty in obtaining its value, as band overlapping is a quite common situation.

From a study of a large number of liquids, Iogansen [6] established the following relationship between the integrated areas and the enthalpy for hydrogen bond formation,

$$\Delta H = -12.2 (A^{1/2} - A_0^{1/2}) \quad (2)$$

where  $\Delta H$  is in  $\text{kJ mol}^{-1}$ .  $A$  and  $A_0$  are the areas of the band in the presence or absence of the hydrogen bond, respectively, expressed in ( $10^4 \text{ cm mmol}^{-1}$ ). It was shown in the same paper that this equation is also valid for crystals.

Infrared spectroscopy is commonly used in characterization of pharmaceutical solids. In a special issue of *J. Therm. Anal. Cal.* dedicated to Thermal Analysis and Calorimetry in Pharmaceutical Technology, infrared spectroscopy appears in a significant number of contributions to characterize drugs, polymorphs, hydrates, excipients [7].

In the present paper infrared spectroscopy is applied to the study of terfenadine (1-(4-tert-butylphenyl)-4-[4'-(diphenyl-hydroxymethyl)-1'-piperidyl]butan-1-ol (Fig. 4). Beside a large non-polar part, the terfenadine molecule has two hydroxyl groups and one

nitrogen atom which can participate in intra- and intermolecular hydrogen bonds. The aromatic rings can also be involved in hydrogen bonding by interaction with the hydroxyl groups.

Research on crystallization of terfenadine led to the conclusion that crystalline and a wide range of proportions of crystalline and amorphous state phases could be obtained depending on the solvent and temperature [8]. The characterization of the solid forms was performed by thermal and calorimetric methods. In the present work terfenadine specimens prepared by crystallization from ethanol-water, ethanol and methanol were studied by infrared spectroscopy. These specimens are considered as crystalline state phases by the thermal methods of analysis.

Frequency shift, band width and integrated intensity are the band features used in the interpretation of the spectra.

### **Preparation of terfenadine specimens and spectroscopic measurements**

The terfenadine specimens to be studied were obtained by crystallization according to the following preparation procedures:

Specimen EW: concentrated solution of terfenadine in ethanol-water prepared at 50°C and maintained at 20°C for 48 h.

Specimen E: slow solvent evaporation at 50°C from an ethanol solution of terfenadine.

Specimen M: slow solvent evaporation at 50°C from a methanol solution of terfenadine.

The original terfenadine used in the preparation of the specimens was supplied by Sigma-Aldrich. The solids obtained by crystallization were dried in vacuum for twenty four hours and kept in a desiccator under vacuum over silica gel. Pellets of 0.7 mg of finely powdered terfenadine dispersed in 120 mg of potassium bromide were prepared for the spectroscopic analysis. Attention was paid to the preparation of samples with the same amount of terfenadine and potassium bromide in order to get, as much as possible, pellets of the same thickness and composition.

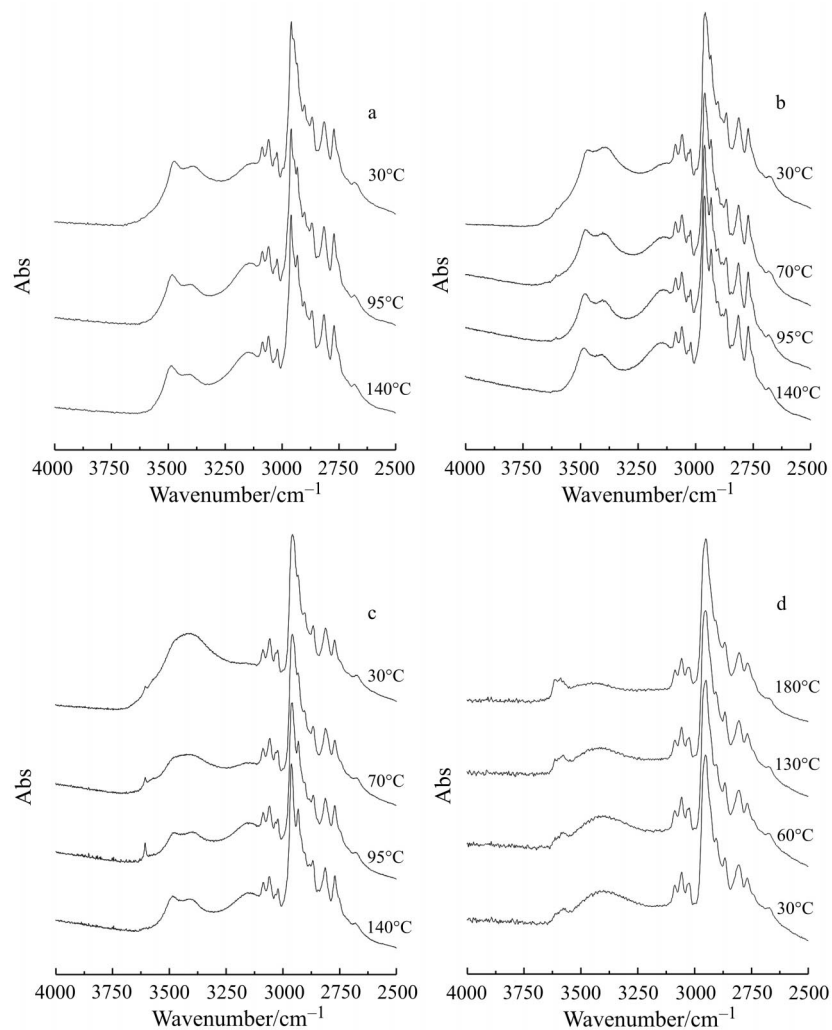
The infrared spectra were recorded with a Philips PU 9800 spectrophotometer. The cell assembly and temperature control device were purchased from Graseby Specac. These accessories allow to record spectra at temperatures from liquid nitrogen to 200°C. In the present case the spectra were recorded in the 30 to 180°C temperature range. No phase transitions were observed below room temperature. The temperature control inside the cell was  $\pm 0.5^\circ\text{C}$ .

### **Stretching vibration spectra**

The stretching vibration region for the terfenadine specimens prepared by crystallization in solution upon heating at different temperatures is presented in Fig. 1. This fig-

ure shows also the spectra obtained for molten terfenadine and for the solid obtained by cooling the melt.

Absorption due to the OH groups is observed between  $3000$  and  $3500\text{ cm}^{-1}$ . A visual inspection shows three maxima at wavenumbers  $3150$ ,  $3390$  and  $3480\text{ cm}^{-1}$  approximately in all spectra. These group frequencies are ascribed to OH intermolecular hydrogen bonds [9]. Terfenadine in condensed matter state is characterized by three hydrogen bonding systems, two weaker with closer energy values and another, stronger and further apart from the others (Fig. 1a and 1b). The absorption in



**Fig. 1** Stretching vibration spectra for terfenadine specimens at different temperatures: a – Specimen EW on heating; b – specimen E on heating; c – specimen M on heating; d – melt on cooling

this spectral region will be matter of detailed study later in the text. For now let us consider the features evidenced by a visual inspection of the spectra.

The spectra for EW and E are similar to one another and neither one seems to be affected on heating. The pattern observed for M is identical to those shown by the other specimens at temperatures above 100°C but is different from them at lower temperatures. In fact in this temperature region only one maximum of an intense broad band,  $\nu_m=3420\text{ cm}^{-1}$  instead of three is exhibited. Furthermore a weak band with maxima at 3576 and 3607  $\text{cm}^{-1}$  is seen. On heating, as the temperature reaches 70°C, the former gives rise to a three maxima profile band and the latter increases its intensity at 3607  $\text{cm}^{-1}$ . At 120°C the spectrum shows a similar pattern to that observed for the other specimens. The phase transitions for specimen M are illustrated in Fig. 1c.

These results can be understood admitting that methanol originates a less crystalline solid phase, than the other solvents, which is accompanied by the precipitation of amorphous solid material. Hence the variety of situations regarding OH groups ranges from strong interactions in ordered crystalline phases to loosely bonded disordered solid material. Upon heating the amorphous solid phase melts and the resulting metastable liquid crystallizes as temperature rises above 100°C.

The spectra corresponding to the cooling process of molten terfenadine are given in Fig. 1d. The OH stretching vibration in the liquid state is described by three bands of  $\nu_m=3203, 3440$  and  $3590\text{ cm}^{-1}$ . The one at higher wavenumber is narrow and exhibits a secondary maximum at 3614  $\text{cm}^{-1}$  while the two others are of identical intensity and give by overlapping an almost uniform absorption along the OH stretching range. Between 150 and 130°C a change of the spectrum pattern occurs, consisting of a strong intensity increase in the band at medium wavenumber while the two others decrease. These structural modifications are gradual and go in the same way as temperature decreases albeit the effect of the temperature becomes smaller. The increase of the intensity is accompanied by a red shift in the maxima of the two lower frequency bands.

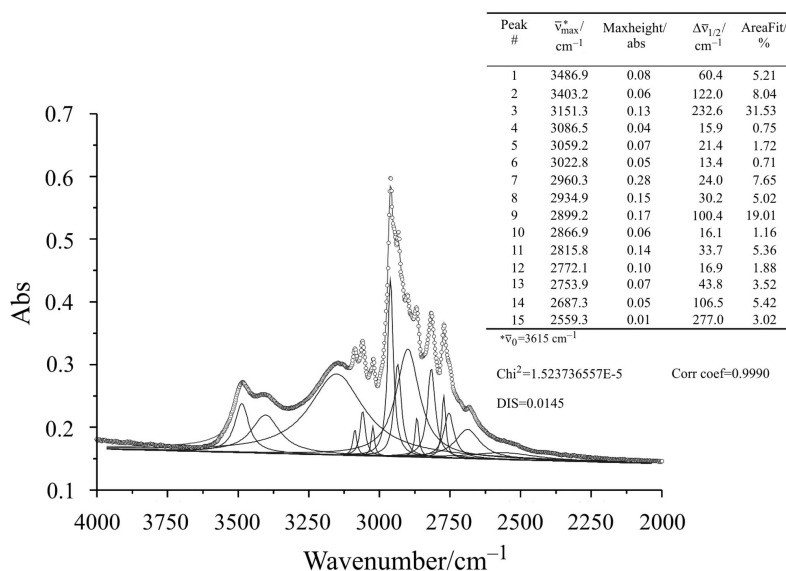
The spectra for specimen E, similarly to what happens with M, shows a weak absorption at 3576 and 3604  $\text{cm}^{-1}$ . This means that the crystalline phase is also accompanied by traces of amorphous solid state.

### Curve fitting analysis of the spectra

The role played by the hydrogen bonding corresponding to OH stretching vibration between 3000 and 3500  $\text{cm}^{-1}$  in the structural framework of the terfenadine was already pointed out. As the bands corresponding to different hydrogen bond systems are markedly superimposed it is necessary to decompose the recorded band profile into its components. From the features of the individual bands a deeper sight of the structure can then be gained.

The band resolution was performed by a peak fitting method. This is the adequate procedure for situations in which indications about the overlapped curves are available [10]. In the case we are dealing with, the curve maxima are in fact located by visual inspection of the spectra.

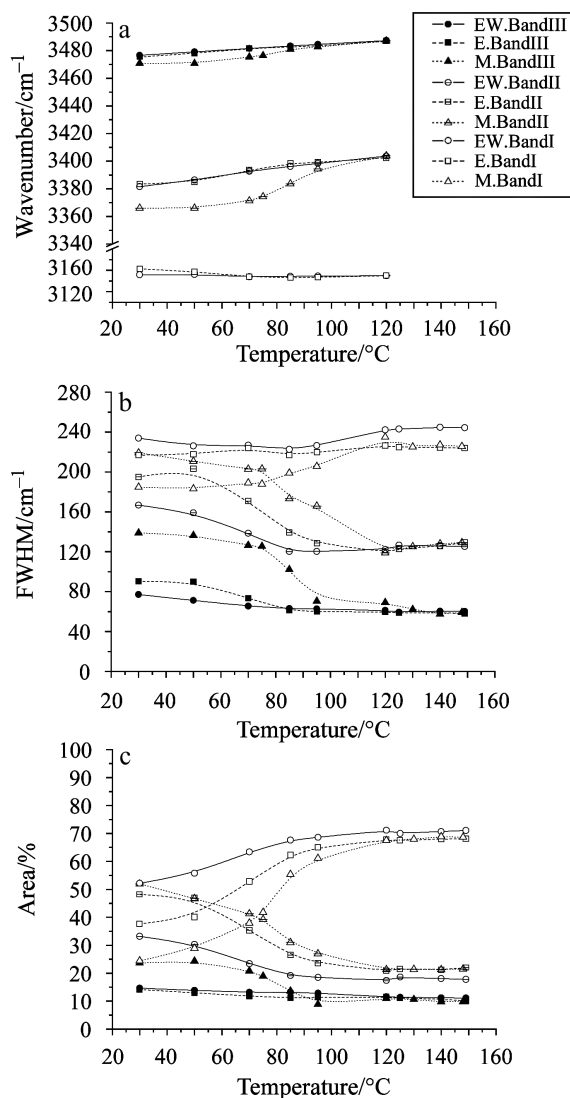
The Microcal Origin version 4.0 peak fitting module was used. The program allows to fit different types of functions and gives position, width, maximum height and area for each overlapped band. The goodness of fit criterion is evaluated by the statistical parameters, chi squared,  $\chi^2$ ; correlation coefficient,  $CC$ ; and discordance,  $DIS$  (square root of the ratio between the sum of the squares, of the differences between the profiles at any particular point divided by the number of points considered). The following limits are observed for these parameters:  $\chi^2 < 10^{-4}$ ,  $CC > 0.9985$ ,  $DIS < 0.015$ . The best fitting was achieved using a Lorentzian function. A typical example of fitting is given in Fig. 2 for the spectrum of specimen EW at 120°C. The three bands ascribed to OH are: band I,  $\nu_m = 3488 \text{ cm}^{-1}$ , band II,  $\nu_m = 3405 \text{ cm}^{-1}$  and band III,  $\nu_m = 3351 \text{ cm}^{-1}$ . Between 3086 and 2554  $\text{cm}^{-1}$  twelve C–H stretching bands corresponding to the diverse groups in different molecular and structural environments are found. Although this study is limited to polar groups, peak analysis had to be extended to the CH stretching region considering the superposition of absorption for both groups.



**Fig. 2** Infrared spectrum for terfenadine in the stretching region and Lorentzian bands fitted to it. Table on the side gives the parameters for the overlapped bands

The values for  $\nu_m$  for the three bands and for the three terfenadine specimens are represented *vs.* temperature in Fig. 3a. The frequency shift throughout this work refers to the  $\text{OH}_{\text{free}}$  band maximum obtained for the spectrum of terfenadine in carbon tetrachloride at 25 °C ( $\nu_m^0 = 3615 \text{ cm}^{-1}$ ). It has been proved that the effect of temperature on  $\nu_m^0$  for the hydroxyl is negligible in the range we are dealing with [11].

The results determined for  $\Delta\nu_m$  upon heating show an increase of this parameter for band I and a decrease for bands II and III. The interactions corresponding to band I are reinforced as temperature increases whereas those corresponding to the others



**Fig. 3** OH stretching band parameters for terfenadine specimens as a function of temperature. a – peak frequency; b – width at half-height; c – integrated intensity

become weaker. A more pronounced variation of  $\Delta v_m$  for the three bands is observed from 30 to 100°C.

The enthalpies for hydrogen bond formation calculated from  $\Delta v_m$  by Eq. (1) to the resolution of the OH stretching vibration at 120°C are: 23 kJ mol<sup>-1</sup> for band I, 15 kJ mol<sup>-1</sup> for band II and 13 kJ mol<sup>-1</sup> for band III. With respect to  $\Delta v_m$  specimens EW and E are alike whilst M in the temperature interval between 30 and 100°C shows higher values for band I and lower ones for bands II and III. However, after the struc-

tural transformations occurring between 70 and 100°C the spectrum becomes identical to those of the other specimens.

The values obtained for the half-width of the three OH stretching bands as function of temperature are represented in Fig. 3b. A general conclusion taken from the observation of this figure is the detailed information given by  $\Delta v_{1/2}$  about the hydrogen bond and the effect of temperature up it. Upon heating up to about 120°C,  $\Delta v_{1/2}$  increases for band I and decreases for the other two bands. A more pronounced variation occurs between 70 and 120°C. Above 120°C the width becomes almost constant for the three bands being the values for  $\Delta v_{1/2}$ : 240  $\text{cm}^{-1}$  for band I, 140  $\text{cm}^{-1}$  for band II and 15  $\text{cm}^{-1}$  for band III. Based on this band feature structure differences between the three specimens can be pointed out.

According to Iogansen's rule the characterization of the hydrogen bond is also performed by the integrated intensity of the OH stretching vibration bands. The results found for this parameter at different temperatures expressed, as percentage of the total absorption intensity due to OH groups, are given in Fig. 3c. A linear base line was assumed in the determination of this quantity. It is a very sensitive quantity accounting for the differences between the specimens and the behaviour of bands on heating and between the specimens referred above.

Although any of the band features under consideration in this discussion account for the hydrogen bonds in terfenadine, different sensitivities for certain details are found. For example, frequency shift is the simplest way to estimate the band strength. However, structural transformations not affecting the number of the hydrogen bond systems or the peak position can not be accompanied by  $\Delta v_m$ . On turn, structure modifications differing in width or punctual absorbance are well studied by  $\Delta v_{1/2}$  or  $A$ . These two parameters used together allow to further discriminate whether the variation of the intensity is due to the width or to the absorbance change. For instance, the steep increase of  $A$  for band I observed between 70 and 100°C comes mainly from the increase of absorbance. On the contrary the decrease of  $A$  for band II in this temperature interval comes mainly from the decrease of the band width. To map the hydrogen bonding network all the band parameters should be considered.

## Band assignment

The assignment of the OH stretching bands to the terfenadine molecular groups is a step further towards the interpretation of the spectroscopic data. Two attempts were undertaken to establish the correspondence between the vibration and the interactions: study of self-association of terfenadine in inert liquid media and computational calculation of dimer formation.

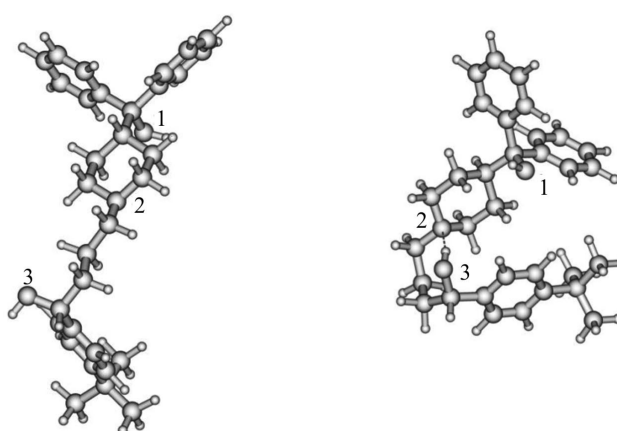
Infrared spectra of very dilute solutions of an inert solvent is a common procedure to investigate the vibration modes of isolated molecules [12].

Absorption bands corresponding to the free groups or the groups involved in internal bonds can be pointed out in these media. Important information on intermolecular interactions can also be obtained from the solute self-assembling as concentration increases [13]. The identification of the molecular groups participating in



cluster formation and the bond energies involved can be carried out by computational methods. As terfenadine has a long and flexible molecular chain the calculations have to be limited to dimer formation. Nevertheless early stages of self-association are crucial for the definite crystalline structure, the study of a dimer formation is valuable for the band assignment.

Spectra for terfenadine in  $\text{CCl}_4$  in the concentration range from 0.23 to 8.61 millimolar were recorded, using a 3 mm pathlength cell (Fig. 5). Three OH stretching bands were observed for any studied concentration: a narrow band ( $\nu_m=3615 \text{ cm}^{-1}$ ,  $\Delta\nu_{1/2}=12.6 \text{ cm}^{-1}$ ) which by frequency and width corresponds to  $\text{OH}_{\text{free}}$  group. The other two are broad and localized in the intermolecular OH hydrogen bonded region.



TERFENADINE-1-(4-tert-butylphenyl)-4-[4'-(diphenyl-hydroxymethyl)-1'-piperidyl]butan-1-ol

Fig. 4 Stretched and folded structures

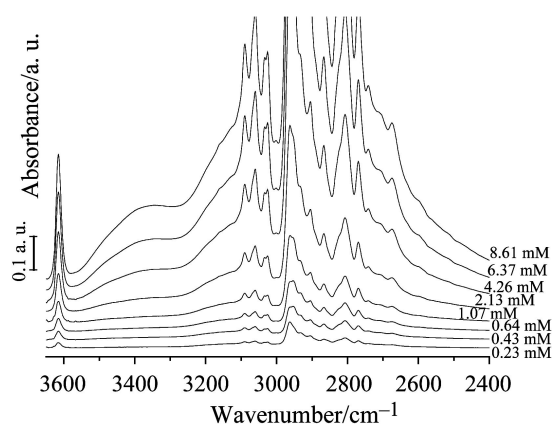


Fig. 5 Stretching vibration spectra for terfenadine in  $\text{CCl}_4$  solutions of different concentrations at  $25^\circ\text{C}$

No stretching vibration was observed in the typical region for OH groups involved in intramolecular hydrogen bonds [5]. Hence this kind of interaction is ruled out in the terfenadine aggregates in solution and a fortiori it should be so in the solid network.

From the spectra patterns one concludes that self-association occurs at a concentration as low as 5 milimolar. Therefore in the range of concentrations under study monomeric terfenadine is in equilibrium with dimer or small oligomers. For this reason the intermolecular bands uprising could not be observed by this method.

The gas phase molecule structure was approached through molecular mechanics. The minimal energy conformer displays an intramolecular hydrogen bond between the nitrogen atom and one of the hydroxyl groups. The energy difference between this conformer and the stretched molecule is estimated as  $6.8 \text{ kJ mol}^{-1}$ . All dynamics calculations carried out in this work used the TINKER set of programs, version 3.8 [14], with the built-in MM3-2000 force field including directional hydrogen bonding [15]. Results pertain to the gas-phase dimeric terfenadine system [16] for temperatures of 25 and 100°C, maintained through coupling to an external bath.

Gas-phase trajectories for the dimer were calculated with a time step of 1 fs, and a total integration time of 4000 ps. For the lower temperature, a set of nine trajectories was considered as described before [16]. Only one trajectory was deemed sufficient in the case of the highest temperature, due to increased randomization.

The bond strength was estimated by the time fraction of the total simulation time during which a specific bond between sites *i* and *j* was established.

The results obtained for intermolecular site-site hydrogen bond in the dimer leads to the following sequences,

25°C: 1,3 $\cong$ 1,1>3,3>1,2>2,3

100°C: 1,3>>2,3 $\cong$ 1,1>1,2>3,3

At 25°C, 1,3 and 1,1 interactions are formed with identical probability and are favoured relatively to the others according the sequence above. At 100°C, 1,3 interactions are strongly favoured whereas the probability for the occurrence of 1,1 and 3,3 decrease. The stable form at higher temperature is characterized by 1,3 HB. Accepting that in crystalline forms the hydrogen bonds follow the same order as in dimers one concludes that band I corresponds to 1,3 interactions, band II to 1,1 and band III to 3,3. The structures of the solid state formed at low temperatures will be the result of such interactive. The evolution of the structure organization by effect of the temperature increasing will be characterized by breaking 1,1 and, to a less extent, 3,3 bonds giving rise to 1,3 bond formation.

## Concluding remarks

With deliberate aim at testing infrared spectroscopy in the investigation of hydrogen bonded solid structures, terfenadine specimens considered on the grounds of thermal methods data as stable crystalline phases were selected. Some conclusions found in

the present work point out the ability of infrared spectroscopy for the characterization this kind of solid structure.

None of the terfenadine specimens just precipitated from the solvents are in the highest crystalline state. The band features, peak frequency shift, half-height width and integrated intensity, indicate a slow transformation in the 30–100°C range involving hydrogen bond breakage and reorganization into a more stable lattice network. The crystallinity degree decrease from ethanol-water to ethanol and from this to methanol.

Crystalline solid phases of terfenadine formed in the solvents used are often accompanied by the precipitation of amorphous solid material. Specimen EW apparently does not contain any amorphous phase whereas traces of this state phase were found in E and M. The amount of amorphous phase is high enough to follow its thermal behaviour during the heating process.

DSC fusion curves of terfenadine specimens obtained from the solvents under consideration show the existence of four polymorphs [17]. The analysis was performed on the solids after being submitted to a heating program up to the melting temperature. The infrared spectra show that all specimens after such thermal treatment do not reveal structural differences.

The results provided by both methods considered together prove that the polymorphs do not differ in hydrogen bonding network but rather in the conformation of the non polar chains between the polar centres. This interpretation is in agreement with close values found for the melting points of the various specimens.

Finally we should bear in mind that the separation of overlapping peaks is a necessary condition to go deep into the structure as it was clearly shown throughout this paper.

\* \* \*

We thank the Fundação para a Ciência e a Tecnologia (FCT), Lisbon, for financial support (research project Sapiens POCTI/35415/QUI/2000).

## References

- 1 J. Tomkinson, *Spectrochim. Acta*, 48A (1992) 329.
- 2 G. A. Jeffrey, *An Introduction to Hydrogen Bonding*, Oxford University Press, New York 1997.
- 3 G. R. Desiraju and T. Steiner, *The Hydrogen Bond*, Oxford University Press, New York 1999.
- 4 R. M. Badger and S. M. Bauer, *J. Chem. Phys.*, 5 (1937) 839.
- 5 M. D. Joesten and L. J. Schaad, *Hydrogen Bonding*, Marcel Dekker, Inc., New York 1974.
- 6 A. V. Iogansen, *Spectrochim. Acta*, 55A (1999) 1585.
- 7 J. M. Rollinger and Cs. Novák (Ed.), *J. Therm. Anal. Cal.*, 68 (2002) 335.
- 8 M. L. P. Leitão, J. Canotilho, S. C. R. Ferreira, A. T. Sousa and J. S. Redinha, submitted to *Thermochim. Acta*.
- 9 K. Kiss-Eröss, *Analytical Infrared Spectroscopy in Comprehensive Analytical Chemistry*, Vol. VI, Elsevier Scientific Publ. Co., Amsterdam 1976.
- 10 W. F. Maddams, *Appl. Spectrosc.*, 34 (1980) 245.
- 11 E. Fishman and T. L. Chen, *Spectrochim. Acta*, 25A (1969) 1231.

- 12 L. P. Kuhn, *J. Am. Chem. Soc.*, 74 (1952) 2492.
- 13 Y. Nakao, H. Sugeta and Y. Kyogoku, *Spectrochim. Acta*, 42A (1986) 251.
- 14 R. V. Pappu, R. K. Hart and J. W. Ponder, *J. Phys. Chem., B* 102 (1998) 9725.
- 15 J. Lii and N. L. Allinger, *J. Comput. Chem.*, 19 (1998) 1001.
- 16 A. F. Sousa, J. Canotilho, A. A. C. C. Pais, M. L. P. Leitão and J. S. Redinha, *Molecular Physics*, in press.
- 17 M. L. P. Leitão, J. Canotilho, M. S. C. Cruz, J. C. Pereira, A. T. Sousa and J. S. Redinha, *J. Therm. Anal. Cal.*, 68 (2002) 397.