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Temperature Effect on the Vibrational Dynamics of Cyclodextrin Inclusion Complexes: Investigation by FTIR-ATR Spectroscopy and Numerical Simulation

Vincenza Crupi, Domenico Majolino, and Valentina Venuti

Dipartimento di Fisica, Università degli Studi di Messina, CNISM, UdR Messina, C. da Papardo, S. ta Sperone 31, P.O. Box 55, 98166 S. Agata, Messina, Italy

Graziano Guella, Ines Mancini, Barbara Rossi,* Paolo Verrocchio, and Gabriele Viliani

Dipartimento di Fisica, Università degli Studi di Trento, Via Sommarive 14, 38123 Povo, Trento, Italy

Rosanna Stancanelli

Dipartimento Farmaco-Chimico, Università degli Studi di Messina, Viale Annunziata, 98168, Messina, Italy

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The vibrational dynamics of solid inclusion complexes of the nonsteroidal anti-inflammatory drug Ibuprofen (IBP) with β-cyclodextrin (β-CD) and methyl-β-cyclodextrin (Me-β-CD) has been investigated by using attenuated total reflection-Fourier transform infrared FTIR-ATR spectroscopy, in order to monitor the changes induced, as a consequence of complexation, on the vibrational spectrum of IBP, in the wavenumber range 600−4000 cm^{-1}. Quantum chemical calculations were performed on monomeric and dimeric structures of IBP, derived from symmetric hydrogen bonding of the two carboxylic groups, in order to unambiguously assign some characteristic IR bands in the IBP spectrum. The evolution in temperature from 250 to 340 K of the C═O stretching vibration, described by a best-fit procedure, allowed us to extract the thermodynamic parameter ΔH associated to the binding of IBP with βCDs in the solid phase. By comparing these results, Me-β-CD has been shown to be the most effective carrier for IBP.

Introduction

Inclusion or host−guest complexes are supramolecular systems where one chemical compound (the *host*) has a cavity, in which molecules of a second compound (the *guest*) are located.[1−4] The study of noncovalent forces involved in the formation of host−guest complexes is of paramount importance for the design of synthetic inclusion compounds, of new drugs and materials, of enzyme-analogue catalysts, and for many other applications.

Ibuprofen (IBP, 2-[4-(2-methylpropyl)phenyl]propanoic acid, see Figure 1) is a nonsteroidal anti-inflammatory drug (NSAID) largely used for relief of symptoms of arthritis, primary dysmenorrhea, fever, and also as an analgesic, especially where there is an inflammatory component.[5,6] It also has been shown to protect neurons from glutamate toxicity (implicated in Alzheimer's, Parkinson's, and other neurodegenerative diseases) in vitro.[7] Again, its potential antifungal activity, in particular against dermatophytes[8] and against several *Candida* species,[9] has been the focus of interest. It exhibits lower toxicity with respect to other anti-inflammatory agents such as indomethacin and diclofenac sodium, which allows this drug to be used without prescription. Nevertheless, at the same time, side effects on the mucous membrane of the stomach usually accompany treatment with this drug.[10] Beside this, IBP is practically insoluble in water (<1 mg/mL at 25 °C). An improvement of its pharmacokinetic parameters together with a reduction of its undesiderable secondary effects can be obtained by increasing its solubility in water and stability by means of complexation with β-cyclodextrins (β-CDs).[11,12]

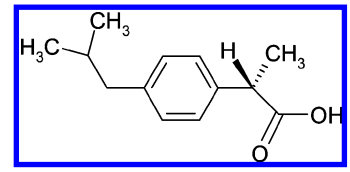

Figure 1. Chemical structure of (*S*)-IBP.

β-CD is a cyclic oligosaccharide consisting of seven glucose units linked by $\alpha(1\rightarrow4)$ bonds, resulting in a hollow truncated cone shape.[13] In water they have a hydrophilic outer surface and a hydrophobic central cavity able to include a wide variety of lipophilic guest molecules, with suitable polarity and dimension, without the formation of any covalent bond.[14−16] Complexation with β-CD has found extensive applications in pharmaceutical technology to enhance the aqueous solubility, dissolution rate, bioavailability, and stability of poorly water-soluble drugs.[17,18]

Unsubstituted β-CD has poor water solubility (16 mg mL^{-1} at 25 °C), whereas random substitution of the hydroxyl groups with alkyl or hydroxyalkyl groups is able to increase solubility. Therefore, several synthetically modified β-CDs were used as multifunctional drug carriers in parenteral formulations, such as methyl-β-cyclodextrin (Me-β-CD).[19] Inclusion complexes of CDs with IBP are of great interest, and several studies have been performed by both experimental and simulation techniques including, among others, pH potentiometric measurements, molecular modeling, nuclear magnetic resonance (NMR), fluorescence spectroscopy, differential scanning calorimetry

* To whom correspondence should be addressed. E-mail: rossi@science.unitn.it.

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(DSC), powder X-ray diffractometry (PXRD), scanning electron microscopy (SEM), and Fourier-transform infrared (FTIR) spectroscopy.[20−26] In addition, the influences of the processing technique on the drug content (HPLC) and the dissolution behavior were also studied.[27]

In a previous paper, by following a combined experimental-numerical approach, already successfully applied in the case of indomethacin/β-CDs inclusion complexes,[28,29] we investigated the modifications to the vibrational spectrum of IBP produced by inclusion into β-CDs cavity by means of Raman spectroscopy.[30] These changes have been discussed and interpreted by comparing the experimental data with the calculated vibrational wavenumbers and Raman intensities obtained for free and complexed IBP by quantum and classical numerical simulation. In this way, we have been able to provide remarkable information concerning the "host−guest" interactions driving the formation and stabilization of these systems, where the IBP molecule is included inside the CD cavity by the isobutyl chain, disentangling the effects directly related to the complexation process from those ascribed to other factors, such as noncovalent dimerization of IBP due to hydrogen bonding.

The thermodynamic parameters for formation of IBP/CD complexes, in aqueous solution, already have been reported in the literature by using calorimetric methods.[31,32] We use here FTIR absorption spectroscopy in ATR geometry[33] to study the effect of the temperature on the vibrational dynamics of inclusion complexes, in order to obtain, for the first time, information on the thermodynamic parameters associated with the host−guest binding in the solid phase. Quantum chemical calculations were performed on monomeric and dimeric structures of IBP, the latter one derived from symmetric hydrogen bonding of the two carboxylic groups, in order to unambiguously assign some characteristic IR bands in the IBP spectrum. The evolution in temperature from 250 to 340 K of the C═O stretching vibration of IBP has been followed; then, deconvolution and curve fitting procedures have been applied to the data, estimating the enthalpy change associated with host−guest binding, in the solid phase. The thermodynamic parameters obtained for β-CD and Me-β-CD complexes have been compared and discussed in order to deeper understand the interactions involved in the formation and stabilization of supramolecular assemblies with CD.

Experimental and Computational Details

A. Synthesis of CD Complexes. β-Cyclodextrin (β-CD) and methyl-β-cyclodextrin (Me-β-CD, degree of substitution ∼1.7−1.9) were purchased from Fluka Chemie (Switzerland). Racemic IBP was purchased from Sigma-Aldrich. All the reagents were used without any further purification.

β-CD (113.5 mg, 0.1 mmol) was dissolved in water to obtain a 0.1 mM solution, which was added to an equimolar amount of dry IBP (20.6 mg). Water (1 mL) was added to this solution and the resulting dispersion was stirred at room temperature for 2 h, obtaining a white mixture. Subsequently, the liquid phase of this suspension was removed from the filtrate and both phases were dried in a vacuum chamber, using P_2O_5 as dehydratant. The same procedure has been followed also for the preparation of IBP/Me-β-CD inclusion complexes.

To verify the effective formation of the complexes and to provide information on the stoichiometry of the systems mass spectrometry via an electrospray interface (ESI-MS, by a Bruker Esquire ion trap spectrometer) in the negative ion mode was used by direct infusion of a 1:1 MeOH/H_2O solution of the complexes. In the spectrum of the IBP/β-CD complex, the signal at m/z 1134 is assigned to the pseudomolecular ion $[M_{CD} - H]^-$ of free β-CD, while the peak at m/z 1340 corresponds to the pseudomolecular ion $[M_{complex} - H]^-$ of the IBP/β-CD 1:1 complex. These assignments are confirmed by tandem fragmentation MS/MS experiments performed on the peak at m/z 1340, which give the signal at m/z 1134 by neutral loss of IBP. The same behavior is observed also for the IBP/Me-β-CD inclusion complex.

B. FTIR-ATR Measurements. FTIR-ATR absorption measurements were performed in the 400−4000 cm^{-1} spectral region. The temperature range investigated extends from 250 to 340 K. Spectra were recorded with a Bomem DA8 Fourier transform spectrometer, operating with a Globar source, in combination with a KBr beamsplitter and a thermoelectrically cooled deuterated triglycene sulfate (DTGS) detector. The powders were contained in a Golden Gate diamond ATR system, just based on the attenuated total reflectance (ATR) technique. The spectra were recorded with a resolution of 4 cm^{-1}, automatically adding 100 repetitive scans in order to obtain a good signal-to-noise ratio and highly reproducible spectra. All the measurements were performed in a dry atmosphere. To check a possible unwanted effect induced by wetting and/or drying phenomena when the sample holder was filled with dry nitrogen, IR spectra in the presence and absence of air were compared without showing any significant difference. All the spectra were normalized for taking into account the effective number of absorbers.

No smoothing was done, and spectroscopic manipulation such as baseline adjustment and normalization were performed with the Spectracalc software package GRAMS (Galactic Industries, Salem, NH, USA). The analysis of the 1500−1800 cm^{-1} region, typical of the C═O stretching intramolecular vibrational mode, which required a band decomposition procedure, was undertaken using the curve fitting routine provided in the PeakFit 4.0 software package, which enabled the type of fitting function to be selected and allowed specific parameters to be fixed or varied accordingly. The strategy adopted was to use well-defined shape components of Voigt functions with all the parameters allowed to vary upon iteration. The statistical parameters were used as a guide to "best-fit".

C. Computational Methods. The ab initio quantum chemical computations on a single molecule of (*S*)-IBP and on the IBP dimer were performed with the GAUSSIAN 03 program suite,[34] using unrestricted DFT.[35] The nonlocal B3LYP functional hybrid method was employed.[36] The standard 6-31G(d) basis set[37] was used for the geometry optimization and vibrational energy analysis. For the plot of the theoretical infrared spectra, a Lorentzian line shape with a line width of 4 cm^{-1} was used; computed IR intensities and Raman activities are expressed in arbitrary units .

Results and Discussion

Quantum chemical calculations were performed on a single (*S*)-IBP molecule (Figure 1) and, according to previous X-ray diffraction and Raman studies,[30,38,39] that suggested the prevalence of IBP dimeric entities in condensed phases, on an IBP dimer (Figure 2) derived from symmetric hydrogen bonding of the two carboxylic groups of a (*R*)-IBP molecule and a (*S*)-IBP molecule.

In Figure 3 we report the experimental FTIR-ATR spectrum, collected in the C−H/O−H stretching region (2250−3750 cm^{-1}) for uncomplexed IBP at $T = 290$ K. The spectrum shows many sharp vibrational bands, indicating that the molecules are in a structurally defined and regular environment (i.e., in a crystalline

Figure 2. Minimized structure of IBP dimer, derived from symmetric hydrogen bonding of the two carboxylic groups of a (*R*)-IBP molecule and a (*S*)-IBP molecule.

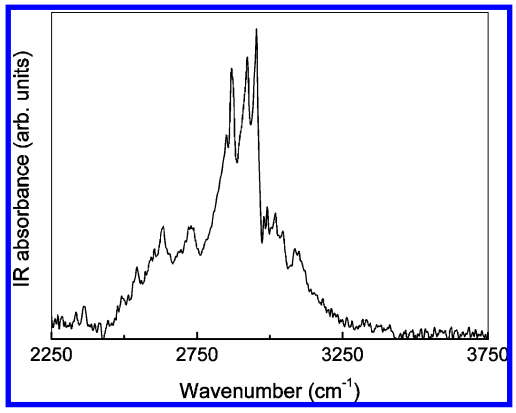

Figure 3. Experimental FTIR-ATR spectrum, in the 2250−3750 cm^{-1} wavenumber range at $T = 290$ K, of uncomplexed IBP.

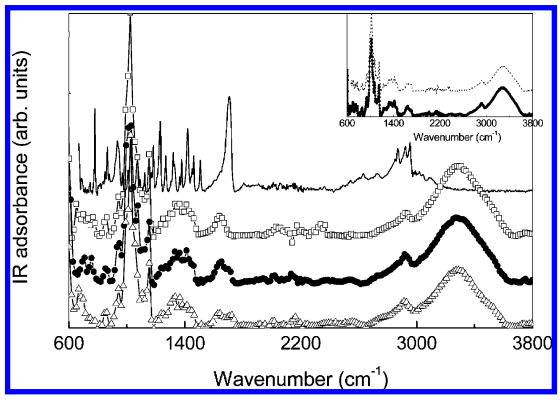

Figure 4. Experimental FTIR-ATR spectra, in the 600−3800 cm^{-1} wavenumber range at $T = 290$ K, of uncomplexed IBP (solid line), β-CD (open squares), IBP + β-CD physical mixture (closed circles), and IBP/β-CD inclusion complex (open triangles). In the inset, the comparison between the experimental spectrum of the IBP + β-CD physical mixture (closed circles) and the calculated weighed addition of the spectra of IBP and β-CD (dashed line) is reported.

field), supporting the hypothesis that pure IBP is in a crystalline phase. Above 3500 cm^{-1}, no peaks are revealed. This result is supported by the lack of peaks in this zone also in the computed spectrum of dimer IBP for which the hydroxyl groups are involved in intermolecular hydrogen bonds with C═O groups, in agreement with previous studies.[30]

In Figure 4 we report the FTIR-ATR spectra collected, in the 600−3800 cm^{-1} wavenumber range, for the pure IBP and β-CD, physical mixture, and complex of IBP and β-CD at $T =$ 290 K. First of all we observe, as a general result, that the spectrum of the physical mixture turned out to be equivalent to the calculated weighed addition of the spectra of IBP and β-CD, as reported in the inset of the same figure. This is indicative of the absence, during simple blending, of well-defined chemical interactions between IBP and β-CD, and of the consequent coexistence, in the physical mixture, of two separate phases:

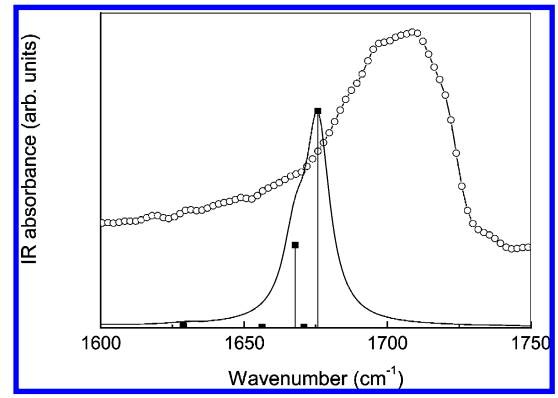

Figure 5. Experimental FTIR-ATR spectra, in the 1600−1750 cm^{-1} wavenumber range at $T = 290$ K, of uncomplexed IBP (open circles), and computed spectra of the IBP dimer (solid line).

crystalline IBP and β-CD. On the contrary, the shapes of the bands of the inclusion complex revealed changes if compared with those of pure IBP, β-CD, and physical mixture, giving evidence of a modification of bond strengths and lengths as a consequence of the activation of "host−guest" interactions upon complexation. Again, in the spectrum of the complex, the characteristic absorption bands of β-CD are superposed over the IBP ones, and the overall spectrum tends to recall that of the corresponding CD. This phenomenon, mainly attributable to the difference in molecular weight between pure drug and CD, also can be considered as an experimental confirmation of the formation of inclusion complex. In fact, as has been reported in the literature,[40,41] complexation induces, in a way, a sort of "shielding" of the guest molecule that, being included and not interposed between β-CDs molecules, completely rearranges its crystal structure, with a final configuration of the resulting binary system that is expected to be similar to that of the pure CD.

In Figure 5 we compare the experimental spectra in the 1600−1750 cm^{-1} range of uncomplexed IBP (open circles) at $T = 290$ K with those computed for IBP dimer (solid line).

We chose to focus our attention on the spectrum of free IBP in this wavenumber range, since the very intense band at ∼1708 cm^{-1} assigned to the carbonyl stretching vibration can constitute an excellent candidate to show some variations attributable to the complexation process.

Potential interesting changes, passing from physical mixture to inclusion complexes, are nevertheless also revealed in the wavenumber regions below 1600 cm^{-1} and above 1750 cm^{-1}, but they have not been discussed here because their interpretation appears quite difficult since they are overlapped with the strong absorption bands of cyclodextrins.

From numerical simulation, two main computed peaks, at ∼1669 and ∼1738 cm^{-1}, are revealed for a single IBP molecule, and four main computed peaks, at ∼1656, ∼1667, ∼1670, and ∼1675 cm^{-1}, for IBP dimer; details are reported in Table 1, together with the assignment derived on the basis of the normal-mode analysis. From inspection of the table, we can conclude that passing from single IBP molecule to IBP dimer the mode at ∼1669 cm^{-1} for single IBP is split into two modes at ∼1667 (IR-active, Raman-inactive) and ∼1670 cm^{-1} (IR-inactive, Raman-active), with very similar energy, involving the aromatic ring of IBP. The mode at ∼1738 cm^{-1} is split into two modes at ∼1656 (IR-inactive, Raman-active) and ∼1675 cm^{-1} (IR-active, Raman-inactive), both involving mainly the group C═OOH.

It is worth remarking that the modes that undergo a splitting in the dimer seem to satisfy the Raman/IR selection rules (see

TABLE 1: Wavenumber ω (cm^{-1}), IR Intensity, and Raman Activity (arbitrary units) of the Main Computed Peaks Obtained from Quantum Chemical Computation with the Assignment Based on the Normal Modes Analysis

ω (cm^{-1})	IR intensity	Raman activity	assignment
		IBP monomer	
1669	1	95	C—H bending, C═C stretching of the aromatic ring
1738	192	7	C═O streching
		IBP dimer	
1656	0.032	10	stretching of the C═O···H bond
1667	152	0.1	C—H bending, C═C stretching of the aromatic ring
1670	0.09	230	C—H bending, C═C stretching of the aromatic ring
1675	400	0.1	C═O stretching

the relative Raman and IR activities). These modes, in fact, involve atoms of both molecules of the dimer, which are located at sites of approximate inversion symmetry with respect to the center of the hexagon of the C═OOH involved in the hydrogen bonds (see Figure 2).

Taking into account the aforementioned considerations and based on the comparison with the wavenumber and relative intensities of the experimental and computed peaks, the most reasonable assignment should identify the experimental peak at ~1708 cm^{-1} with the very active IR peak computed at ~1675 cm^{-1} in the spectrum of IBP dimer corresponding to a C═O stretching mode. In the experimental Raman spectrum of uncomplexed IBP, previously collected in the same region,[30] we observed a not very intense peak at ~1650 cm^{-1}, corresponding to the computed peak at ~1656 cm^{-1} that is IR-inactive. These results confirm once again the hypothesis of the presence of IBP dimeric entities in condensed phases.

In Figure 6 we show the FTIR-ATR spectra, in the 1200−1800 cm^{-1} wavenumber range, of IBP/β-CD (a) and IBP/Me-β-CD (b) complexes, together with those of the pure compounds and their physical mixtures, at $T = 290$ K.

For both inclusion complexes, we observe a shift of the C═O stretching vibration to the higher frequencies that, on average in the T-range explored, turned out to be ~25 cm^{-1} for IBP/β-CD and ~17 cm^{-1} for IBP/Me-β-CD systems, with respect to the corresponding frequencies in pure IBP and the physical mixture (in both cases at ~1708 cm^{-1}). This effect, indicative of a strengthening of the carbonyl bond, already has been widely observed in literature, and attributed to the breakdown of the intermolecular hydrogen bonds of the dimeric structures, followed by the establishment of a less intense association, i.e., a monomeric dispersion of the drug as a consequence of its interaction with CDs, that could result in the inclusion of the drug monomer in the hydrophobic cavity of the carrier.[11,26]

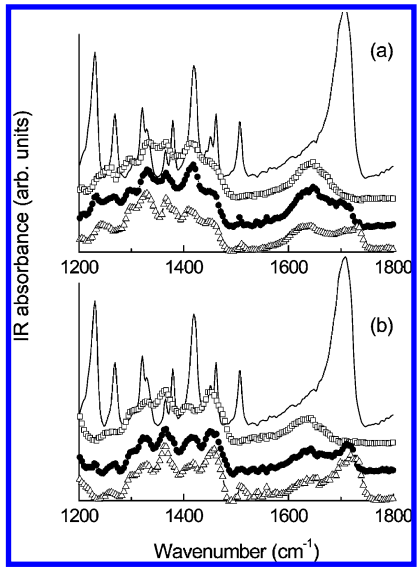

Figure 6. Experimental FTIR-ATR spectra, in the 1200−1800 cm^{-1} wavenumber range at $T = 290$ K, of (a) uncomplexed IBP (solid line), β-CD (open squares), IBP + β-CD physical mixture (closed circles), and IBP/β-CD inclusion complex (open triangles) and (b) uncomplexed IBP (solid line), Me-β-CD (open squares), IBP + Me-β-CD physical mixture (closed circles), and IBP/Me-β-CD inclusion complex (open triangles).

The high quality of the infrared spectra obtained by FTIR-ATR technique makes their quantitative analysis feasible. Among the mathematical procedures available, we used second derivative computation and curve-fitting in order to separate the contribution of the individual vibrations to the experimental spectra in the 1500−1800 cm^{-1} region.

The second derivative computation, not reported here, allowed us to evaluate the wavenumber of the maxima for the band components, by looking at the minima in the second derivative profile. The curve fitting procedure was applied to the experimental profiles based on these wavenumber values. Three minima were observed in the second derivative profile, suggesting that three contributions are necessary to reproduce the experimental spectra, centered respectively at ~1640, ~1710, and ~1730 cm^{-1}. According to the literature, and on the basis of the comparison with the wavenumbers of the peaks in the experimental and computed spectra of uncomplexed and complexed IBP, the sub-band at ~1640 cm^{-1} will reflect the δ-HOH bending of water molecules attached to β-CDs,[42,43] the sub-band at ~1710 cm^{-1} is attributed to the contribution of the stretching of hydrogen-bonded carbonyls of uncomplexed IBP in dimeric form, and finally, the sub-band at ~1730 cm^{-1} will correspond to the stretching of carbonyls of complexed monomeric IBP. A problem that arises in the analysis of our spectra is, then, the partial overlapping of the δ-HOH bending and C═O stretching vibrations. We choose to fit simultaneously the whole spectrum (δ-HOH bending and C═O stretching vibrations), with all the fitting parameters left free to vary upon iteration until the convergence is reached. Then, the contributions coming from δ-HOH bending of water molecules attached to β-CDs have been subtracted and more detailed fits have been performed just for the C═O stretching vibrations. Again, two components for the C═O stretching band, i.e., $\omega_u \approx 1710$ cm^{-1} and $\omega_c \approx 1730$ cm^{-1}, correctly describe the existing types of C═O oscillators, coming respectively from uncomplexed and complexed IBP molecules.

Figures 7 and 8 show the fitting results for IBP/β-CD and IBP/Me-β-CD inclusion complexes, respectively, at $T = 250$, 290, and 340 K, as examples.

Even if the well-known difficulties of uniquely fitting IR band profiles impose caution against over-interpretation of the data, it is worth underlining that the procedure adopted here makes use of the minimum number of parameters and, at the same

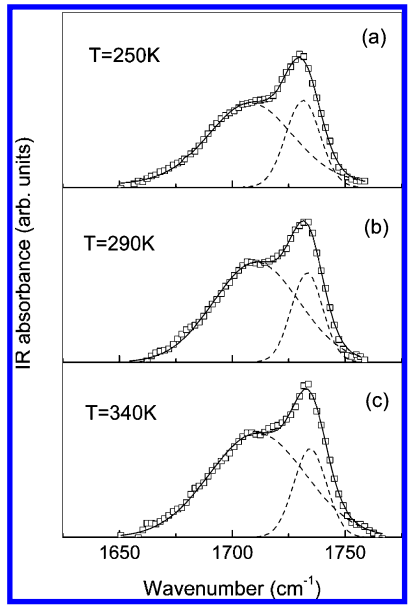

Figure 7. Fitting results for the C═O stretching band for IBP/β-CD inclusion complex at $T = 250$ (a), 290 (b), and 340 K (c).

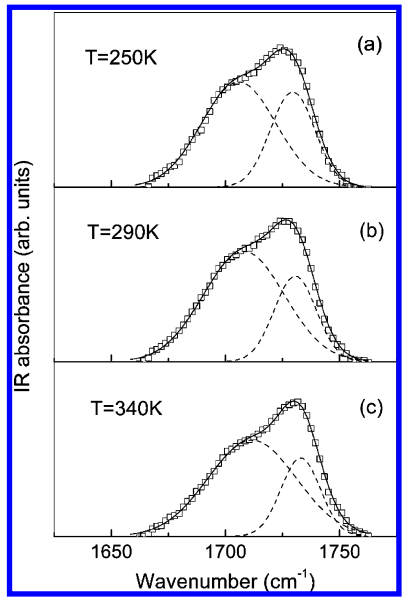

Figure 8. Fitting results for the C═O stretching band for IBP/Me-β-CD inclusion complex at $T = 250$ (a), 290 (b), and 340 K (c).

time, furnishes extremely good fits to the data. The best-fit is, in fact, characterized by $r^2 \approx 0.99$ for all the investigated systems.

The main fitting parameters, i.e., peak wavenumber and percentage intensity, for all the investigated systems in the explored T-range are reported in Table 2.

Only minor changes are revealed, in the T-range explored, in the center-frequency of each sub-band. As far as percentage intensities are concerned, we focused our attention on the evolution in temperature of the intensities, indicated as $I_u(T)$ and $I_c(T)$, of the contributions assigned to the C═O stretching of uncomplexed (sub-band ω_u) and complexed (sub-band ω_c) IBP. They are reported in panels a and b of Figure 9 for IBP/β-CD and IBP/Me-β-CD inclusion complex, respectively. We notice that the population of complexed IBP molecules, as expressed by the percentage intensity of the corresponding contribution $I_c(T)$, is slightly higher, in the T-range explored, for IBP/Me-β-CD inclusion complex with respect to IBP/β-CD,

TABLE 2: Main Fitting Parameters, i.e., Peak Wavenumber and Percentage Intensity, for the 1500−1800 cm^{-1} Region for All the Investigated Systems in the Explored T-Range

T (K)	ω_u (cm^{-1})	I_u (%)	ω_c (cm^{-1})	I_c (%)
IBP/β-CD inclusion complex				
250	1708 ± 3	71.7 ± 7.6	1731 ± 1	28.3 ± 6.9
260	1709 ± 1	71.9 ± 7.7	1732 ± 1	28.1 ± 7.1
270	1710 ± 2	73.6 ± 7.8	1732 ± 1	26.4 ± 7.0
280	1709 ± 2	73.8 ± 7.2	1733 ± 1	26.2 ± 6.8
290	1711 ± 3	75.0 ± 7.5	1733 ± 1	25.0 ± 6.7
300	1712 ± 4	74.6 ± 8.2	1734 ± 1	25.3 ± 7.2
310	1712 ± 2	75.4 ± 7.7	1733 ± 1	24.6 ± 7.4
320	1712 ± 4	76.4 ± 7.9	1734 ± 1	23.6 ± 7.3
330	1714 ± 5	77.9 ± 7.9	1734 ± 1	22.1 ± 7.5
340	1711 ± 1	78.4 ± 7.5	1734 ± 1	21.6 ± 7.1
IBP/Me-β-CD inclusion complex				
250	1705 ± 5	62.7 ± 7.9	1729 ± 2	37.3 ± 8.7
260	1705 ± 5	64.0 ± 7.7	1729 ± 2	36.0 ± 8.4
270	1706 ± 5	64.1 ± 7.3	1730 ± 2	35.9 ± 8.0
280	1706 ± 5	64.7 ± 7.7	1730 ± 1	35.2 ± 8.3
290	1707 ± 5	66.3 ± 8.0	1730 ± 1	33.7 ± 8.8
300	1708 ± 7	67.4 ± 7.5	1731 ± 2	32.6 ± 8.1
310	1709 ± 7	68.7 ± 7.7	1731 ± 1	31.6 ± 8.5
320	1710 ± 3	69.7 ± 7.4	1732 ± 1	30.3 ± 8.6
330	1712 ± 7	71.8 ± 8.1	1733 ± 1	28.2 ± 8.4
340	1711 ± 9	72.6 ± 7.7	1733 ± 1	27.4 ± 8.2

revealing a relatively more favorable accessibility offered by Me-β-CD to the IBP molecules.

To extract thermodynamic parameters, we first checked that the inclusion process is reversible. This was accomplished by comparing the IR spectra of complexes recorded at 300 K with the ones obtained by (i) heating the system to 340 K and (ii) then cooling it again to 300 K. The two spectra were identical within experimental error.

On this basis, we extracted the thermodynamic parameters associated with binding of IBP and β-CDs for 1:1 stoichiometry in solid phase according to the following approach: as is well-known, the complex formation, in solution, between IBP and β-CD (or Me-β-CD, the treatment is the same) is characterized

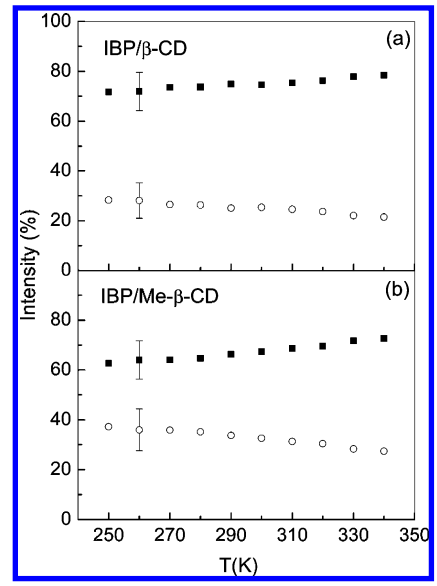

Figure 9. Evolution in temperature of the percentage intensities of the contributions assigned to the C═O stretching of uncomplexed ($I_u(T)$, closed squares) and complexed ($I_c(T)$, open circles) IBP: (a) refers to IBP/β-CD inclusion complex and (b) refers to IBP/Me-β-CD inclusion complex. The error bars represent the average uncertainty on the obtained values.

by an equilibrium constant K. Now, in the case of our solid inclusion complexes, we put our attention on the C═O stretching normal mode and we considered all the species that, at the thermodynamic equilibrium, contribute to that vibration.

In particular, according to the performed deconvolution of the 1500−1800 cm^{-1} region, β-CD does not contribute to the C═O stretching signal, whereas the contributions of IBP and IBP/β-CD are the ones given by respectively uncomplexed and complexed IBP molecules, previously indicated by ω_u (∼1710 cm^{-1}) and ω_c (∼1730 cm^{-1}). Now, assuming that the observed FTIR-ATR intensities are representative of the population of the corresponding species, we can write an "affinity" constant, let us say A, as:

$$A(T) = \frac{I_c(T)}{I_u(T)} \tag{1}$$

Even if a direct comparison of $A(T)$ with the usually defined equilibrium constant K is not meaningful, being K referred to the inclusion reaction in liquid phase, nevertheless we remind that our solid inclusion complexes always contain the crystallization water molecules coming from cyclodextrins. Again, we will show that the behavior of $A(T)$ as a function of temperature furnishes a reasonable picture of the complexation mechanism.[11,44]

Assuming that our system may be described by a collection of independent pairs of CD and IBP molecules that can only exist in the complexed and uncomplexed state one has that

$$A(T) = \frac{n_c(T)}{n_u(T)} \tag{2}$$

where n_c (respectively n_u) is the fraction of complexed (respectively uncomplexed) pairs, and the T-dependence of A is found to be well described by the equation:

$$\ln A = \left(\frac{-\Delta H}{RT}\right) + \frac{\Delta S}{R} \tag{3}$$

where ΔH and ΔS represent respectively the enthalpy and entropy changes associated with the binding of IBP and β-CD in solid phase, and R is the gas constant.

In Figure 10 we report the semilog plot of A vs $1/T$ for (a) IBP/β-CD and (b) IBP/Me-β-CD inclusion complex, respectively, together with the linear-fit performed according to eq 3.

From the intercept of the linear plot we estimated $\Delta H = -2748 \pm 245$ J·mol^{-1} for IBP/β-CD and -3573 ± 317 J·mol^{-1} for IBP/Me-β-CD inclusion complexes, respectively.

We can hypothesize, then, that the main driving force for the formation of both IBP/β-CD and IBP/Me-β-CD inclusion complexes is the release of water molecules from the CD cavity. In fact these water molecules cannot satisfy, inside the hydrophobic cavity of cyclodextrins, their hydrogen bond potentials, and are, therefore, enthalpy-rich. The replacement of these H_2O molecules with suitable guest molecules, less polar than water, contributes to diminish the energy of the system. The slightly more marked lowering for the IBP/Me-β-CD inclusion complex, with respect to β-CD, indicative of the best performance of this host as carrier for IBP, can be explained taking into account that, as already observed,[11] Me-β-CD combines the expansion of hydrophobic region of the cavity with the minimum steric hindrance for inclusion. The contribution of van der Waals forces can be, in this case, neglected; van der Waals forces are, in fact, weak and critically dependent on the separation distances and, then, on the guest size. Therefore, they become important when the guest can snugly fit in the CD cavity, but this condition is not satisfied in the case of IBP and β-CDs.

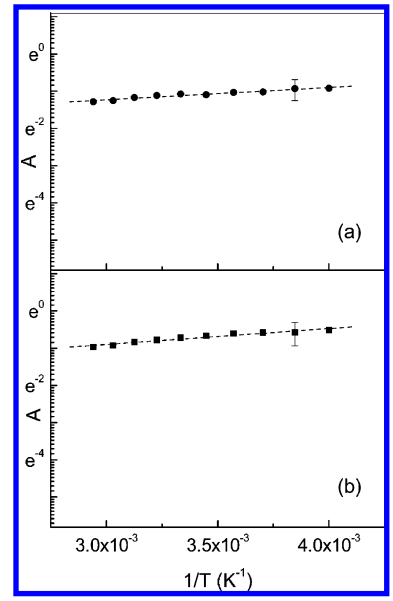

Figure 10. Semilog plot of A vs $1/T$ for (a) IBP/β-CD and (b) IBP/Me-β-CD inclusion complex, together with the best-fit performed according to eq 3. See text for details.

On the basis of these results, a study as a function of the hydration degree of the complexes could be a reasonable development of the research in order to check the overall validity of the proposed approach.

Conclusions

Solid inclusion complexes of ibuprofen (IBP) with native and modified β-cyclodextrins (β-CDs), namely β-CD and Me-β-CD, have been investigated by means of Fourier transform infrared spectroscopy in attenuated total reflectance geometry (FTIR-ATR) and ab initio numerical simulation.

The combined use of experimental and numerical techniques was successful for the interpretation of the modifications induced by complexation in the vibrational spectrum of IBP. Focusing our attention on the wavenumber range 1600−1800 cm^{-1}, typical of the very intense C═O stretching FTIR band, we verified that this vibration is very sensitive to the nearby environment of the C═O bond, and we attributed the shifts to the higher frequencies, observed for both the analyzed complexes, to the complexation-induced breakdown of the intermolecular hydrogen bonds in the IBP dimer.

From the temperature-dependent studies, the enthalpy changes associated with "host−guest" interactions in the solid phase have been estimated and the obtained results reveal Me-β-CD to be the optimal partner for IBP.

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