Solid state inclusion compound of *S*-ibuprofen in β-cyclodextrin: structure and characterisation†

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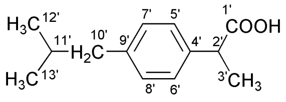
A crystalline inclusion complex was isolated from the reaction of β-cyclodextrin (βCD) with aqueous *S*-(+)-ibuprofen (*S*-Ibu). The existence of a true inclusion complex in the solid state was confirmed by a combination of powder X-ray diffraction (XRD), single crystal X-ray diffraction, thermogravimetric analysis (TGA), FTIR and ^{13}C CP MAS NMR spectroscopies. The inclusion compound crystallises in the non-centrosymmetric monoclinic space group *C*2 with a 2:1 host:guest stoichiometry. The crystal structure consists of a head-to-head dimer of βCD molecules stacked along the crystallographic *c* axis, thus forming a slightly tilted channel-type structure.

Introduction

Ibuprofen [2-(*p*-isobutylphenyl)propanoic acid, **A**] is generally available as a racemic mixture. The *S* isomer is the more active as an anti-inflammatory drug with pain relief activity. For many years, it has been used in the treatment of rheumatoid arthritis and other inflammatory diseases. Recently, renewed interest in this compound has arisen as new therapeutic properties have been discovered. Ibuprofen was shown to protect neurons from glutamate toxicity *in vitro*.[1] Glutamate cytotoxicity has been implicated in Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases, meaning that ibuprofen could be a promising protective agent against these ailments.



A

Another set of studies has focused on the potential antifungal activity of this drug. Indeed, ibuprofen was shown to be active against dermatophytes[2] (fungi responsible for skin infections) and against several *Candida* species; these yeast are responsible for infections in the mucosas.[3] In both situations, ibuprofen may become a drug of choice for topical treatment of fungal infections, taking advantage of its classical anti-inflammatory activity combined with the newly discovered antifungal activity. Aside from its interesting active effects, ibuprofen has an undesirable secondary effect on the gastric mucosa, which may also suffer direct injury from this molecule, a weak acid, that presents itself in the non-ionic form at gastric pH. In fact, this form passes easily through the gastric cell membrane and becomes ionised at inner cell pH. As a result, it accumulates in the gastric mucosa cells.

β-Cyclodextrin (βCD) is a cyclic oligosaccharide formed by 7 D-glucose units linked by α(1 → 4) bonds, resulting in a hollow truncated cone shape. It has a hydrophobic cavity capable of including lipophilic molecules such as ibuprofen. This association is used to reduce the toxicity related to ibuprofen acidity and improve its water solubility. Several applications of inclusion compounds are used in the pharmaceutical field, comprising solutions for oral delivery,[4] tablets or capsules,[5] *etc.* Since inclusion compounds of cyclodextrins with anti-inflammatory drugs are of great interest, several studies have been performed on these systems. The solid state characterisation of βCD compounds with flurbiprofen[6] and fenoprofen[7] was performed by several techniques, in particular, X-ray crystallography. More recently, it has been shown that βCD increases the stability of ibuprofen.[8] The single crystal X-ray structure of the inclusion compound between *S*-ibuprofen and heptakis(2,3,5-trimethyl-βCD) was reported by Brown *et al.*[9] In this work, we study the solid state inclusion of *S*-Ibu in βCD in the crystalline state. The crystals were analysed by X-ray diffraction, thermogravimetry, FTIR and ^{13}C CP MAS NMR spectroscopies.

Experimental

Materials and methods

Powder XRD data were collected on a Philips X'pert diffractometer using Cu-Kα radiation filtered by Ni ($\lambda = 1.5418$ Å). TGA studies were performed on a Shimadzu TGA-50 thermogravimetric analyser, using a heating rate of 1 °C min^{-1}, under air atmosphere, with a flow rate of 30 mL min^{-1}. The sample holder was a 5 mm Ø platinum plate and the sample mass was about 5 to 10 mg. Microanalyses were performed at Aveiro University. Infrared spectra were obtained in a Mattson 700 FTIR spectrometer (resolution 2.0 cm^{-1}; 32 scans per spectrum). Solid state ^{13}C CP MAS NMR spectra were recorded at 100.62 MHz, on a 9.4 T Bruker Avance 400 spectrometer (25 °C; 4.5 μs ^{1}H 90° pulses, 2.0 ms contact time, 9 kHz spinning rate; 12 s recycle delays). Chemical shifts are quoted in parts per million (ppm) from TMS.

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† Electronic supplementary information (ESI) available: crystal and data collection parameters and relevant O···O contacts (divided in six different groups) for **β**CD:*S*-Ibu. See: http://www.rsc.org/suppdata/nj/b2/b207272f/

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βCD, kindly donated by Wacker-Chemie, München, was recrystallised prior to use. *S*-Ibuprofen (*S*-Ibu) was obtained from Fluka (retailed in Portugal by Sigma-Aldrich, Sintra) and used as received. Distilled water was used as solvent.

Synthesis of inclusion compound 2 · βCD:*S*-Ibu

βCD (0.20 g, 0.15 mmol) was dissolved in water (10 mL) with heating at 80 °C and *S*-Ibu (0.04 g, 0.15 mmol) was added in stoichiometric proportion. The resulting mixture was stirred for 7 h then slowly cooled; the suspension was filtered and the white powder dried under vacuum. Yield 0.37 (91%). Found: C, 43.1%; H 7.03%; calcd for $2(C_{42}H_{70}O_{35})\cdot(C_{13}H_{18}O_2)\cdot 14H_2O$: C 42.70%; H 6.87%. Recrystallisation of 2·βCD:*S*-Ibu in water affords good crystals after 2 weeks.

X-ray crystallography

Details of the X-ray experiment, data reduction, and final structure refinement calculation are summarised in Table 1. Crystals obtained by slow evaporation of a saturated equimolar aqueous solution of βCD and *S*-Ibu were found suitable for an X-ray structure determination. A clear colourless fragment (0.34 × 0.42 × 0.57) was stored under perfluorinated ether, transferred to a Lindemann capillary, fixed and sealed. Preliminary examination and data collection were carried out on a Nonius Kappa CCD area detector at the window of a rotating anode X-ray generator (NONIUS FR591; 50 kV; 60 mA; 3.0 kW) and graphite-monochromated MoK_α radiation ($\lambda = 0.71073$ Å).

Data collection was performed at 123 K with an exposure time of 60 s per film (phi scan, rotation modus, $\Delta\varphi = 1.0°$), and controlled by the Collect software package.[10a] Collected images were processed using Denzo. The unit cell parameters were obtained by full-matrix least-squares refinements of 22 688 reflections.[10b] The structure was solved by using the results of an isomorphous compound and difference Fourier synthesis.[10c] All non-hydrogen atoms of the asymmetric unit were refined with anisotropic thermal displacement parameters except those of the ibuprofen molecule. All hydrogen atoms were calculated in ideal positions (riding model), except those of the water molecules, which could not be found nor calculated. Full-matrix least-squares refinements were carried out by minimising $\Sigma w(F_o^2 - F_c^2)^2$ with SHELXL-97 weighting scheme and stopped at maximum shift/error < 0.001.[10d] Neutral atom scattering factors for all atoms and anomalous dispersion corrections for the non-hydrogen atoms were taken from the *International Tables for Crystallography*.[10e] All other calculations (including ORTEP graphics) were done with the program PLATON.[10f] Calculations were performed on a PC workstation (Intel Pentium II) running LINUX.

Table 1 Crystallographic data for 2·βCD:*S*-Ibu

Formula	$2(C_{42}H_{70}O_{35})\cdot C_{13}H_{18}O_2\cdot 25(H_2O)$
FW	2926.61
Crystal system	Monoclinic
Space group	*C*2 (No. 5)
a/Å	19.4095(4)
b/Å	24.4145(5)
c/Å	15.8976(2)
β/°	109.026(1)
U/Å^3	7121.9(2)
Z	2
ρ_{calcd}/g cm^{-3}	1.365
μ/mm^{-1}	0.121
T/K	123
$R_1(F_o^2)$ [$I > 2\sigma(I)$]	0.0717
$wR_2(F_o^2)$ [$I > 2\sigma(I)$]	0.1951
$R_1(F_o^2)$ (all data)	0.0726
$wR_2(F_o^2)$ (all data)	0.1968

CCDC reference number 196 125. See: http://www.rsc.org/suppdata/nj/b2/b207272f/ for crystallographic files in CIF or other electronic format.

Results and discussion

Powder XRD

The 2βCD:*S*-Ibu adduct precipitates as a microcrystalline powder as evidenced by powder XRD (Fig. 1). In addition, its powder XRD pattern does not contain reflections corresponding to those of either the βCD hydrate or the pure non-included ibuprofen. This can be taken as an initial indication for the occurrence of a true inclusion compound.[11]

Single crystal XRD

Crystals of the prepared inclusion compound crystallise in the non-centrosymmetric monoclinic space group *C*2 with 25 equivalents of solvent. Isomorphous structures have already been studied.[12] The only significant differences between the various βCD macrocycles are in the orientation of the primary hydroxyl groups C(6)–O(5), which generally turn away from the centre of the βCD. The torsion angles O(2)–C(5)–C(6)–O(5) are negative and correspond to a (+)-*gauche* conformation. Normal bond lengths and bond angles are observed in the βCD macrocycle.

One hydroxyl group appears to be disordered over two positions: O(20A) and O(20B). All primary hydroxyl groups and the major part of the disordered moiety show a (+)-*gauche* conformation. The minor part of the disordered hydroxyl group O(20B) is rotated inwards to the centre of the channel and shows a (−)-*gauche* conformation.

The crystal structure of the inclusion compound consists of a head-to-head dimer of βCD molecules stacked along the crystallographic *c* axis, thus forming a slightly tilted channel-type structure (Fig. 2 and 3). The two βCD rings of one dimer are related by a two-fold axis perpendicular to the channel axis. The dimers are linked together by hydrogen bonds between the secondary hydroxyl groups, with O···O contacts ranging from 2.711(7) Å for O14···O24′ to 3.221(7) Å for O18···O19′. A full list of all short O···O contacts, including the water molecules, is available as electronic supplementary information (ESI). The guest molecule was found to have one of the atoms from the propionyl residue located on the two-fold axis, at the interdimeric region; this would cause a mutual overlap if both cavities of the dimer were occupied. However, the refinement of the occupancy of all atoms of the guest molecule yielded a value very close to the ideal value of 0.5 and therefore it was restricted to that during the final

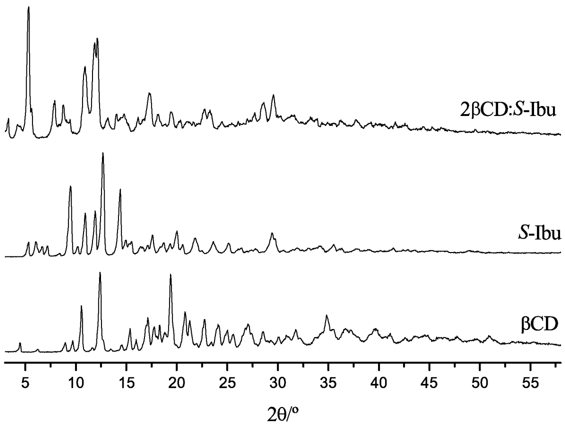


Fig. 1 Powder X-ray diffraction patterns for βCD, *S*-Ibu and 2·βCD:*S*-Ibu.

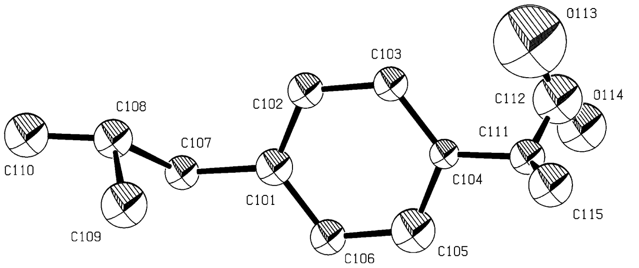


Fig. 2 ORTEP representation of the guest *S*-Ibu in the solid state showing the labelling of the atoms. Hydrogen atoms omitted for clarity.

refinements. Consequently, the inclusion complex is composed of two βCD molecules and one ibuprofen guest molecule, which is disordered over two positions related by a two-fold axis passing through O114. The 2:1 host-to-guest ratio is in agreement with the low difference electron density observed inside the host cavity.

The carboxylic end of the *S*-ibuprofen molecule is facing the smaller rim of the βCD; its position is further stabilised by a hydrogen bond with one of the primary hydroxyl groups of the host [O114···O20B contact distance of 2.76(3) Å]. This mode of inclusion is the opposite of that reported for *S*-ibuprofen encapsulated in permethylated βCD, where the propionic acid group protrudes from the secondary (more open) face instead of the primary (more narrow) face.[9]

Adjacent channels are held together by a widespread system of intermolecular hydrogen bonds between the hydroxyls and/or the water molecules. Twelve and a half water molecules are found in the asymmetric unit of the unit cell. Refinements on the site occupancy yielded no partially occupancies.

FTIR spectra

Since the host-guest interactions are non-covalent, the vibrational spectrum of the inclusion compound should not appreciably differ from the spectrum of the corresponding physical mixture, apart from the C=O stretching group frequency in the ibuprofen molecule, which is expected to be sensitive even to relatively weak interactions provided these change the relative contributions of the non-polarised and polarised resonance structures of the C=O bond (>C=O and >C–O$^-$, respectively). In addition, considering the 2:1 stoichiometry found for the inclusion compound and the relative number of oscillators of each type in the cyclodextrin and ibuprofen molecules, the spectra of both the inclusion compound and the physical mixture should be largely dominated by the vibrational bands of the cyclodextrin molecule. These general expectations were both confirmed by the FTIR spectra of the inclusion compound and of the 2:1 physical mixture.

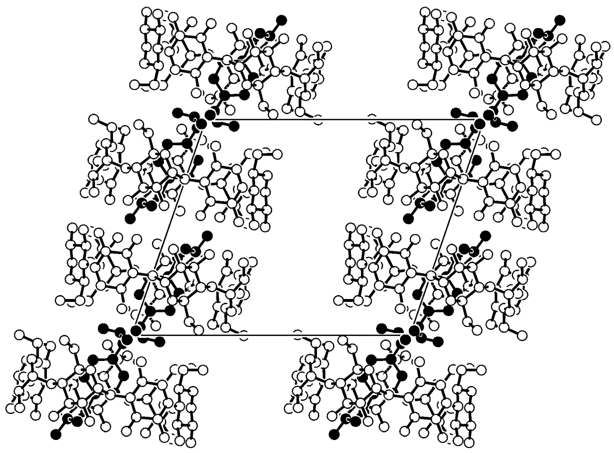
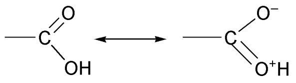


Fig. 3 View of the inclusion compound showing a head-to-head dimer of βCD molecules stacked along the crystallographic *c* axis, thus forming a slightly tilted channel-type structure. Both cavities of the βCD dimer are occupied in a statistical fashion (50% of an ibuprofen molecule in each cavity) as a result of the two-fold symmetry.

As mentioned above, the most relevant spectral feature was observed for the C=O stretching vibration. In the physical mixture, a relatively sharp peak occurs at 1706 cm^{-1} corresponding to the single intense feature at 1707 cm^{-1} in pure ibuprofen. In addition to this feature, the spectrum of *S*-Ibu in acetonitrile solution presents a more intense and well defined peak at 1740 cm^{-1}. Since this band is shifted to higher frequencies by 33–34 cm^{-1} with respect to the corresponding frequencies in pure ibuprofen and the physical mixture, one may infer that the C=O oscillators in the 1740 cm^{-1} band should have an additional contribution of the non-polarised C=O resonance structure. In turn, the FTIR spectrum of the inclusion compound presents a well defined intensity maximum at 1735 cm^{-1} surrounded by two less intense and not so well defined features at 1707 and 1757 cm^{-1}. Being shifted to higher frequencies by 28 and 50 cm^{-1} with respect to the 1707 cm^{-1} band, the features at 1735 and 1757 cm^{-1} point also to the occurrence of less polarised C=O bonds. Since the C=O bond is part of a carboxylic group, its degree of polarisation interacts with the polarisation state of the adjacent C–O bond through the following canonical forms.



B **C**

Unlike the hydroxylic oxygen atom of form **C**, the hydroxylic oxygen atom of form **B** can act as a hydrogen bond acceptor through the use of one of its lone electron pairs. A hydrogen bond interaction of this type has the effect of improving the contribution of form **B**, thus reducing the extent of the polarised form **C** and shifting the νC=O vibrational mode to higher frequencies, as observed. In fact, this interpretation finds support in the single crystal X-ray resolved structure for the inclusion compound of *S*-Ibu in βCD (Fig. 2), in particular, by the position of the carboxylic group in the interstitial space between the primary hydroxylic groups of two adjacent βCD molecules, as well as in its orientation roughly perpendicular to the major axis of the βCD macrocycles. The single crystal analysis also shows that the hydrogen bond donor is the disordered primary hydroxyl group O20B.

Thermogravimetric analysis

Fig. 4 shows the thermogravimetric traces for the inclusion compound and the 2:1 physical mixture, for comparison. Shown also are the thermogravimetric traces for the βCD hydrate and *S*-Ibu, for reference. First of all, the trace of the physical mixture shows well defined steps that can be easily made to correspond to the temperatures at which βCD dehydrates (from ambient temperature up to 74 °C), *S*-Ibu sublimes (a step between approximately 100 °C and 150 °C), and finally βCD melts and subsequently decomposes (starting temperature at approximately 260 °C). Interestingly, the thermogravimetric traces of the inclusion compound and the 2:1 physical mixture almost coincide above 280 °C.

From room temperature to 43 °C, the trace of the inclusion compound presents a mass loss of 5.7% that corresponds to dehydration. From that temperature up to approximately 250 °C, decomposition occurs in a very gradual and smooth way, with an overall 7.5% mass loss, suggesting the gradual dissociation of *S*-Ibu (one *S*-Ibu molecule *per* 2·βCD:*S*-Ibu). At roughly 250 °C, an abrupt mass loss suggests the onset of

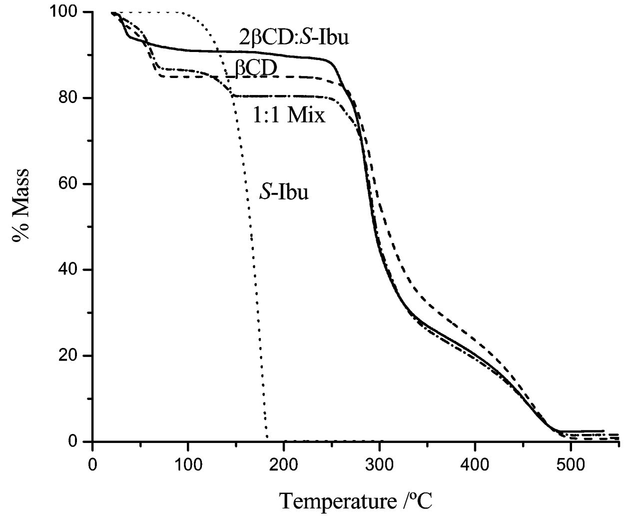


Fig. 4 Thermogravimetric traces of βCD, *S*-Ibu, the 2:1 physical mixture, and 2·βCD:*S*-Ibu.

chemical decomposition of βCD. At *ca.* 510 °C, total mass loss is accomplished.

The slow release of guest molecules from the inclusion complex suggests the formation of an well-organised lattice that retains the guest molecules, consistent with the channel-like structure determined in the single crystal X-ray diffraction analysis (Fig. 3).

^{13}C CP MAS NMR

The solid state ^{13}C CP MAS NMR spectrum for the inclusion compound is shown in Fig. 5. Also shown for comparison are the spectra of βCD and pure *S*-Ibu. The multiple resonances exhibited by each type of βCD carbon atom (C_1, 101–104 ppm; C_4, 78–84 ppm; $C_{2,3,5}$, 71–76 ppm; C_6, 57–65 ppm) have been previously correlated with distinct values of the dihedral angles about the glycosidic α(1 → 4) bond for carbons 1 and 4, and with the dihedral angles describing the position of the hydroxyl groups.[13]

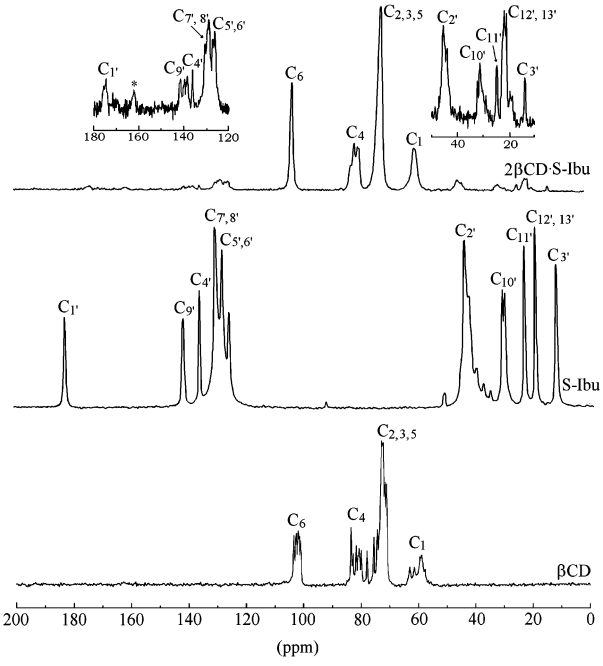


Fig. 5 ^{13}C CP MAS NMR spectra for βCD, *S*-Ibu, and 2·βCD:*S*-Ibu.

The spectrum of *S*-Ibu (see **A** for carbon labelling) shows one peak for the acid carbon atom at 182 ppm, five peaks assigned to the aromatic carbon atoms (126–142 ppm), $C_{10'}$ at 45 ppm, a singlet for $C_{11'}$ at 44 ppm, a doublet for $C_{2'}$ (31.5 and 32.4 ppm), and three more peaks that are assigned to the methyl groups, $C_{3'}$ at 14 ppm, and $C_{12'}$ and $C_{13'}$ at 21 ppm and 25 ppm, respectively.

In contrast with βCD, the spectrum for the inclusion compound presents single featureless peaks for C_1, $C_{2,3,5}$ and C_6 at 104, 73 and 61 ppm, respectively, and a peak with some structure at 80–82 ppm that corresponds to C_4. Considering the C_4 carbons, the decrease in the chemical shift range from 78–84 to 80–82 ppm indicates that the C_4 carbons are becoming more equivalent, presumably due to a partial relief of the strained linkage conformations.[13] In other words, βCD adopts a more symmetrical conformation in the inclusion compound, with each glucose unit in a similar environment, as a result of guest encapsulation. The spectrum of the inclusion compound also exhibits several resonances that can be assigned to the carbon atoms of the guest. In particular, the carbonyl carbon atom is represented by a peak at 175 ppm, shifted upfield compared to that of free *S*-Ibu, in consonance with the FTIR results. The aromatic carbon atoms are represented by multiplets with peaks at 126, 127, 129, 130, 136, 138, 139 and 141 ppm, and the remaining carbon atoms, $C_{10'}$, $C_{11'}$, $C_{2'}$, $C_{12',13'}$ and $C_{3'}$, give rise to a peak at 45 ppm, a small peak at 44 ppm, a triplet (29, 31 and 32 ppm), two singlets at 25 and 22 ppm, and a peak at 14 ppm, respectively.

Conclusions

A channel-type inclusion compound has successfully been prepared between βCD and *S*-ibuprofen. The two βCD rings of one dimer are linked together by hydrogen bonds between the secondary hydroxyl groups and are related by a two-fold axis perpendicular to the channel axis. One *S*-Ibu molecule is encapsulated within one of the cavities of each βCD dimer. The guest molecule was found to have one of its atoms located on the two-fold axis, which would cause a mutual overlap if both cavities of the dimer were occupied. The C=O stretching vibration (*v*C=O) is found to be particularly sensitive to the nearby environment of the C=O bond, and the observed shifts to higher frequencies (28 and 50 cm^{-1} with respect to the 1707 cm^{-1} band of *S*-Ibu in the physical mixture) are in accord with the X-ray diffraction results, in particular, with the location and orientation of the carboxylic group and with the possible orientations found for the disordered primary hydroxyl group O(20). In the thermogravimetric trace of the inclusion compound, the slow release of guest molecules over a temperature range of more than 200 °C, in comparison with the trace of the 2:1 physical mixture, suggests the formation of an well-organised lattice that retains the guest molecules, in consonance with the channel-like structure determined by single crystal X-ray diffraction analysis. In contrast with βCD, the ^{13}C CP MAS NMR spectrum reveals a more symmetrical conformation for the βCD macrocycles in the inclusion compound, with each glucose unit in a similar environment. In addition, the multiplicity of the signals presented by included *S*-Ibu is consistent with restricted guest rotation inside the cyclodextrin cavity and suggests tight encapsulation.

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