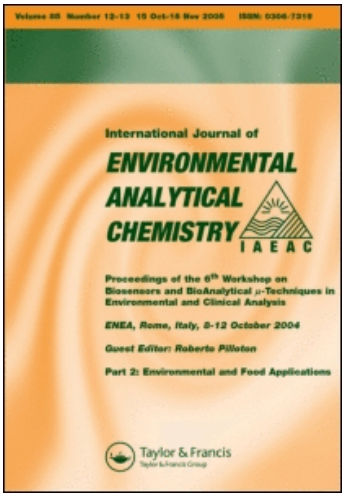

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INCLUSION OF ORGANIC POLLUTANTS IN CYCLODEXTRINS AND DERIVATIVES

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Both (-)-geosmin and (+)-2-methyl-isoborneol are the main compounds responsible for the unpleasand smells found in the vicinity of water-processing plant. Attempts to eliminate them using oxidation, filtration and/or biologic degradation processes are only partly efficient. The use of cage molecules could provide an alternative solution. In this respect, cyclodextrins and derivatives have demonstrated their role as candidates as hosts for these highly hydrophobic compounds. In this paper, we evidence the complexation of above mentionned pollutants by cyclodextrins using high-resolution proton Nuclear Magnetic Resonance spectroscopy. The latter method is also used to afford a three-dimensional structure of inclusion complexes in solution and to show that cyclodextrins can as well discriminate between the optical isomers of synthetic geosmin and methyl-isoborneol. Finally, a solution to the problem of waste waters is proposed.

Keywords: Cyclodextrins; ^{1}H NMR; (±)-geosmin; (±)-2-methyl isoborneol; molecular inclusion; water pollution

INTRODUCTION

In the vicinity of water-processing plant, several compounds have long been identified as the stench substances responsible for the degradation of the organoleptic quality of drinking water.

Two natural pollutants produced by bio-conversion of organic matter, (-)-geosmin **I** and (+)-2-methyl isoborneol **II** (Figure 1), appear as the main compounds producing musty and earthy smells[1]. For over ten years, attempts to eliminate them using oxidation[2], filtration[3] and/or biologic degradation[4,5] processes failed. Therefore, it appears that the use of cage molecules as molecular traps

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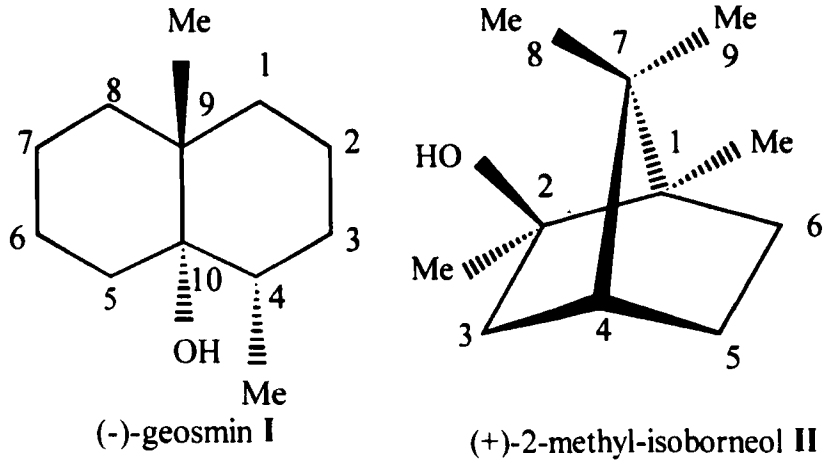

FIGURE 1 Structures of compounds I and II

could provide alternative solutions. In this respect, cyclodextrins (CDs) and derivatives could be used as scavengers owing to proper adequation in terms of molecular sizes between host and guest.

CDs[6] (Figure 2) are cyclic oligosaccharides composed of 6, 7 or 8 α(1–4) linked glucopyranose units (αCD, βCD or γCD, respectively) and have the overall molecular shape of a truncated cone. The available internal cavity increases in size with the number of glucose units. Each glucopyranoside unit (Figure 2 c) adopts a $^4C_1$ chair conformation implying that all primary hydroxyl groups are located on the narrower side of the ring while all secondary hydroxyl groups are on the wider side. Protons H-3 and H-5 (Figure 2 b) are located in the cavity whereas protons H-1 and H-4 point outwards. Because of this geometry, the interior of the cavity retains a relatively hydrophobic character while the exterior of the cavity remains hydrophilic. One of the most specific property of these hosts is their ability to form inclusion complexes with a large number of guests. These complexes are stabilized by weak non-covalent interactions. Therefore, the requirement[7] for the inclusion complex formation to occur is a correct fitting of at least a part of the guest molecule into the CD's cavity.

βCD being available in large quantities at low cost appeared as the most convenient molecule for the inclusion of **I** and **II**. Nevertheless, when considering βCD, the main feature to be improved is the solubility in water the purpose being to obtain highly soluble complexes. The use of highly water-soluble chemically modified βCD derivatives is suitable because it is expected that the improvement will be reflected in a much higher solubilty of inclusion complexes.

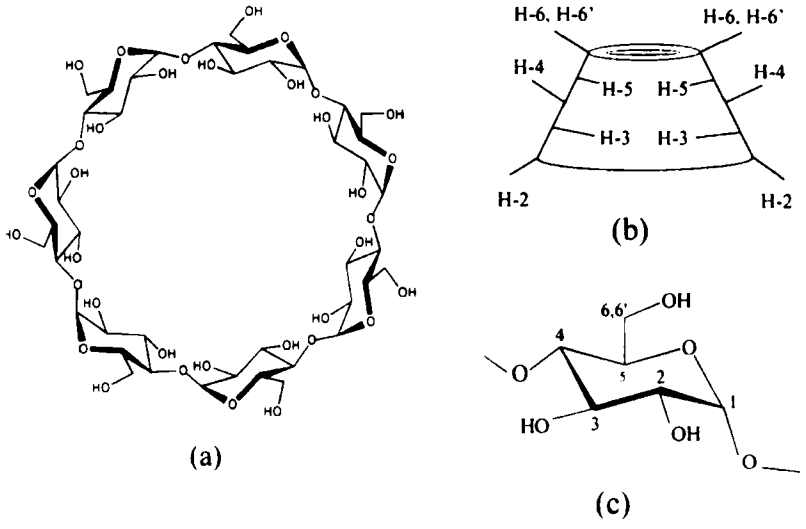

FIGURE 2 Structure (a) and lateral view (b) of βCD and of glucosidic unit (c)

We report here on the experimental conditions of the inclusion of **I** and **II** in βCD and highly water-soluble derivatives and on the solubility of the corresponding complexes. The inclusion process and the chiral discrimination are evidenced and supported by Nuclear Magnetic Resonance (NMR) data. Further detailed NMR investigation is performed in order to propose a molecular model for the complexes in solution and to evidence the chiral discrimination properties of CDs towards **I** and **II**. Finally, a solution to the problem of the waste water is suggested.

EXPERIMENTAL

NMR Experiments

All one (1D) and two-dimensional (2D) experiments were recorded on a Bruker DRX500 spectrometer operating at 500.13 MHz for proton with a 5 mm probe. 1D NMR spectra are collected using 16K data points. All 2D experiments are acquired using 2K data points and 256 time increments using the phase sensitive mode (TPPI) and processing resulted in 1K × 1K (real-real) matrix. Chemical shifts are given in p.p.m. downfield from external tetramethylsilane as reference

and the temperature was carefully controlled within 0.1 °C by means of Haake exchange device.

Materials

βCD (Roquette, Lestrem, France) and 2,6 dimethyl-βCD (DIMEB) (synthetized in the laboratory) are lyophilized twice in D_2O. For the preparation of a 5mM solution of **I** or **II**, the required amounts of **I** or **II** are taken from a 100 mM stock solution in acetone.

RESULTS AND DISCUSSION

Inclusion of I and II in βCD and derivatives

The first step to support the use of the CDs and derivatives in scavenging the title pollutants requires to prove that the complexation of **I** and **II** by CDs occurs and, if this is the case, that the corresponding complexes are soluble. Therefore, preliminary assays have been carried out in order to determine the solubility of **I** in the presence of βCD. An equimolar mixture of **I** and βCD leads to a weakly soluble complex. In that case, the solubility of **I** in water remains lower than 1 mM at 25°C in presence of a 5 mM aqueous solution of βCD. In order to enhance the solubility of this complex, DIMEB (Figure 3)[8,9,10] was also considered and found to provide optimal performances. Indeed DIMEB which displays a much higher intrinsic solubility in water (353 mM at 25°C) than the parent βCD (15 mM at 25°C) induces a highly improved solubilization power for **I** which can reach 5 mM in the presence of an equimolar quantity of DIMEB.

Similar performances were obtained with **II** for which the solubility is 5 mM in 5 mM DIMEB at 25°C.

If only the solubilization power is considered, DIMEB appears as a better candidate than βCD although to a lesser extent than expected from its intrinsic solubility. The use of high water-soluble modified βCD resulting in an increase in the solubilization power for sparingly soluble guests as such **I** and **II**, DIMEB will be only considered in the following sections.

Although the solubilization is a first clue for the formation of an inclusion complex, it is not a sufficient criterion. In this case, NMR spectroscopy can evidence this inclusion process using modifications of chemical shifts of host (and guest) with special attention to those located in the cavity of the cyclodextrin, i.e.

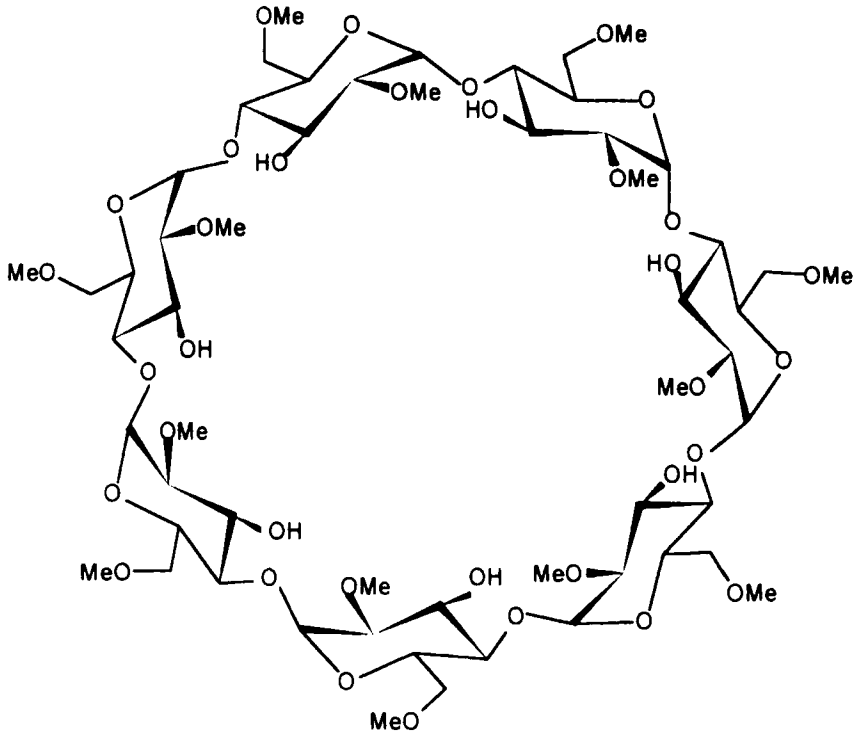

FIGURE 3 Structure of 2,6 dimethyl-βCD (DIMEB)

H-3 and H-5, these being the most prone to experience shifts upon the formation of an inclusion complex.

Figure 4 displays the ^{1}H NMR spectra of DIMEB in the absence and in the presence of (-)-geosmin. Spectrum (b) clearly shows that H-5 and H-6 experiences the largest shifts upon addition of **I** and confirms the formation of an inclusion complex. A similar effect is also observed for **II** encouraging more detailed NMR investigations to derive the geometry of the inclusion complexes.

Geometries of inclusion complexes of I and II in DIMEB

More detailed indications concerning the geometry of inclusion complexes of **I** and **II** with DIMEB can be derived from the evidence of spatial proximities between protons of the host and the guest. This can be achieved using 2D ROESY experiments. In this method as described elsewhere[11], spatial proximities (dipolar interactions) between the protons of the guest and the host mole-

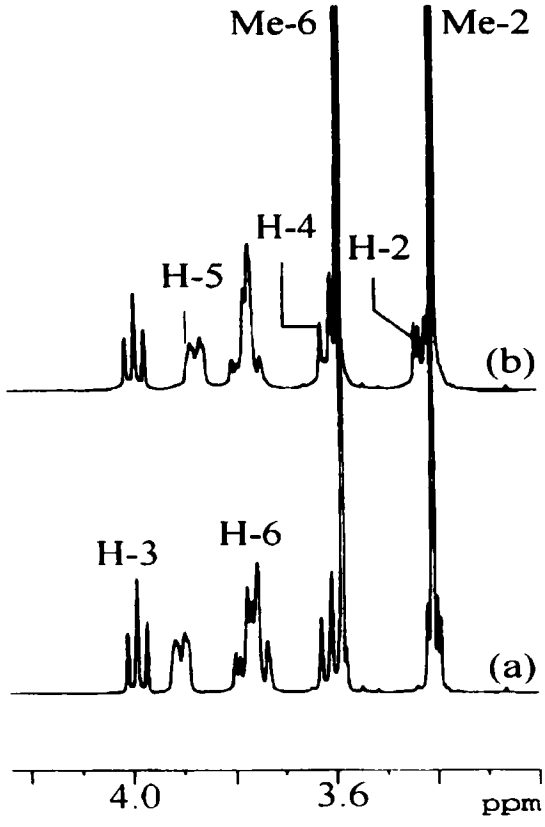

FIGURE 4 Partial ^{1}H NMR spectra (298 K, 500 MHz) of DIMEB (5 mM) in D_2O in the absence (a) and in the presence (b) of **I** (5 mM)

cules can be deduced from cross-peaks observed in ROESY experiment. The cross-peak corresponds to an internuclear distance of ≤ 5 Å between relevant protons.

Figure 5 displays a partial contour plot of a ROESY experiment performed on an equimolar mixture of DIMEB and (-)-geosmin. The spots (Figures 5 d, e, f and g) represent the cross-peaks or spatial proximities between the protons of (-)-geosmin and DIMEB. For clarity, the ^{1}H NMR spectra of (-)-geosmin and DIMEB of which the complete assignment has been described[8] are displayed in both dimensions.

Concerning the ^{1}H NMR spectrum of (-)-geosmin showed on the left hand side of figure 5, the signals of Me-4 and Me-9 are clearly identified. The Me-4 of geosmin shows a spatial proximity (Figure 5 d) with the proton H-3 of the

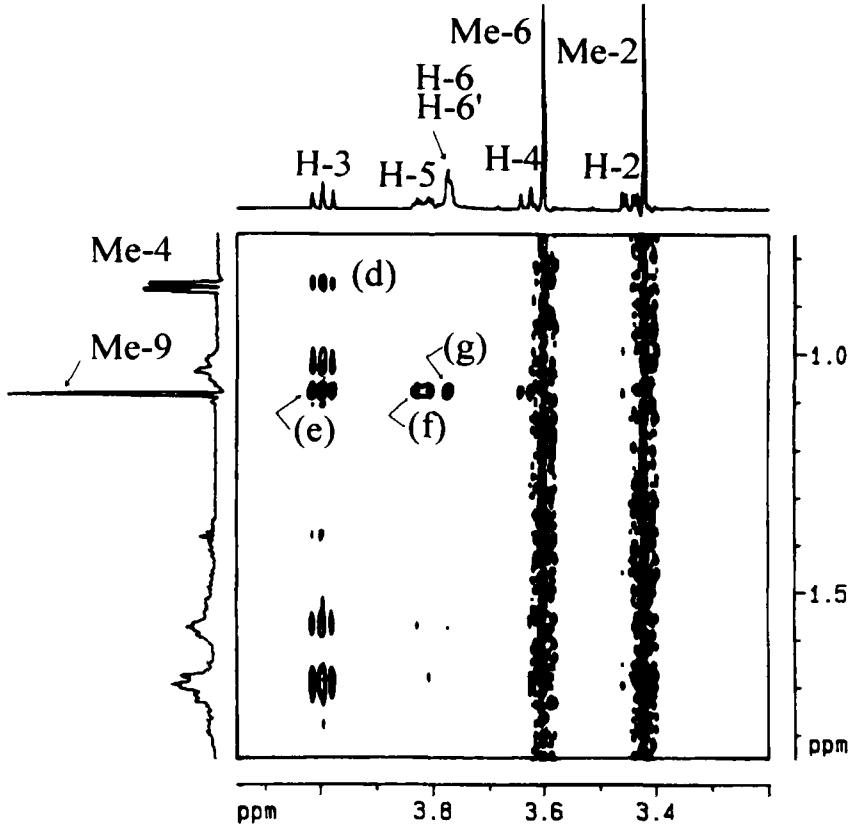

FIGURE 5 Partial contour plot of a ROESY experiment (Spin lock time 300ms; 256 scans per time-increment) performed at 500 MHz on a mixture of DIMEB (5 mM) and of (-)-geosmin (5 mM) in D_2O at 298 K

DIMEB only while the Me-9 presents dipolar effect with the protons H-3, H-5 and H-6 (Figures 5 e, f and g, respectively) of the host molecule. This suggests the Me-9 to be located at the vicinity of the the narrow side of DIMEB while Me-4 is closer to located at the vicinity of the the narrow side of DIMEB while Me-4 is closer to wide side of the host molecule. A schematic model consistent with the NMR data can therefore be proposed and is displayed on Figure 6.

Likewise, cross-peaks are observed from a similar ROESY experiment performed under identical conditions as described on Figure 5 on an equimolecular mixture (5 mM) of (+)-2-methyl-isoborneol and DIMEB. Spatial proximity observed between the Me-1 of guest molecule and H-3 of DIMEB indicates that this methyl is located near the wider side of the host molecule. Me-8 and Me-9 of

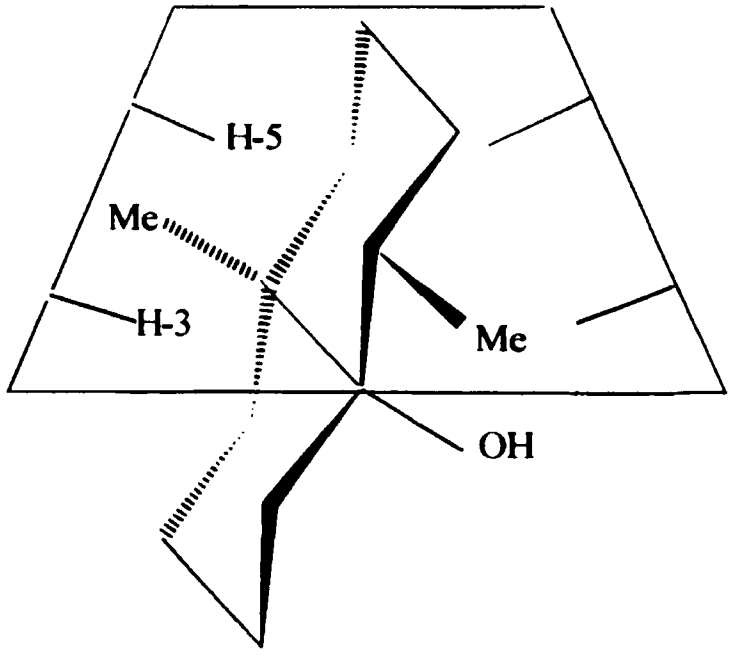

FIGURE 6 Proposed structure of the inclusion complex in solution of (-)-geosmin in DIMEB as deduced from ROESY data

(+)-2-methyl isoborneol are located near the primary side of the host molecule according to their spatial interactions with H-3, H-5 and H-6 of DIMEB. One weak interaction between Me-2 of guest molecule and H-3 of DIMEB is observed suggesting that Me-2 located near the wider side of the host molecule is probably less deeply inserted in the cavity than Me-1.

Chiral discrimination properties

The previous results showed that interactions between host and guest molecules depend on the geometry of both partners. In case of racemic mixture, interactions of each optical isomer with host molecule can be different enough to allow discrimination.

It is well documented[12] that CDs are chiral molecules and play a key role in chiral discrimination. Interactions with a racemic guest molecule can lead to the formation of pseudo-diastereoisomeric complexes of which the evidence can be also investigated using ^{1}H NMR spectra[13]. We demonstrate here that the forma-

tion of complexes with synthetic racemic (±)-**I**[14] and (±)-**II** can be highly informative in this respect. Indeed the ^{1}H NMR spectra of (±)-**I** and (±)-**II** show separate signals for each enantiomer in presence of CDs. For example, the partial NMR spectrum of (±)-**I** in presence of DIMEB (Figure 7) displays distinct resonances for Me-4 and Me-9 of geosmin. The chiral Me-9 and Me-4 which give rise to a singlet and a doublet, respectively, in the pure compound are duplicated in the racemic mixture*. Both methyls of (+)-**I** appear at lower field those of (-)-**I**. This separation suggests that each optical isomer occupies a different position in DIMEB.

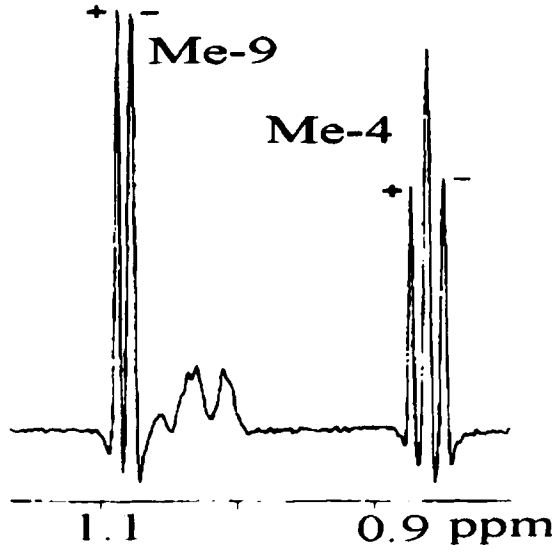

FIGURE 7 Partiel ^{1}H NMR spectrum of a mixture of (±)-**I** (6 mM) and DIMEB (5 mM) (D_2O, 298 K, 500 MHz)

These observations show that CDs exhibit efficient recognition properties towards (±)-**I** and (±)-**II** and can therefore be used as convenient chiral shifts reagents for the determination of the optical purity **I** and **II**

Prospectives for the use of CDs for the removal of the title pollutants in water

A possible solution to remove **I** and **II** from water pollution could involve the grafting of CDs on an insoluble support as described in column chromatogra-

* The Me-4 signals of (±)-**I** appear as a triplet due to overlapping of two doublets araising from each optical isomer.

phy[15]. Such a process would allow the CD to interact with **I** and **II**. In that case, the water filtered through the CD chemically bonded on a solid phase would be cleared from **I** and **II**. After saturation, the column could be regenerated with methanol.

CONCLUSION

The above NMR data has allowed not only to evidence the inclusion of **I** and **II** in CDs but also to determine the likely position of **I** and **II** in these host molecules. A further detailed ^{1}H NMR study has evidenced the selectivity of CDs towards the chiral guests **I** and **II** and showed that these host molecules could behave as resolving agents for enantiomers (±)-**I** and (±)-**II**.

These results show that CDs appear as the most versatile class of cage molecules to scavenge **I** and **II**. The inclusion process provides a single non destructive method for the removal of **I** and **II**. In this respect, the grafting of CDs on a solid phase could solve the problem of the treament of drinking water (16).

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