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Structural investigations of pyridin-4-yl indolizine modified β-cyclodextrin derivatives as fluorescent chemosensors for organic guest molecules

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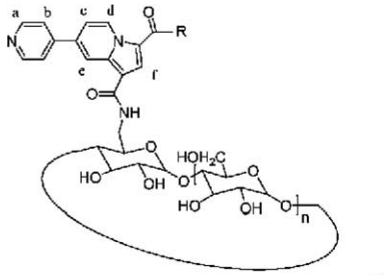
Abstract—In order to investigate the substituent effects on their conformations and spectroscopic properties, a series of pyridin-4-ylindolizine modified β-cyclodextrin derivatives were studied by 2D NMR (ROESY spectra) in D_2O, circular dichroïsm, and fluorescence spectroscopy. It was found that the linked indolizin-β-cyclodextrin compounds exhibited two types of conformations, as a function of the substituent, in which fluorescent moieties formed either an intramolecular complex or were not included in the hydrophobic cavity of the macrocycle. Under addition of organic guest species in a phosphate buffer at neutral pH, the variation of emission fluorescence intensity showed that these compounds are of significance for detection of volatile organic molecules and adamantane derivatives and might be used as molecular chemosensor.

Keywords: Cyclodextrin; Indolizine; NMR; CD; Fluorescence; Chemosensor

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides, involving six or more D-glucopyranose units, which form truncated cone-shaped molecules with a hydrophobic cavity. They form inclusion complexes with a variety of organic compounds in aqueous solution and are largely studied for their host–guest interaction properties, and as building blocks for supramolecular structures.[1] Cyclodextrins being essentially inert to photochemical excitation, their chemical modification with chromophoric entities can allow to associate spectroscopic properties to the inclusion of guest molecules.[2–12] Thus, modified CDs bearing fluorophores such as dansyl[3] and *p*-(dimethylamino)-benzoyl (DMAB) moieties[4] are examples of sensoring systems with which spectroscopically inert organic molecules could be detected by variations in their emissions spectra in aqueous solution.



R = OC_2H_5 **1a**
Ph **1b**
4-CH_3-C_6H_4 **1c**
4-MeO-C_6H_4 **1d**
4-Cl-C_6H_4 **1e**

Chart 1. Structure of pyridin-4-ylindolizine modified β-cyclodextrin derivatives **1a**–**e**.

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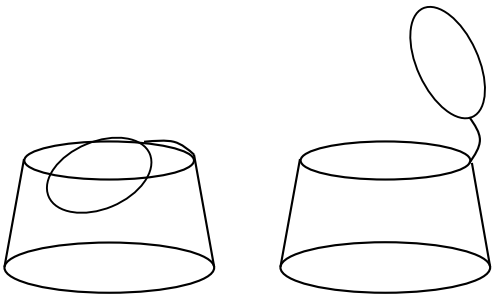

Figure 1. Possible conformations of β-CD derivatives **1a**–**e**.

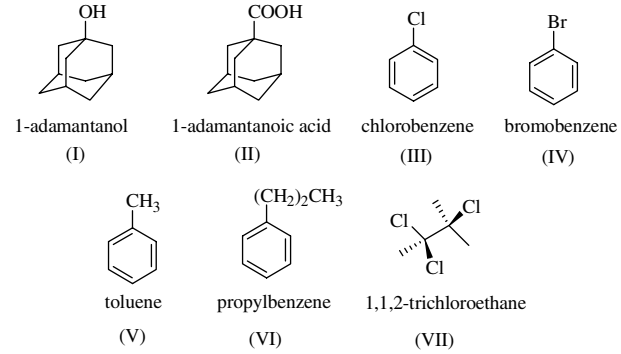

Chart 2. Structure of guest molecules.

In previous papers,[13] we reported the synthesis of a series of a 6^{I}-(*N*-deoxy-β-cyclodextrin-6^{I}-yl)-1-amido-3-substituted-7-pyridin-4-yl indolizine derivatives **1a**–**e** (Chart 1) using two different approaches based on 1,3-dipolar cycloadditions.

Examination of fluorescence properties of compounds **1a**–**e** shows that **1a** has a fluorescence quantum yield (φ_f) much higher than **1b**–**e**, $\varphi_f = 0.51$ and $\varphi_f \sim 0.01$, respectively.[13a] This difference cannot solely be explained by the effect of the ethoxy substituent compared to the *p*-substituted benzoyl group. These results suggest two kinds of observable conformations: (i) on one hand the pyridin-4-yl indolizine moiety of **1a** is self-included in the hydrophobic cyclodextrin cavity,[†] which could explain the good fluorescence quantum yield[14] and (ii) on the other hand the pyridin-4-yl indolizine moiety of **1b**–**e** is released from the macrocycle in the bulk water environment (Fig. 1). In this context, we planned to elucidate the orientation of the pendant groups in order to explain the difference in their spectroscopic properties by using NMR spectroscopy experiments, circular dichroism (CD) and fluorescence spectroscopy. Subsequently, the ability of the 6^{I}-(*N*-deoxy-β-cyclodextrin-6^{I}-yl)-1-amido-3-substituted-7-pyridin-4-yl indolizine derivatives **1a**–**e** to act as host–guest sensoring systems has been evaluated by fluorescence spectroscopy. In this study, we focused our interest on five volatile organic compounds (III–VII, Chart 2) whose detection is of importance for environmental applications.

2. Results and discussion

2.1. Circular dichroïsm spectra

Figures 2 and 3 show CD spectra of **1a** and **1b**, alone or in the presence of 1-adamantanol in 0.1 M pH = 7 phosphate buffer. The results show two types of evolution of the CD signal according to the concentration in

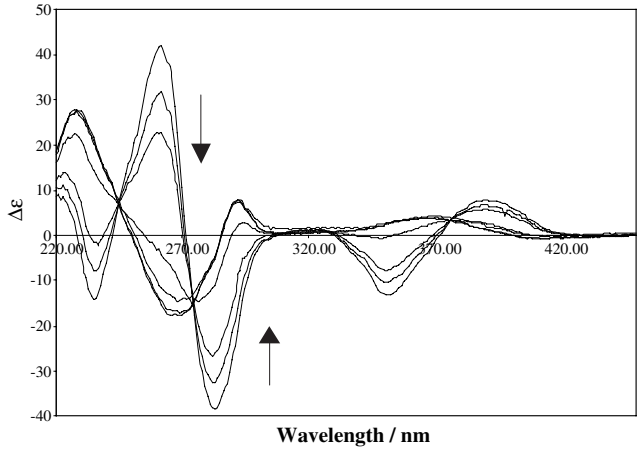

Figure 2. CD spectra of **1a** (5×10^{-5} mol dm^{-3}) upon addition of 1-adamantanol (1: 0, 2: 5.5×10^{-5}, 3: 1.0×10^{-4}, 4: 3.5×10^{-4}, 5: 8.5×10^{-4}, 6: 1.3×10^{-3}, 7: 3.8×10^{-3} mol dm^{-3}) in aqueous phosphate buffer solution of pH 7.0.

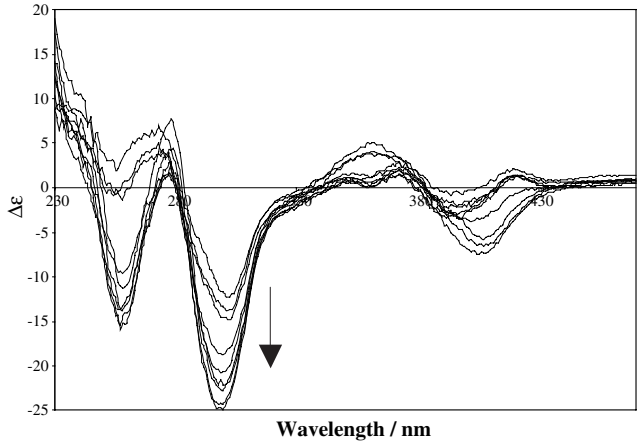

Figure 3. CD spectra of **1b** (10^{-4} mol dm^{-3}) upon addition of 1-adamantanol (1: 0, 2: 1.0×10^{-5}, 3: 2.0×10^{-5}, 4: 8.0×10^{-5}, 5: 1.8×10^{-4}, 6: 3.8×10^{-4}, 7: 7.8×10^{-4}, 8: 1.4×10^{-3}, 9: 2.4×10^{-3} mol dm^{-3}) in aqueous phosphate buffer solution of pH 7.0.

[†] The fluorescence quantum yield experiments of **1a**–**e** were carried out in dilute solution (10^{-7}–10^{-5} mol^{-1} dm^{3}), which precludes the assumption of intermolecular complexes between the pyridinoindolizinic moiety and the cavity of β-cyclodextrin.

1-adamantanol as guest molecule. In the case of **1a**, the CD spectrum shows two positive bands at 263 and 392 nm and three negative bands around 236, 284 and 352 nm. Concerning the fluorescent host **1b**, the CD pattern is basically similar to **1c**–**e** and shows three weak positive bands around 350, 374 and 424 nm and three negative bands around 260, 301 and 397 nm.

Initially, the addition of 1-adamantanol decreased the intensity of the absorption bands of **1a** (Fig. 2), then an inversion of the CD signals was observed when the concentration of the guest molecule was greater than that of the host. In the case of **1b**–**e** (Fig. 3), the presence of guests did not reverse the dichroic signal, as a function of guest molecules, but increased the intensity of the absorption bands. These results indicate that **1a** and **1b**–**e** have different conformations, which are reflected on the CD spectra in the presence of hosts alone and during the addition of 1-adamantanol.

The Kirkwood–Tinoco equation[15] established for the study of cyclodextrin complexes predicts a positive signal for a parallel transition along the axis of cyclodextrin and a negative signal for a perpendicular transition to this axis. Moreover, Kodaka[16] showed that the sign of the CD band depends on the position of the chromophore with respect to the non-polar cavity of the macrocycle and proposed that the CD signal could be inversed when the position of a chromophoric guest is changed from inside the cavity to the outside.

Thus, the results suggest that the polarity around the fluorescent moiety of **1a** could be changed during the addition of guests when moving from the interior of the cyclodextrin cavity towards the outside bulk water environment while a guest is included in the cavity. The CD spectral patterns of **1b**–**e** are almost similar to the spectra without guests, except for an increase in intensity, which indicates no change in the environment around the fluorophore and suggests that the fluorescent entity is outside the cavity of the macrocycle.

2.2. NMR spectroscopy

In order to clarify the conformation of **1a**–**e**, we carried out 1D and 2D NMR experiments in deuterium oxide. At 298 K, the ^{1}H NMR data show that the pyridinoindolizinic modified β-cyclodextrin **1a** presents a strong spectral dispersion of the cyclodextrin signals (Fig. 4a) compared to **1b**–**e**. The largest dispersion of the ^{1}H NMR oligosaccharide region of **1a** compared to **1b**–**e** is in good agreement with the formation of an intramolecular self-inclusion complex.[17] This suggestion is coherent with the relatively high fluorescence quantum yield ($\varphi_f = 0.51$) compared to compounds **1b**–**e** ($\varphi_f \approx 0.01$) and CD experiments.

To observe any conformational changes of **1a**, which might be induced by temperature changes, we have measured the ^{1}H NMR spectra at various temperatures

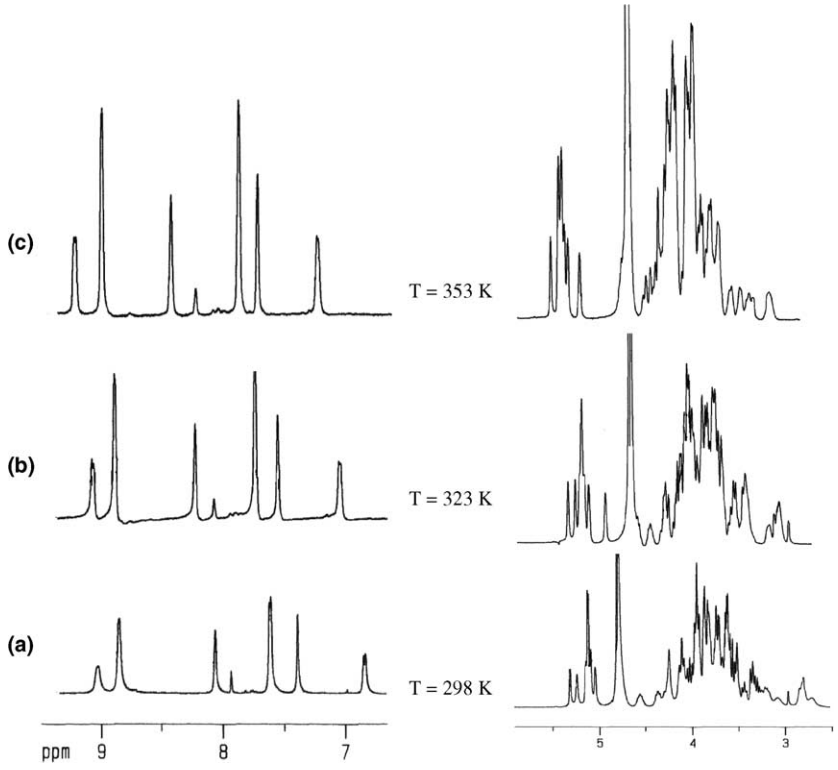

Figure 4. ^{1}H NMR spectra of **1a** (4 mmol dm^{-3}) in D_2O at various temperatures (a: 298 K; b: 323 K; c: 353 K).

(298, 323 and 353 K). When the temperature increased, the aromatic and macrocyclic protons showed reversible spectral shifts accompanied by a spectral simplification of the cyclodextrin region (Fig. 4b and c). These results indicate that the equilibrium of conformational isomers is displaced, which is in agreement with an inside–outside cavity conformational isomerism, that is, that the pyridinoindolizinic moiety could be embedded at ambient temperature in the hydrophobic cavity and excluded at higher temperatures.

To confirm the position of the pyridinoindolizinic substituent relative to the cavity of the macrocycle, ^{1}H ROESY NMR measurements were performed on **1a**–**e**. At 298 K, only ROESY experiments for **1a** showed spatial interactions between the aromatic protons and the interior of the cyclodextrin core (Fig. 5).

Although a complete ^{1}H NMR assignment of the cyclodextrin hydrogen atoms between δ 3.0 and 4.0 ppm is difficult due to insufficient resolution, the cross-peak correlations indicate that the pyridinoindolizinic moiety of **1a** is enclosed within the β-cyclodextrin cavity from the primary hydroxyls side. Indeed, the partial contour plot of **1a** shows dipolar interactions between the protons of the fluorescent moiety and the protons H-3 and H-5 of the cyclodextrin, which are localized inside the macrocycle (Fig. 5). The strong differences observed between the correlations of protons H-c and H-e with protons H-3 and H-5 of cyclodextrin suggest that the pyridinoindolizinic part takes a non-axial position and that it is not deeply included inside the cavity.

While at a temperature of 323 K the ROESY spectrum of **1a** did not show any cross-peak changes, the partial ROESY spectrum at 353 K showed a strong attenuation of the dipolar correlations between the macrocyclic part and the aromatic moiety (Fig. 6). These results are in agreement with CD results and show that the exclusion of the aromatic part of the cavity is difficult and that the fluorophore remains near the primary face of macrocycle.

These results were confirmed by a ROESY spectrum of the **1a**/1-adamantanol complex in which we can observe the inclusion of the guest in the cyclodextrin cavity (Fig. 7a) and the presence of the fluorophore moiety in the vicinity of the adamantanol (Fig. 7b).

All NMR data suggest that two types of conformations are involved for **1a**–**e**, which is coherent with the CD experiments and their respective fluorescence

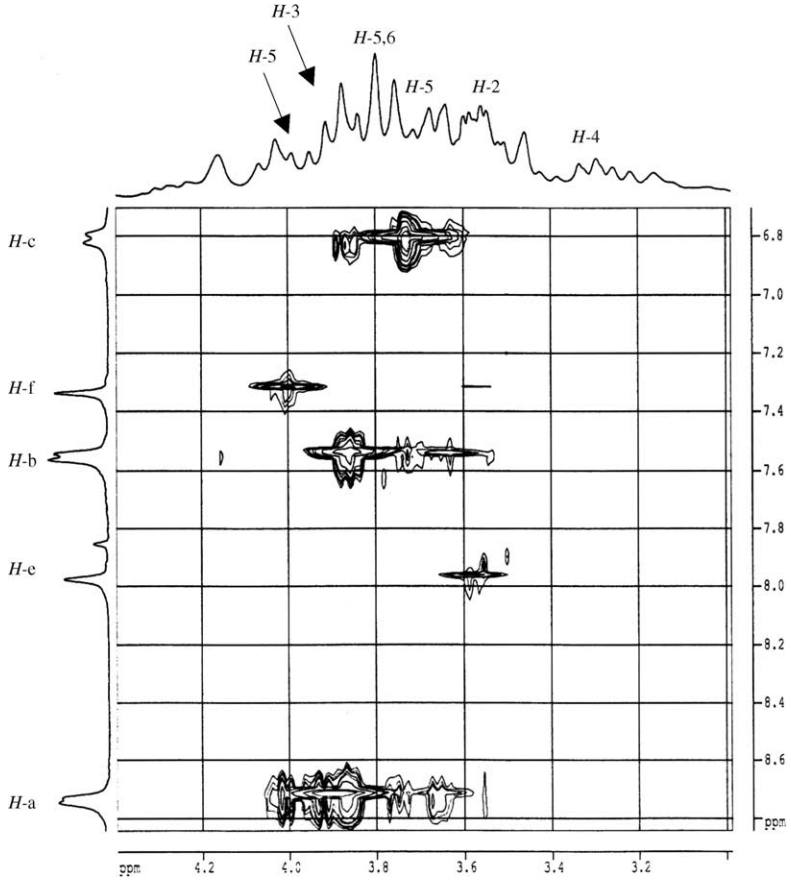

Figure 5. Partial contour plot of the ROESY experiment of **1a** (spin-lock time: 300 ms; [**1a**] = 4 mmol dm^{-3}) in D_2O at 298 K. Horizontal scale: cyclodextrin region; vertical scale: aromatic region.

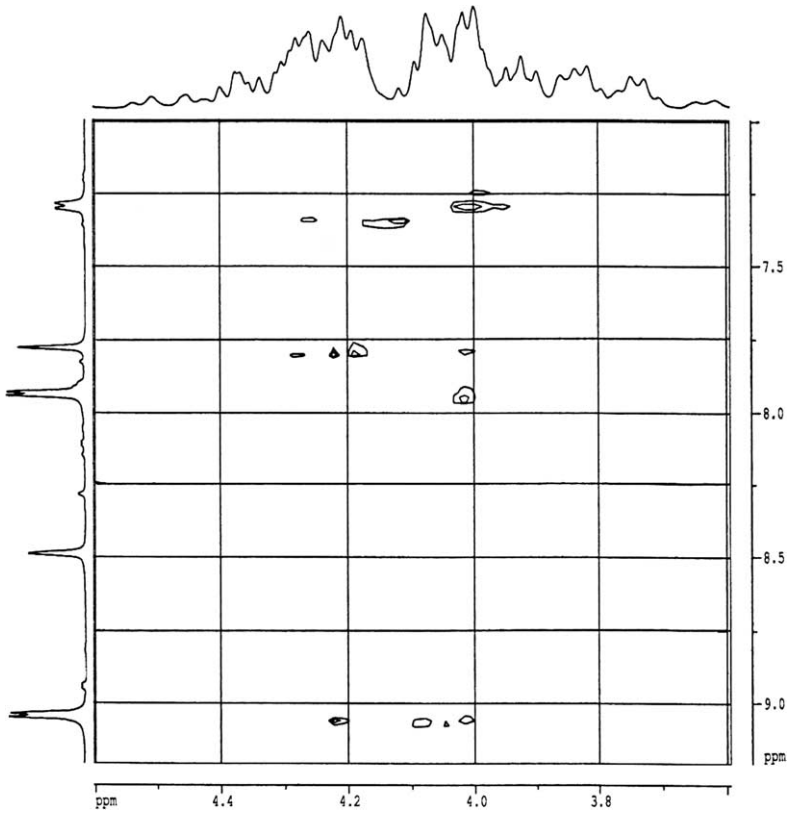

Figure 6. Partial contour plot of the ROESY experiment of **1a** (spin-lock time: 300 ms; [**1a**] = 4 mmol dm^{-3}) in D_2O at 353 K. Horizontal scale: cyclodextrin region; vertical scale: aromatic region.

quantum yields. This highlights the prevailing role of the substituents on the geometry adopted by these molecular sensors.

2.3. Fluorescence spectroscopy

To validate the sensitivity of compounds **1a**–**e**, we carried out a study of guest-induced variation of fluorescence intensity by complexation with a series of organic compounds (Chart 2). We chosed as guests two adamantane derivatives (I–II), which are known for having strong binding constants with β-cyclodextrin and are usually used in complexation studies, and five volatile organic compounds (III–VII). Figures 8 and 9 show the fluorescence spectra, respectively, of **1a** and **1b** in a phosphate buffer solution at pH = 7 in the presence or absence of 1-adamantanol.

The fluorescence spectrum of **1a** (Fig. 8), alone, exhibits a fluorescence peak at 446 nm (λ_{exc} = 269 nm), and shows an increase in intensity upon addition of adamantane derivatives. This guest-induced variation of fluorescence intensity indicates that the appended moiety is not clearly excluded from the cavity during inclusion phenomenon but is closed to the aromatic part forming a host–guest complexation.[8,9,18] This is coherent with NMR experiments and confirms that the fluorescent moiety of **1a** has a reduced mobility and tends to remain in the vicinity of the macrocyclic cavity. In the case of **1a**/III–VI complexation, the experiments do not show significant variation of fluorescence. These results are in agreement with low values of binding constants of these compounds with β-cyclodextrin.[19]

On the other hand, the addition of guest compounds I–VII to an aqueous solution of the fluorescent derivatives **1b**–**e** shows a decrease, in all cases, of the fluorescence intensity (see Fig. 9 as an example) associated with a displacement of the peak towards larger wavelengths in the following order **1d** > **1c** > **1e** > **1b**. These results may be explained by dipolar variations induced by the addition of guests in solution causing changes in location of the fluorescent moiety in bulk water environment. It can be noted that contrary to the derivative **1a**, a guest-induced variation of fluorescence intensity was found for all the selected guests even when these have weak binding constants for the β-cyclodextrin as volatile organic compounds (III–VI).

The value of $\Delta I/I_0$ of compounds **1a**–**e** (Table 1) was used as the classical measure of the sensing ability,[5] where $\Delta I = I_0 - I$ and I and I_0 are the emission intensities in the presence and absence of a guest, respectively. The factor $(\Delta I/I_0)_{max}$ corresponds to the maximum theoretical variation of fluorescence in the presence of an infinite quantity of guest and allows to indicate the maximum response, which could be provided by the

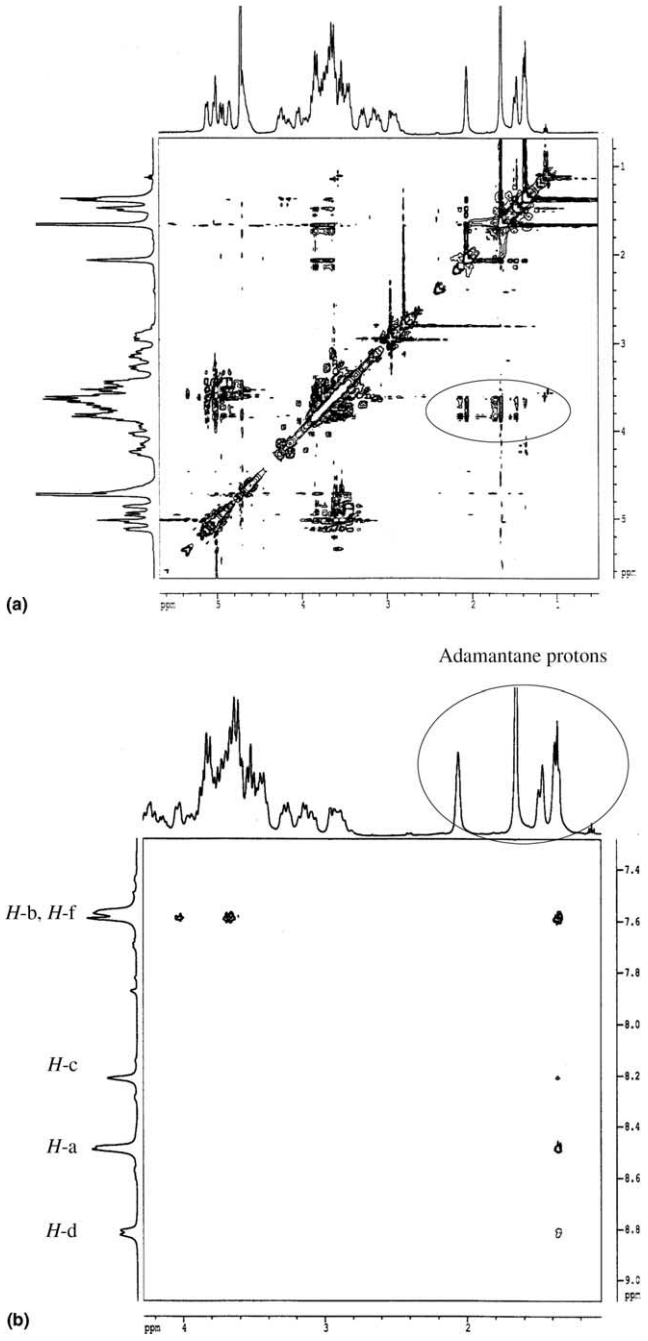

Figure 7. Partial contour plots of the ROESY experiment of **1a**/1-adamantanol complex (spin-lock time: 600 ms) in D_2O at 298 K. Horizontal scale: cyclodextrin and adamantane region; vertical scale: (a) cyclodextrin and adamantane region, (b) aromatic region.

fluorescent studied sensor. We show that the conformational differences between compounds **1a** (fluorescent moiety enclosed in the cavity) and **1b**–**e** (fluorescent moiety in bulk water environment) are reflected in values of sensitivity factors. However, the short negative values of **1a** are due to the fact that the fluorescent moiety is in the vicinity of the guests having a strong binding constant (I–II) and that this phenomenon induces less variation

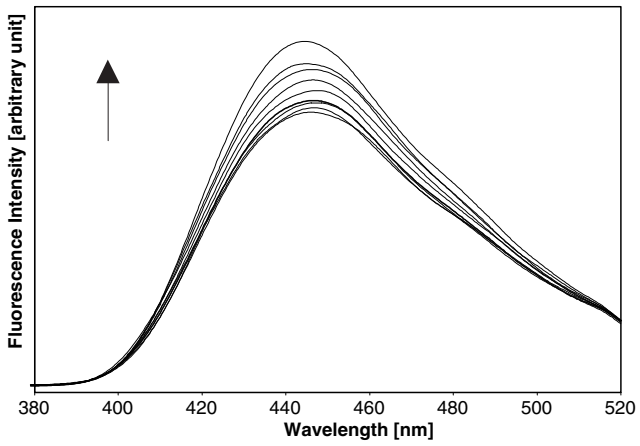

Figure 8. Fluorescence spectra of **1a** (10^{-7} M) in aqueous phosphate buffer at pH 7 in the presence of various concentrations of 1-adamantanol (1: 0, 2: 3×10^{-7}, 3: 1.7×10^{-6}, 4: 5.7×10^{-6}, 5: 1.17×10^{-5}, 6: 5.17×10^{-5}, 7: 1.12×10^{-4}, 8: 7.12×10^{-4}, 9: 1.81×10^{-3} mol dm^{-3}).

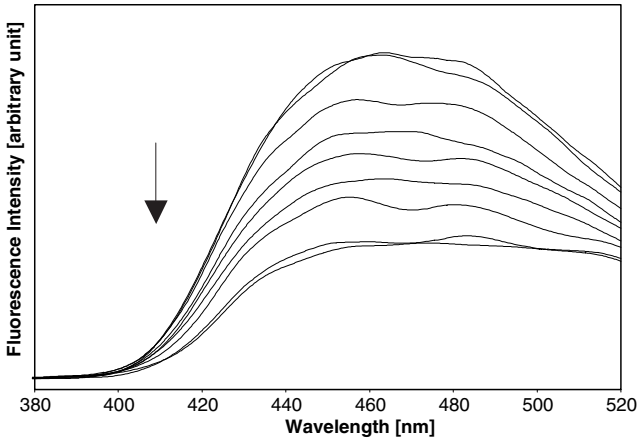

Figure 9. Fluorescence spectra of **1b** (10^{-5} M) in aqueous phosphate buffer at pH 7 in the presence of various concentrations of 1-adamantanol (1: 0, 2: 1.5×10^{-6}, 3: 5.5×10^{-6}, 4: 1.15×10^{-5}, 5: 3.15×10^{-5}, 6: 7.15×10^{-5}, 7: 1.32×10^{-4}, 8: 3.32×10^{-4}, 9: 1.82×10^{-3} mol dm^{-3}).

of fluorescence compared to a change of environment like resulting from a complete exclusion towards bulk water environment. In this context, the volatile organic compounds III–VI do not generate a sufficient fluorescence variation resulting in non-quantifiable sensitivity factors. Although the fluorescence quantum yield is higher compared to **1b**–**e**, the detection ability of the sensor **1a** is lower.

The sensitivity parameters for hosts **1b**, **1c** and **1e** showed remarkable values for guests I–II associated with a good response, compared to the maximum values of sensitivity $(\Delta I/I_0)_{max}$ but denote a weak sensitivity for the volatile organic compounds III–VII, which are barely recognized. The host **1d** has not shown a sufficient binding ability for any guest. This suggests that the appended moiety of **1d** has an inappropriate

Table 1. Sensitivity parameters of **1a**–**e** ([**1a**] = 10^{-7} M; [**1b**–**e**] = 10^{-5} M) in aqueous phosphate buffer at pH 7 and 25 °C for guests I–VII ([I–VII] = 10 × [**1a**–**e**])

	1a		**1b**		**1c**		**1d**		**1e**	
	$\Delta I/I_0$	$(\Delta I/I_0)_{max}$	$\Delta I/I_0$	$(\Delta I/I_0)_{max}$	$\Delta I/I_0$	$(\Delta I/I_0)_{max}$	$\Delta I/I_0$	$(\Delta I/I_0)_{max}$	$\Delta I/I_0$	$(\Delta I/I_0)_{max}$
I	−0.024	0.23	0.449	0.61	0.306	0.34	0.094	0.11	0.321	0.34
II	−0.029	0.23	0.442	0.50	0.301	0.36	0.090	0.12	0.205	0.33
III	—	—	0.018	0.58	0.032	0.59	0.027	0.43	0.059	0.56
IV	—	—	0.012	0.56	0.036	0.59	0.078	0.41	0.031	0.55
V	—	—	0.016	0.54	0.013	0.27	0.009	0.19	0.052	0.32
VI	—	—	0.010	0.63	0.075	0.49	0.032	0.57	0.049	0.50
VII	−0.018	0.23	0.032	0.57	0.044	0.51	0.017	0.34	0.116	0.46

configuration, which does not allow any convenient dipolar variation upon complexation. The results obtained for the sensitivity factors of fluorescent derivatives **1b**, **1c** and **1e**, according to the concentrations in adamantane derivatives, are comparable with those obtained in the literature for various fluorescent sensors containing β-cyclodextrin.[4–6] However, these sensors do not give any satisfactory results in the detection of the organic molecules with low values of binding like guests III–VII. Indeed, the sensitivity factors are generally evaluated starting from the variations of fluorescence obtained by a proportion of 10 guests for 1 host which is inadequate ratio in this context. Thus, the examination of sensitivity factors obtained from [1 guest/100 hosts] ratio (Fig. 10) shows an improvement of the values of the sensitivity factors of compounds **1b**–**e**, which place them in an acceptable range of detection.

Figure 10 shows that fluorescent modified β-cyclodextrins **1b**–**e** have a improved capacity to detect halogenated organic compounds (III, IV and VII) with respect to alkylbenzene (V and VI) in particular compound **1e**, which shows an $S_f = 0.62$ for 1,1,2-trichloroethane.

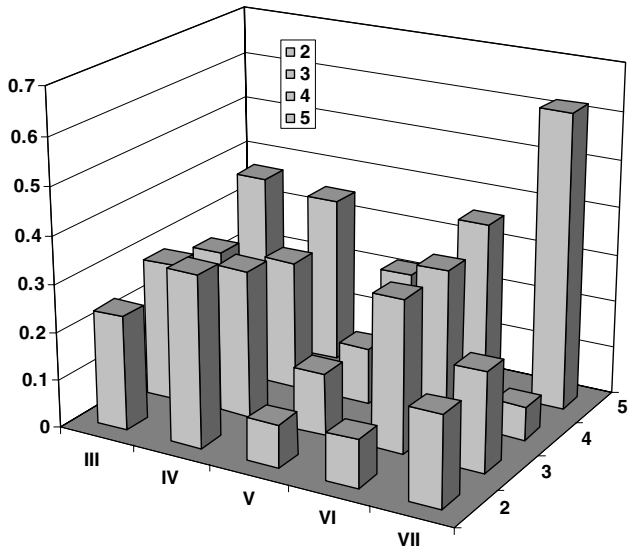

Figure 10. Sensitivity factors ($\Delta I/I_0$) of hosts **1b**–**e** for guests III–VII: [**1b**–**e**] = 10^{-5} M^{-1} and [III–VII] = 10^{-3} M^{-1} at 25 °C in phosphate buffer at pH 7.

Table 2. Binding constants (K_b/mol^{-1} dm^3) of **1a**–**e** in aqueous phosphate buffer pH 7 at 25 °C for guests I–VII

	1a	**1b**	**1c**	**1d**	**1e**
I	209,200	79,500	91,000	192,000	127,800
II	7200	88,200	54,000	104,200	757,00
III	—	1350	1030	1000	1480
IV	—	1460	1030	2080	1460
V	—	610	1000	1230	2110
VI	—	2270	1970	1640	2780
VII	12,700	610	510	730	540

The binding constants of the 1:1 complex of the hosts **1a**–**e** (Table 2) with the guests I–VII were obtained, as reported previously,[4,6] to correlate the fluorescence variations and the binding ability of the hosts. Table 2 shows a relative coherence between the values of sensitivity parameters and binding constants. In fact, the guests having a higher binding ability give an improved variation of fluorescence compares with results of the literature.[5,20] However, binding constants and sensitivity factors for hosts **1a**, **1d** and adamantane derivatives do not correlate and the order of the binding constants of each host is not parallel with the order of the sensitivity factor.

3. Conclusions

This study is the first example of a series of fluorescent markers appended to β-cyclodextrin and highlights the role of the substituents in the pyridinoindolizinc moiety. Thus, only the fluorescent β-cyclodextrin derivative **1a** exhibits a self-inclusion conformation compared to derivatives **1b**–**e**. These conformational differences generate an opposed guest-induced variation of fluorescence intensity between **1a** and **1b**–**e** and affect the sensing ability of these hosts, in which the 6^I-(*N*-deoxy-β-cyclodextrin-6^I-yl)-1-amido-3-(*p*-substituted benzoyl)-7-pyridin-4-yl indolizine derivatives **1b**–**e** have the highest sensitivity. It was shown that the detection of VOC is

possible with an acceptable range of detection. With the purpose of improving the capacities of detection, we are now planning to vary the substituents R in the pyridinoindolizinic part in order to modulate the sensory abilities of these fluorescents sensors and use the second reactional site carried by free nitrogen to synthesize a fluorescent dimer of β-cyclodextrin, which may be a more suitable sensor.

4. Experimental

The NMR spectra were recorded with a Brüker AMX 400 spectrometer. Mass spectra were performed by using a Platform II Micromass Apparatus. UV–vis spectra and fluorescence spectra were measured in a conventional quartz cell on a Perkin–Elmer Lambda 2S spectrometer and on a LS50B spectrometer. CD spectra were recorded on an YVON JOBIN CD6 spectropolarimeter. UV absorption, steady fluorescence and CD measurements were performed in 0.1 M pH 7.0 phosphate buffer at 25 °C.

Stock solutions of the host molecule had concentrations of 10^{-5} or 10^{-6} mol dm^{-3}, depending on the experiment. The fluorescence measurements have required an excitation and emission slits were set at 4 nm width, respectively. No oxygen quenching of the fluorescence was observed.

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