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Photochemical behaviour upon the inclusion for some volatile organic compounds in new fluorescent indolizine β-cyclodextrin sensors

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Abstract

The potentialities of three new fluorescent indolizine modified β-cyclodextrin have been investigated as molecular chemosensors. The pyridin-4-ylindolizine β-cyclodextrin derivatives were synthesised by an amidation between the fluorescent indolizine derivatives and 6-deoxy-6-amino-β-cyclodextrin. The multiconformational search by MM3 and AM1 method in gaseous state and in water respectively suggest the "open cavity" structure as the most probable. These compounds have been characterised spectroscopically by their emission spectra and their sensing ability towards 1-adamantanol, phenol and *p*-cresol. The fluorescent properties and sensitivity factor of the sensor containing an indolizine product with a perfluored aromatic fragment recommended it fairly as sensor for the detection of volatile organic compounds (VOCs), while the other two sensors, with an aliphatic fragment, can be utilised as biological markers. Finally, a significant bathochromic shift is observed for the sensor containing a *t*-butyl fragment, in such a way that this sensor may also lead to the detection of VOCs.

Keywords: Indolizine β-cyclodextrin; Sensors; Host–guest systems; Fluorescence; Molecular modelling

1. Introduction

Cyclodextrins (CDs) are a family of cyclic oligosaccharides that are composed of α-1,4 linked glucopyranose subunit. β-Cyclodextrin (β-CD) is the most accessible, the lowest priced and generally the most useful cyclodextrin [1–3]. CDs can form host–guest complexes with a large variety of solid, liquid and gaseous organic compounds by inclusion phenomena [4]. Inclusion in cyclodextrins exerts a profound effect on the physicochemical properties of guest molecules as they are temporarily locked or caged within the host cavity [5]. Therefore, CDs are used as carriers for biologically active substances [6], as enzyme model [7], sensor or solubilising agent for volatile organic compounds (VOCs) [8,9], protection agents for perfumes [10–12], and also as intermediates in organic chemistry. Cyclodextrins being essentially inert to photochemical excitation, their chemical modification with chromophoric entities may associate spectroscopic properties to the inclusion ability towards guest molecules [13–22]. Thus, modified CDs bearing fluorophores such as dansyl [13] and *p*-(dimethylamino)-benzoyl (DMAB) [14] moieties are examples of sensoring systems with which spectroscopically inert organic molecules could be detected, by variations in the emissions spectra in aqueous solution. Indolizinic systems are a common structural unit found in natural products, which have received particular attention due to their wide range of biological and medicinal activity [23,24]. In addition to their pharmacological effects, synthetic indolizine derivatives, and more specially those including a pyridine subunit, have also been recently studied extensively for their fluorescent properties and some of them already have practical applications as markers [25–27].

In previous papers [28–31] we reported the synthesis of a new class of fluorescent sensors based on a β-cyclodextrin fragment and an indolizine unit (Scheme 1).

Two different synthetic ways have been used for their synthesis: (i) an amidation between 4-nitrophenyl-3-(carbetoxy or 4-substituted benzoyl)-7-pyridin-4-ylindolizine-1-carboxylate

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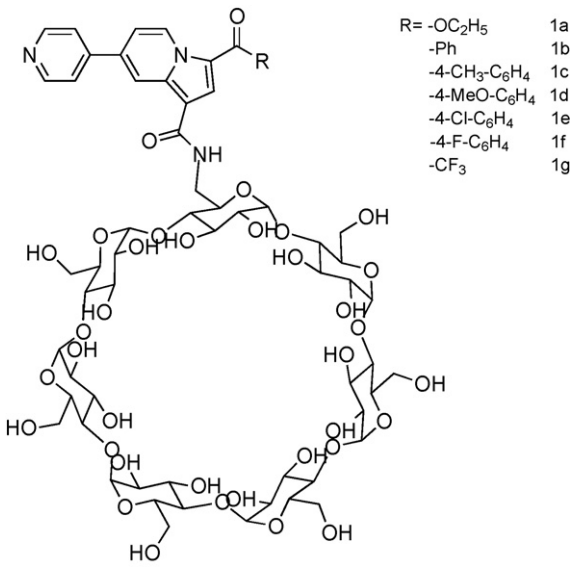


Scheme 1. Pyridin-4-yl indolizine modified β-cyclodextrin derivatives.

and 6-deoxy-6-amino-β-cyclodextrin and (ii) a 3 + 2 cycloaddition between 4-(pyridin-4-yl)-pyridinium methylides and 6-deoxy-6-propynamido β-cyclodextrin. The characterisation of these fluorescent compounds [29,31–34] have shown that the higher sensitivity towards VOCs was obtained for the fragment containing R = 4-F–C_6H_4.

As a part of our on going research program of synthesizing a new range of fluorescent β-cyclodextrins, we herein describe the synthesis of two new products with R = O-*n*-propoxy and R = O-*t*-butoxy groups, in order to extend the series of R = alkoxy groups, and a new fluorescent indolizine product containing a perfluorated aromatic fragment, R = –C_6F_5. Fluorescence properties of these compounds are also described through the evaluation of their sensitivity factors $\Delta I/I_0$ in the presence of 1-adamantanol, phenol and *p*-cresol. A multiconformational search by MM3 method in gaseous state and in water has been undertaken in order to find the most stable structure of these new sensors.

2. Experimental

2.1. Synthesis

2.1.1. General

^{1}H NMR spectra were recorded with a Brüker AM 400 spectrometer with tetramethylsilane as internal standard. Chemical shift values δ are reported in ppm and coupling constant J are in Hz. The abbreviations used are: s (singlet), d (doublet), t (triplet) and m (multiplet). Mass spectra were measured using a Platform II Micromass Apparatus. IR spectra were recording on a Perkin-Elmer instrument. Melting points were obtained with a Reichert Thermopan apparatus and are uncorrected. Chromatographic separations were carried out on Sephadex G25 and G15. All reagents were used as purchased unless otherwise stated. Solvents were dried according to standard procedure. All reactions were performed under argon.

2.1.2. General procedure for the synthesis of 1-substitued-[4,4′]-bipyridinium bromides **4a–c**

The *n*-propyl, *t*-butyl and pentafluoro ω-bromoacetates are commercially available. To a solution of 4,4′-bipyridine (2 g, 1.28 mmol), in acetone (25 mL) was added gradually at room temperature a solution of compound **2** (1 mmol) in acetone (10 mL). The solution was warmed under argon at 318 K for 12 h. The crude product precipitated, filtered off and next washed with acetone furnishes with good yields the solid salts **4a–c** after recrystallisation in ethanol.

*2.1.2.1. 1-(Pentafluorobenzoylmethyl)-[4,4′]-bipyridinium bromides **4a***. m.p. > 623 K, η = 79%; ^{1}H NMR (DMSO-d_6/TMS, 298 K) δ = 9.64 (d, J = 6.7 Hz, 2H, $H_{ortho/N+}$); 8.92 (d, J = 5.7 Hz, 2H, $H_{ortho/N}$); 8.78 (d, J = 6.7 Hz, 2H, $H_{meta/N+}$); 8.10 (d, J = 5.7 Hz, 2H, $H_{meta/N}$); 6.30 (s, 2H, CH_2/N^+); IR (KBr, cm^{-1}): 3020; 1719; 1646; 1489; 1154; 811; MS (ES^+, cone 10), *m/z* (%) 365 [M–Br] (100); $C_{18}H_{10}BrF_5N_2O$: calcd. C 49.42, H 2.28, N 6.40; found C 49.54, H 2.37, N 6.54.

*2.1.2.2. 1-(n-Propoxycarbonylmethyl)-[4,4′]-bipyridinium bromides **4b***. m.p. > 623 K, η = 61%; ^{1}H NMR (DMSO-d_6/TMS, 298 K) δ = 9.07 (d, J = 7.0 Hz, 2H, $H_{ortho/N+}$); 8.88 (d, J = 5.0 Hz, 2H, $H_{ortho/N}$); 8.59 (d, J = 7.0 Hz, 2H, $H_{meta/N+}$); 8.04 (d, J = 5.0 Hz, 2H, $H_{meta/N}$); 5.77 (s, 2H, CH_2/N^+); 4.11 (t, J = 4.0 Hz, 2H, –O–CH_2-); 1.55 (m, 2H, –CH_2–CH_3); 0.79 (t, J = 7.0 Hz, 3H,–CH_3); IR (KBr, cm^{-1}): 3425; 1735; 1639; 1365; 1199; 825; MS (ES^+, cone 10), *m/z* (%) 257 [M–Br] (17); $C_{15}H_{17}BrN_2O_2$: calcd. C 53.57, H 5.06, N 8.33; found C 53.41, H 5.10, N 8.47.

*2.1.2.3. 1-(t-Butylcarbonylmethyl)-[4,4′]-bipyridinium bromides **4c***. m.p. > 623 K, η = 70%; ^{1}H NMR (DMSO-d_6/TMS, 298 K) δ = 9.09 (d, J = 6.2 Hz, 2H, $H_{ortho/N+}$); 8.82 (d, J = 6.0 Hz, 2H, $H_{ortho/N}$); 8.62 (d, J = 6.2 Hz, 2H, $H_{meta/N+}$); 7.99 (d, J = 6.0 Hz, 2H, $H_{meta/N}$); 5.51 (s, 2H, CH_2/N^+); 1.41 (s, 9H, –CH_3); IR (KBr, cm^{-1}): 3424; 1746; 1647; 1148; 825; MS (ES^+, cone 10), *m/z* (%) 271 [M–Br] (32); $C_{16}H_{19}BrN_2O_2$: calcd. C 54.85, H 5.42, N 8.00; found C 54.91, H 5.51, N 8.20.

2.1.3. General procedure for the synthesis of 3-(substitued-carbonyl)-1-(4-nitrophenylcarbonyl)-7-pyridin-4-ylindolizines **7a–c**

A solution of freshly distilled Et_3N (7.84 mmol) in 3 mL dry DMF was added to a stirred solution of salt **4** (5.23 mmol) and 4-nitrophenylpropiolate **6** (5.23 mmol) in 20 mL dry DMF, at 273 K under N_2, in the absence of light. The reaction mixture was diminished by distillation of DMF under vaccum up to 7 mL. By addition of methanol (10 mL), the crude product was precipitated, filtered and washed with a large amount of methanol.

*2.1.3.1. 3-(Pentafluorobenzoyl)-1-(4-nitrophenylcarbonyl)-7-pyridin-4-ylindolizines **7a***. m.p. 553 K, η = 31%; ^{1}H NMR (DMSO-d_6 + 5% CF_3COOD/TMS, 298 K) δ = 9.90 (d, J = 8.0 Hz, 1H, H'_4); 8.89 (d, J = 7.1 Hz, 2H, H'_1); 8.77 (s, 1H, H'_5); 8.48 (d, J = 7.1 Hz, 2H, H'_2); 8.39 (d, J = 8.0 Hz, 2H, H_{ortho/NO_2}); 7.95 (s, 1H, H'_6); 7.90 (d, J = 8.1 Hz, 1H, H'_3); 7.62

(d, $J = 8.1$ Hz, 2H, H_{meta/NO_2}); IR (KBr, cm^{-1}): 3120; 1721; 1633; 1523; 1490; 1343; 1158; 1080; 988; 861; 795; MS (ES^+, cone 40), *m/z* (%) 554 $[M + H]^+$ (100); $C_{27}H_{12}F_5N_3O_5$: calcd. C 59.34, H 2.19, N 7.69; found C 59.50, H 2.39, N 7.81.

2.1.3.2. 3-(n-Propoxycarbonyl)-1-(4-nitrophenylcarbonyl)-7-pyridin-4-ylindolizines ***7b***. m.p. 511 K, $\eta = 30\%$; ^1H NMR (DMSO-d_6 + 5% CF_3COOD/TMS, 298 K) $\delta = 9.67$ (d, $J = 8.0$ Hz, 1H, H'_4); 9.06 (d, $J = 7.0$ Hz, 2H, H'_1); 8.84 (s, 1H, H'_5); 8.56 (d, $J = 7.0$ Hz, 2H, H'_2); 8.33 (d, $J = 8.0$ Hz, 2H, H_{ortho/NO_2}); 8.18 (s, 1H, H′); 7.90 (d, $J = 8.0$ Hz, 1H, H'_3); 7.66 (d, $J = 8.0$ Hz, 2H, H_{meta/NO_2}); 4.31 (t, $J = 6.0$ Hz, 2H, –O–CH_2–); 1.79 (m, 2H, –CH_2–CH_3); 1.01 (t, $J = 8.0$ Hz, 3H,–CH_3); IR (KBr, cm^{-1}): 2969; 2363; 1691; 1523; 1346; 1209; 1168; 987; 805; MS (ES^+, cone 20), *m/z* (%) 468 $[M + Na]^+$ (33); 446 $[M + H]^+$ (100); $C_{24}H_{19}N_3O_6$: calcd. C 64.71, H 4.26, N 9.43; found C 64.80, H 4.38, N 9.59.

2.1.3.3. 3-(t-Butoxycarbonyl)-1-(4-nitrophenylcarbonyl)-7-pyridin-4-ylindolizines ***7c***. m.p. 503 K, $\eta = 35\%$; ^1H NMR (DMSO-d_6 + 5% CF_3COOD/TMS, 298 K) $\delta = 9.65$ (d, $J = 8.0$ Hz, 1H, H'_4); 9.03 (d, $J = 7.0$ Hz, 2H, H'_1); 8.81 (s, 1H, H'_5); 8.52 (d, $J = 7.0$ Hz, 2H, H'_2); 8.39 (d, $J = 8.0$ Hz, 2H, H_{ortho/NO_2}); 8.10 (s, 1H, H'_6); 7.85 (d, $J = 8.0$ Hz, 1H, H'_3); 7.66 (d, $J = 8.0$ Hz, 2H, H_{meta/NO_2}); 1.41 (s, 9H, –CH_3); IR (KBr, cm^{-1}): 2971; 2359; 1690; 1524; 1346; 1210; 1168; 985; 807; MS (ES^+, cone 20), *m/z* (%) 482 $[M + Na]^+$ (33); 460 $[M + H]^+$ (100); $C_{25}H_{21}N_3O_6$: calcd. C 65.35, H 4.57, N 9.15; found C 65.49, H 4.70, N 9.37.

2.1.4. General procedure for the synthesis of N-(6^A-deoxy-β-cyclodextrin-6^A-yl)-1-(aminocarbonyl)-3-(substitutedcarbonyl)-7-pyridin-4-ylindolizines ***9a–c***

To a solution of 6-amino-6-deoxy-β-cyclodextrin **7** (1 mmol) in dry DMF (20 mL) was added a solution of fluorescent indolizine **8** (1 mmol) also in dry DMF (10 mL). The reaction mixture with stirring under N_2 was maintained at 323 K over hours. The liquid reaction mixture was then poured in acetone (250 mL). The crude solid collected by filtration was dissolved in water (200 mL) and the unreacted starting material **7** was removed by filtration. The resultant precipitate was passed through a CM-25 column by elating with water. The fractions containing the fluorescent sensor **9** were combined and concentrated in vacuum. Finally a new purification by a gel Sephadex G-15 was applied to furnish the sensor as fine powder.

2.1.4.1. N-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-1-(aminocarbonyl)-3-(pentafluorobenzoyl)-7-pyridin-4-ylindolizines ***9a***. $\eta = 32\%$; ^1H NMR (DMSO-d_6/TMS, 298 K) $\delta = 9.25$ (d, $J = 8.0$ Hz, 1H, H'_4); 8.52 (s, 1H, H'_5); 8.48 (d, $J = 8.0$ Hz, 2H, H'_1); 7.99 (s, 1H, H'_6); 7.94 (m, 1H, NH); 7.75 (d, $J = 6.0$ Hz, 2H, H'_2); 7.65 (d, $J = 7.0$ Hz, 1H, H'_3); 6.15–5.35 (m, 14H, OH_2, OH_3); 4.90–4.75 (m, 7H, H_1); 4.70–4.30 (m, 6H, OH_6); 3.85–3.02 (m, 42H, –H_2, –H_4, –H_3, –H_5, –$H_{6A,B}$); IR (KBr, cm^{-1}): 3404; 2920; 1736; 1473; 1323; 1215; 1074; 810; MS (ES^+, cone 40), *m/z* (%) 1563 $[M + K]^+$ (33); 1579 $[M + Na]^+$ (100); $C_{63}H_{78}F_5N_3O_{36}$: calcd. C 49.09, H 5.06, N 2.70; found C 49.30, H 5.17, N 2.88.

2.1.4.2. N-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-1-(aminocarbonyl)-3-(n-propoxycarbonyl)-7-pyridin-4-ylindolizines ***9b***. $\eta = 25\%$; ^1H NMR (DMSO-d_6/TMS, 298 K) $\delta = 9.48$ (d, $J = 8.0$ Hz, 1H, H'_4); 8.88 (s, 1H, H'_5); 8.71 (d, $J = 6.0$ Hz, 2H, H'_1); 8.28 (s, 1H, H'_6); 8.20 (m, 1H, NH); 7.80 (d, $J = 6.0$ Hz, 2H, H'_2); 7.63 (dd, $J = 2.0$ Hz and $J = 6.0$ Hz, 1H, H'_3); 5.90–5.54 (m, 14H, OH_2, OH_3); 5.01–4.78 (m, 7H, H_1); 4.60–4.25 (m, 8H, –O–CH_2–, OH_6); 3.90–2.91 (m, 42H, –H_2, –H_4, –H_3, –H_5, –$H_{6A,B}$); 1.77 (m, 2H, –CH_2–CH_3); 1.02 (t, $J = 8.0$ Hz, 3H, –CH_3); IR (KBr, cm^{-1}): 3376; 2913; 1676; 1619; 1213; 1146; 743; MS (ES^+, cone 40), *m/z* (%) 1478 $[M + K]^+$ (30); 1462 $[M + Na]^+$ (100); $C_{60}H_{85}N_3O_{37}$: calcd. C 50.03, H 5.90, N 2.91; found C 50.31, H 6.02, N 3.04.

2.1.4.3. N-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-1-(aminocarbonyl)-3-(t-butoxycarbonyl)-7-pyridin-4-ylindolizines ***9c***. $\eta = 30\%$; ^1H NMR (DMSO-d_6/TMS, 298 K) $\delta = 9.45$ (d, $J = 8.0$ Hz, 1H, H'_4); 8.86 (s, 1H, H'_5); 8.71 (d, $J = 8.0$ Hz, 2H, H'_1); 8.14 (s, 1H, H'_6); 8.09 (m, 1H, NH); 7.81 (d, $J = 6.0$ Hz, 2H, H'_2); 7.63 (d, $J = 7.0$ Hz, 1H, H'_3); 6.20–5.30 (m, 14H, OH_2, OH_3); 4.99–4.75 (m, 7H, H_1); 4.65–4.25 (m, 6H, OH_6); 4.05–2.95 (m, 42H, –H_2, –H_4, –H_3, –H_5, –$H_{6A,B}$); 1.60 (s, 9H, –CH_3); IR (KBr, cm^{-1}): 3378; 2915; 1680; 1620; 1212; 1148; 750; MS (ES^+, cone 40), *m/z* (%) 1492 $[M + K]^+$ (33); 1476 $[M + Na]^+$ (100); $C_{61}H_{87}N_3O_{37}$: calcd. C 50.37, H 5.98, N 2.80; found C 50.49, H 6.10, N 3.01.

2.2. Spectroscopic measurement

2.2.1. Chemicals

Phenol, *p*-cresol, 1-adamantanol, methyl orange, sodium hydroxide and potassium dihydrogenophosphate (Aldrich) were all of analytical reagent grade and were used as received. Deionised water was used throughout this work.

2.2.2. Fluorescence measurements

The measurements were carried out with a Perkin-Elmer LS-50B fluorimeter at 293 K and a quartz cell with an excitation angle of 90°. Excitation and emission slits were 4 nm. The excitation wavelengths of the fluorescence spectra were 380, 315 and 365 nm for compounds **9a–c** (absorbance equal respectively to 0.356, 0.013 and 0.002 for the concentrations used in fluorescence experiments). The absorbance of the studied guests are negligible at the excitation wavelengths used. The emission spectra were recorded from 300 to 700 nm with a scan rate fixed to 120 nm/min. The control of temperature is realised by the use of a thermostated bath linked to the cell holder (accuracy: ±0.1 K).

2.2.3. Visible spectra

Spectra were recorded using a Perkin-Elmer Lambda 2S double beam spectrometer and a quartz cell with optical path length

of 1.00 cm at 293 K. All compounds were dissolved in phosphate buffer at pH 5.8. The control of temperature is realised by the use of a thermostated bath linked to the cell holder (accuracy: ±0.1 K). The stability of the complexes formed between methyl orange (MO) and the hosts (sensor and genuine β-cyclodextrin) is first obtained by the use of the direct titration method; then, the complexing ability of both hosts is evaluated towards phenol, *p*-cresol and 1-adamantanol by means of a spectral displacement method with MO [35]. Dedicated algorithmic treatments were used to calculate the various formation constants, and they were applied to the first derivatives of UV spectra in order to avoid any spectral influence of diffraction phenomena [35,36]. Spectra were recorded between 520 and 530 nm for a MO concentration fixed at 0.1 mM. This wavelength range corresponds to the optimal spectral variation between the free and complexed forms of MO.

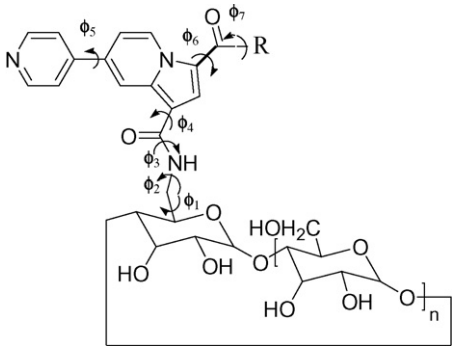
2.3. Molecular modelling

The sensors were built starting from the data provided by the Structural Data Base System of the Cambridge Crystallographic Data Center. The simulations were made using the CAChe software [37] on a PC-computer.

2.3.1. Sensors conformations

Seven dihedrals are controlling the structure of sensors **9a–c** (Scheme 2). Nevertheless, the proximity of the toroïdal cycle of β-CD restricts the variation of the φ_1 and φ_2 dihedral angles. In addition, the torsions according to φ_5, φ_6 and φ_7 do not control directly the position of the fluorescent fragment in respect to the primary face of β-CD. The φ_3 and φ_4 dihedrals are thus considered as the key variables controlling the sensor structure, and only these two dihedrals have to undergo systematic variations during the conformational search. The energetic variation (according to the MM3 force field) is thus recorded in function of the φ_3 and φ_4 dihedral angles (rotational increments of 15° for each variable), while the φ_1, φ_2, φ_5, φ_6 and φ_7 dihedrals are only energy minimised [32].

This conformational search permitted us to choose the most stable conformers of the sensors **9a–c**. The final geometry optimisations were carried out at two stages: a preliminary minimisation with MM3 method, followed by AM1 minimisation without imposing any restrictions.



Scheme 2. Dihedrals controlling the sensors structure.

2.3.2. Inclusion compounds conformation for sensor **9c**

The docking of each guest into the β-CD unit has been performed using four dummy atoms [38]. Each orientation has been taken in consideration for each guest. Three parameters were varied to explore the conformational space of the inclusion compound: the distance between host and guest, the orientation of the guest ring inside the host cavity, and its tilt angle [38]. For this purpose, a sequential conformational search has been employed with the MM3 force field, with a systematic variation of each parameter. The most stables structures obtained by this procedure are then energy minimised without any constraint. The difference (ΔE, kcal/mol) between the energy of the inclusion complex and the sum of their individual components in their optimized ground states was then used as the theoretical parameter to evaluate the inclusion ability of sensor **9c**.

3. Results and discussion

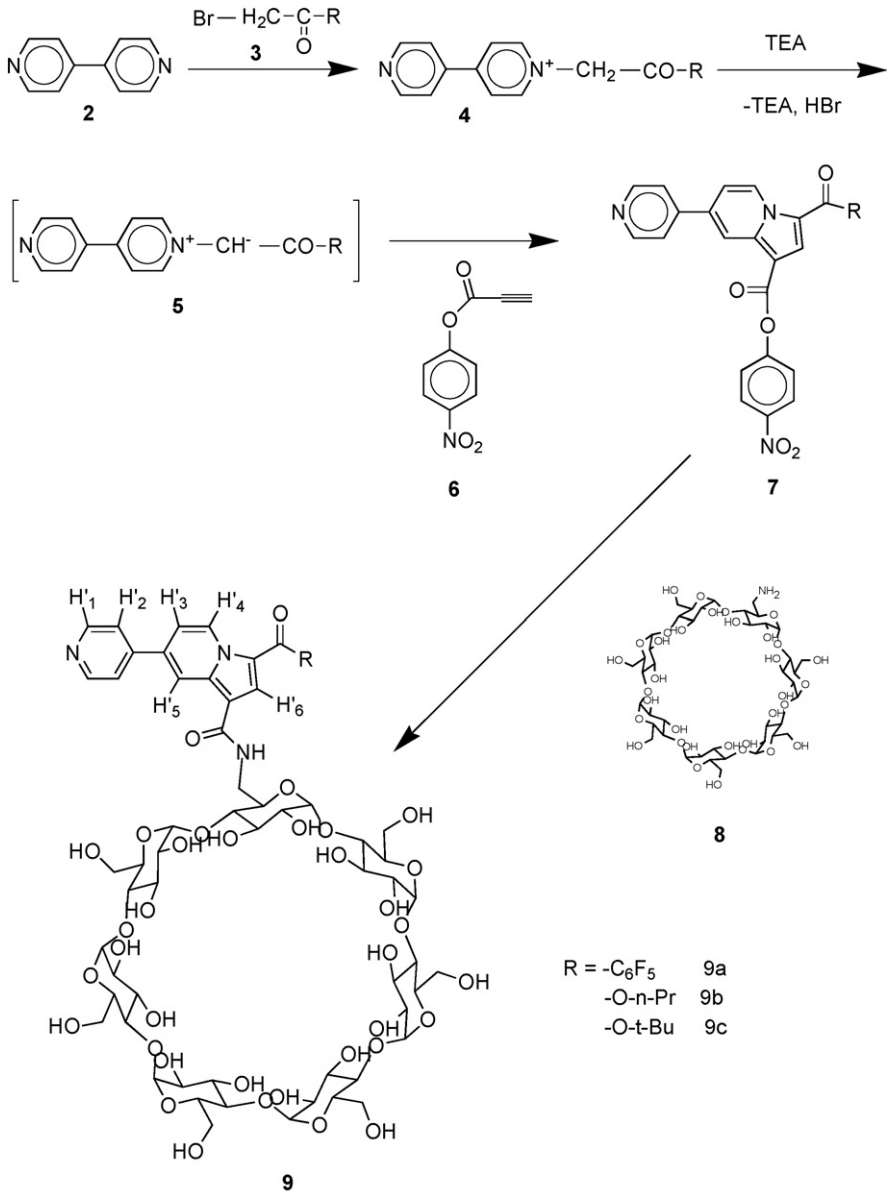
3.1. Synthesis

The *N*-(6-deoxy-β-cyclodextrin-6-yl)-1-(aminocarbonyl)-3-(substitutedcarbonyl)-7-pyridin-4-ylindolizines **9a–c** were synthesised by the chemical way (i) detailed in Scheme 3.

First, the "salt method" has been applied in order to obtain the bipyridinium ylides **5** [39,40]. Thus the 4,4′-bipyridine was reacted with *n*-propyl and *t*-butyl 2-bromo acetates, to furnish the corresponding salts **4**. This salt, in the presence of the mild base triethylamine (TEA) gave in situ the red–violet monosubstituted carbanions ylides **5**. It should be noted that this reaction must be carried out without light in order to prevent the cleavage of the N^+–C^- ylide bond [41]. The 6-deoxy-6-amino-β-cyclodextrin **8** was prepared according to the Hamasaki method [42]. The ester **6** could be obtained by direct esterification of propynoic acid with 4-nitrophenol in presence of dicyclohexylcarbodiimide (DCC) [43]. Next, the ylide **5**, generated in situ was reacted with propynoate **6** to generate the indolizine **7** after an intermediate aromatisation of a primary cycloadduct. The last step of synthesis is an amidation between 6-amino-β-cyclodextrin **8** and the fluorescent indolizine **7** to give the corresponding fluorescent β-cyclodextrin **9**. Evidence for the structures of new compounds was obtained from their elemental analysis and their spectroscopic data (MS, IR, and ^{1}H spectrometries). Complete spectral characterisation of new compounds is provided in the Section 2. For the final fluorescent indolizine β-cyclodextrin derivatives **9a–c** only the peaks *m/z* +23 and *m/z* +39 corresponding to $[M+Na]^+$ and $[M+K]^+$ could be identified. The structures of the sensors **9a–c** have been established by comparison of their ^{1}H NMR data with previously published results on similar sensors [28–31].

3.2. Structural study of the sensors

The inclusion ability of our chemosensors should be depending on the relative position between the cyclodextrin cavity and the fluorescent moiety. Thus, we have realised a MM3 multiconformationnal search on each sensor. The most stables structures are then optimised by AM1 methods (in absence and in presence



Scheme 3. Synthesis of sensors **9a**–**c**.

of water). The obtained conformation are presented in Fig. 1, while the corresponding energies are listed in Table 1.

The results clearly recommends the open cavity structures depicted in Fig. 1 as the most stable conformers of sensor **9a**–**c**. Such results are essential, since a greater ability may be expected if the indolizine moiety is excluded from the macrocycle, if compared to a self inclusion of the sensors.

To confirm the theoretical results, we have extended the NMR study for the sensor **9c**. The ^{1}H NMR spectra of the sensor **9c** in D_2O revealed all nine methyl protons as a thin signal, leading to think that interactions between esteric *t*-butyl group and the β-cyclodextrin inner cavity are not probable. We also carried out a 2D NMR experiment in deuterium oxide: the ^{1}H ROESY NMR spectrum (Fig. 2) shows no spatial interaction between the protons of the indolizine and cyclodextrin moieties. This result is thus in good agreement with the "open cavity" structure obtained by molecular modelling.

Table 1
Energies (kcal/mol) of the most stable conformers of sensors **9a**–**c**

Sensor	E_{MM3}	E_{AM1}	E_{AM1/H_2O}	$E_{Solvatation}$
9a	747.7	−1298.9	−1367.6	−68.7
9b	773.0	−1173.9	−1243.8	−69.9
9c	760.3	−1180.2	−1248.8	−68.6

3.3. Inclusion ability

Since the fluorescence sensitivity is depending on the fraction of complexed sensor, we have first determined the inclusion ability of each sensor towards three guests: 1-adamantanol, because of its ability to bind strongly to β-CD, phenol and *p*-cresol which are semi-volatile compounds and which may be considered as

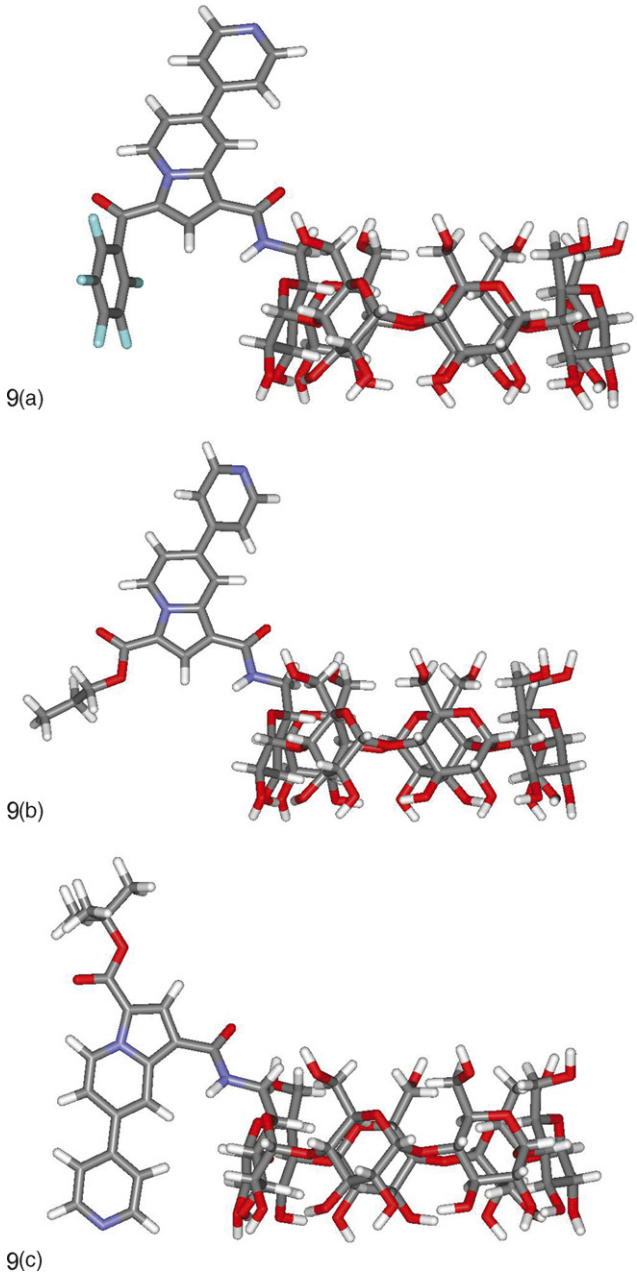


Fig. 1. Structures of the most stable conformers of sensors **9a–c**.

the water soluble models for benzene and toluene VOCs. The determination of the formation constants has been realised by means of a spectrophotometric spectral displacement with MO. The resulting formation constants (for 298 K) are summarised in Table 2.

First of all, if one compares the genuine β-cyclodextrin to the sensors, it seems that the inclusion compounds stabilities

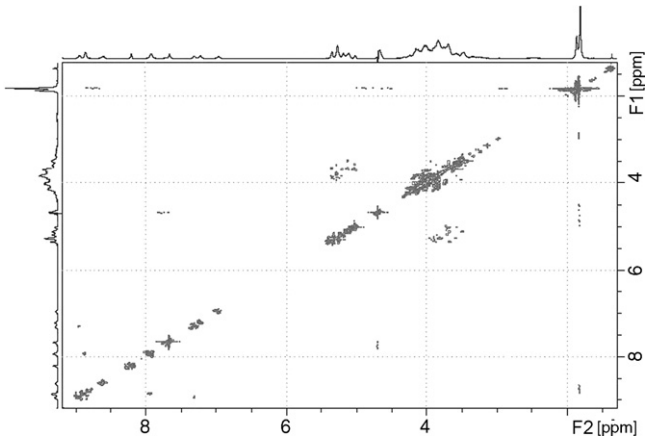


Fig. 2. ^{1}H ROESY NMR spectrum of sensor **9c** in D_2O at 330 K.

Table 3
MM3 energetic data for the complexes of sensor **9c** (kcal/mol)

ΔE	Phenol	*p*-Cresol	1-Adamantanol
Total	−7.6	−8.3	−10.5
van der Waals interactions	−7.4	−8.2	−9.3
Electrostatics interactions	0.0	−0.2	−0.3

are very similar, leading to think that few steric interactions occurs between the various guests and the indolizine moiety of the sensor. Such analogous behaviours confirm the fact that the fluorescent part is kept away from the cyclodextrin cavity. In addition, and as could be expected from the β-cyclodextrin inclusion ability, there is a strong difference of recognition between the aromatic guest and 1-adamantanol. While the stabilities are closed for phenol and *p*-cresol, 1-adamantanol leads to a significantly greater value of formation constant. Indeed, the 3-dimensional geometry of 1-adamantanol, if compared to the planar phenol and *p*-cresol, should lead to a greater filling of the internal cavity, thus increasing the van der Waals stabilisation of the inclusion compound. To illustrate this assumption, we have realised the docking of each guest into the sensor **9c**. The resulting conformations, given in Fig. 3, confirms the greater filling in the case of 1-adamantanol, since a significant part of the cyclodextrin cavity is not occupied in the case of phenol and *p*-cresol.

The corresponding energetic data, expressed as the difference (ΔE) between the energy of the inclusion complex and the sum of their individual components, are given in Table 3. The calculated values for ΔE are in good agreement with the experimental formation constants, since the greatest stabilisation is obtained for the 1-adamantanol inclusion compound, while the *p*-cresol complex is a little more stable than the phenol one. The van

Table 2
Formation constants (M^{-1}) determined in this study by UV–vis spectroscopy (at 298 K)

Guest	β-CD	Sensor **9a**	Sensor **9b**	Sensor **9c**
Phenol	115 ± 10	130 ± 10	120 ± 10	122 ± 10
p-Cresol	195 ± 20	205 ± 20	181 ± 20	194 ± 20
1-Adamantanol	34100 ± 2500	34500 ± 3000	32700 ± 2900	33800 ± 2800

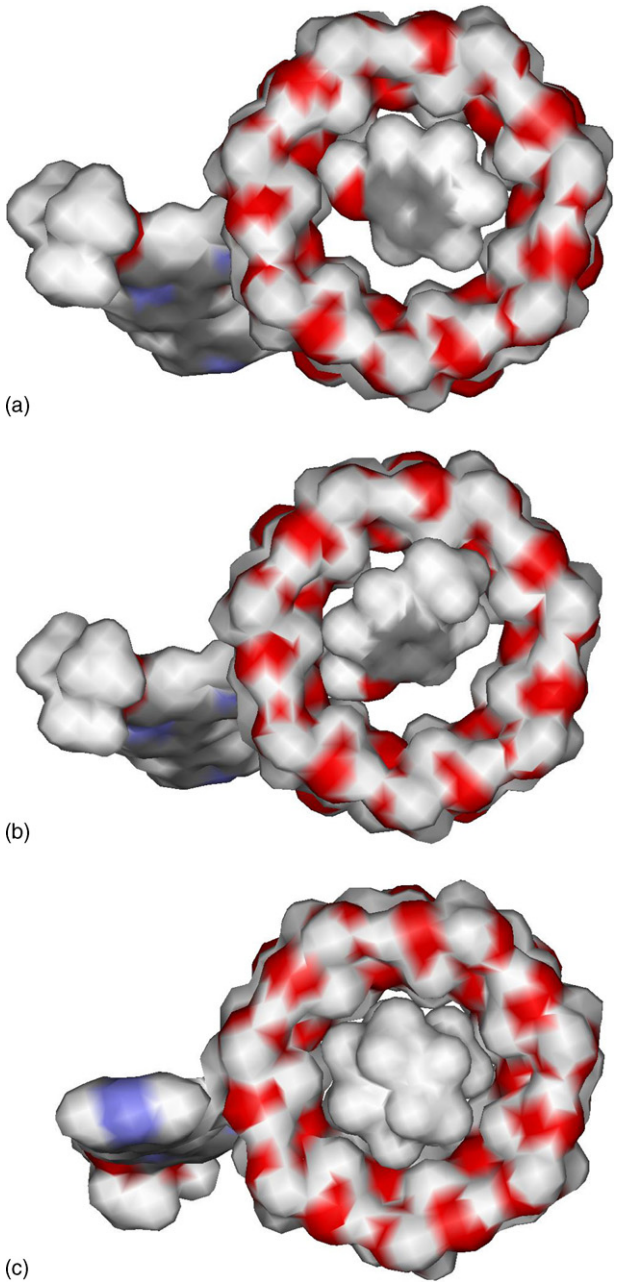


Fig. 3. Most stable conformations of the inclusion compounds formed between sensor **9c** and phenol (a), cresol (b) and 1-adamantanol (c).

der Waals interactions seem to be the main factor governing the recognition, while electrostatic interactions have a very weak contribution to the binding. Thus, we may conclude that the filling of the cavity really controls the stability of the inclusion compound.

3.4. Fluorescence sensitivity upon inclusion

To characterise the sensing ability of the three new fluorescent β-cyclodextrins, we investigated the change induced in the fluorescence emission of these compounds upon addition of 1-adamantanol, phenol and *p*-cresol. The concentration of added guest was defined individually in order to lead to the complexation of 50% of the studied sensor, according to the formation constants determined in Section 3.3. The fluorescence spectra of the sensors **9a–c** in presence of the various guests are given respectively in Sections 3.4.1–3.4.3. (Figs. 4–6). The corresponding molar concentrations of the sensors and the guest have been specified in figures captions. Hence, the sensitivity

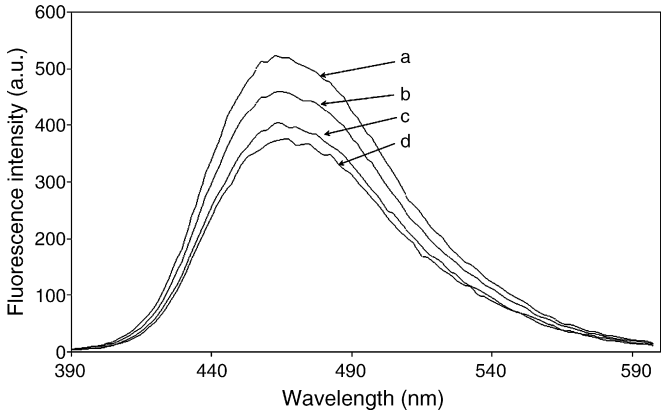


Fig. 4. Fluorescence spectra of (a) the sensor **9a** in aqueous solution (3.10^{-5} M, 298 K), in presence of (b) 1-adamantanol $4.5.10^{-5}$ M, (c) *p*-cresol 5.10^{-3} M, (d) phenol 8.10^{-3} M. Excitation wavelength: 380 nm.

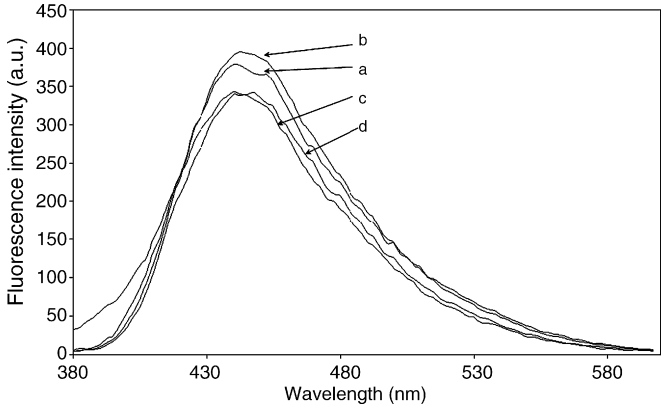


Fig. 5. Fluorescence spectra of (a) the sensor **9b** in aqueous solution (3.10^{-6} M, 298 K), in presence of (b) 1-adamantanol $3.0.10^{-5}$ M, (c) *p*-cresol 5.10^{-3} M, (d) phenol 8.10^{-3} M. Excitation wavelength: 315 nm.

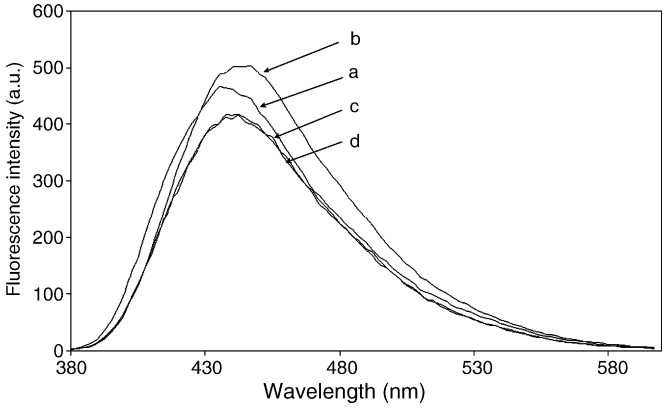


Fig. 6. Fluorescence spectra of (a) the sensor **9c** in aqueous solution (2.10^{-7} M, 298 K), in presence of (b) 1-adamantanol $3.0.10^{-5}$ M, (c) phenol 8.10^{-3} M, (d) *p*-cresol 5.10^{-3} M. Excitation wavelength: 365 nm.

Table 4
Sensitivity factors (calculated for the maximum of emission of each sensor, at 298 K)

Sensor	$\Delta I/I_0$		
	Phenol	*p*-Cresol	1-Adamantanol
9a	−0.23	−0.28	−0.11
9b	−0.07	−0.10	+0.07
9c	−0.11	−0.10	+0.08

factor $\Delta I/I_0$ was used to quantify the sensing abilities, where ΔI is $I - I_0$, and I and I_0 are the emission intensities in the presence and absence of guest, respectively [44]. The sensitivity factors of all three sensors in presence of the studied guests are summarised in Table 4.

From these data, some trends may be pointed out. In presence of 1-adamantanol, the two sensors with R = O-alkyl present an increase of the fluorescence intensity while the sensor with an aromatic moiety presents a decrease of the intensity. These results are in good agreement with previous published results for similar sensor [31,33]. The specific behaviour of each sensor is discussed in the following sections.

3.4.1. Sensor *9a*

In the case of sensor **9a**, which presents a fluorescence peak at 465 nm (λ_{exc} = 380 nm), the addition of the three guests leads to a decrease of the fluorescence intensity.

From the numerical values of the sensitivity factors given in Table 3, the sensor **9a** shows more interesting properties as sensing agent towards these three organic compounds, since greater spectral variations are observed if compared to sensors **9b** and **9c**. Thus, this sensor may be considered as a potential product for the detection of volatile organic compounds. This result is in good agreement with our data on the sensing ability of the sensor **1f** ($\Delta I/I_0$ = −0.54, −0.66 and −0.65 for 1-adamantanol, phenol and *p*-cresol, respectively). However, the presence of five fluorine atoms instead of one for sensor **1f**, does not increase its sensing ability. Also, we could consider the sensor **9a** as a suitable drug carrier taking into account the significant effect exercised by the fluorinated groups on the level of cellular membranes [45].

3.4.2. Sensor *9b*

The fluorescence spectrum of **9b** alone exhibits a fluorescence peak at 447 nm (λ_{exc} = 315 nm) and shows an increase in intensity upon addition of 1-adamantanol. The addition of phenol and *p*-cresol leads to a decrease of the fluorescence intensity (Fig. 5).

The modification of the fluorescence intensity is thus rather low, like what was observed for sensor containing an alkyl ester group (sensors **1a** and **1g**). As a consequence, the product **9b** may be recommended as a biological marker, but not as a sensing device.

3.4.3. Sensor *9c*

The sensor **9c** shows similar variation than sensor **9b** with a fluorescence peak at 438 nm (λ_{exc} = 365 nm). But among the three sensors, only the sensor **9c** presents such a bathochromic shift upon inclusion of each guest.

The relatively low values of sensitivity would recommend the sensor **9c** as biological marker, by analogy to the results of sensor **9b**. Nevertheless, these sensitivities are estimated for the maximum of emission in the fluorescence spectra: since there is a bathochromic shift (5 nm in our experiments), measurements realised around 410 nm may allow the use of compound **9c** as a sensor, and not only as a biological markers. Indeed, the sensitivity factors for this wavelength are equal to −0.27, −0.29 and −0.25, respectively for phenol, *p*-cresol and 1-adamantanol. Moreover, it is interesting to note that the extent of the bathochromic shift does not seem to be depending on the nature of the guest. Since each guest concentration leads to the complexation of 50% of the sensor, the bathochromic shift seems to be only controlled by this fraction, and as a consequence by the stability of the inclusion compound if identical concentrations would have been used for each guest.

4. Conclusion

Three new fluorescent indolizine β-cyclodextrin compounds **9a–c** have been synthesised and characterised for their fluorescence sensing ability towards three organic compounds, namely 1-adamantanol, phenol and *p*-cresol. The theoretical and experimental study led to think that the so-called "open cavity" structures are the most probable both in gaseous and aqueous states, assumption which is confirmed by the fact that the inclusion ability is similar to the genuine β-cyclodextrin. Moreover, this study highlights the influence on the fluorescence sensitivity of the substituent located on the pyridinoindolizinic moiety. Indeed, the aliphatic substituents lead to weaker value of $\Delta I/I_0$ for the entire guests and an increase of the fluorescence intensity with 1-adamantanol. Thus, the two sensors **9b** and **9c** with alkyl groups linked to the indolizine fragment could be used as potential biological markers. On the other hand, the sensor **9a** with an aromatic group linked to the indolizine fragment shows fairly properties for detection of organic compounds and mainly VOCs. In addition, such detection may also be realised by the use of compound **9c**, as a consequence of the observed bathochromic shift upon inclusion.

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