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Tuneable fluorescent marker appended to β-cyclodextrin: a pH-driven molecular switch

Matthieu Becuwe,[a] Francine Cazier,[a] Marc Bria,[b] Patrice Woisel[c] and François Delattre[a,*]

[a]*Laboratoire de Synthèse Organique et Environnement, E.A. 2599, Université du Littoral Côte d'Opale, 145 Av. M. Schumann, 59140 Dunkerque, France*
[b]*CCM-RMN Lille 1, USTL, 59655 Villeneuve d'Ascq, France*
[c]*Laboratoire de Chimie Organique et Macromoléculaire, UMR 8009, USTL, 59655 Villeneuve d'Ascq, France*

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Abstract—The photophysical properties of a pH dependent molecular switch based on pyridin-4-yl indolizin β-cyclodextrin **1** in water are described. The reversibility phenomena of fluorescent emission is attributed to a molecular motion of enclosed fluorescent moiety to inside/outside location.

The development of elaborate molecular devices became an important challenge since the rise of supramolecular chemistry and self-assembled molecular materials.[1] These molecular systems have a broad variety of specialized functions like switches,[2] shuttles,[3] scissors[4] or motors.[5] The control of molecular motion can be obtained in response to an appropriate external stimuli such as light,[4,6] electrochemistry[7] or pH-driven.[8] In the case of tuneable motion by protonation–deprotonation, it is also possible to modulate the photophysical properties to obtain a reversible change in the emission wavelength. In this Letter, we report the behaviour of a controllable motion driven by pH of fluorescent sensor incorporating a β-cyclodextrin unit as molecular receptacle. The β-cyclodextrin are well known to form complexes with a large variety of organic compounds and are used in the construction of rotaxanes, catenanes, and molecular sensors.[9] We now demonstrate that reversible fluorescent quenching of molecular sensor **1** are due to the location change of pyridin-4-yl indolizin unit appended to β-cyclodextrin caused by a protonation–deprotonation of included pyridinyl moiety.

Recently, we have reported the synthesis[10a,b] and the study of inclusion phenomena[10c] of fluorescent macrocycle **1** (Fig. 1) in water. We have shown that the molecular sensor presents, at neutral pH, a stable self-inclusion conformation of aromatic part in the hydrophobic cyclodextrin cavity (Scheme 1a) inducing a good fluorescence quantum yield ($\varphi_F = 0.51$ at pH 7). Thus, in order to investigate the quaternization effects of the pyridyl nitrogen on the structure and emission properties of derivative **1**, we investigated the protonation–deprotonation effects in aqueous solution by absorption, fluorescence, circular dichroism, and NMR spectroscopy experiments at neutral and acidic pH.

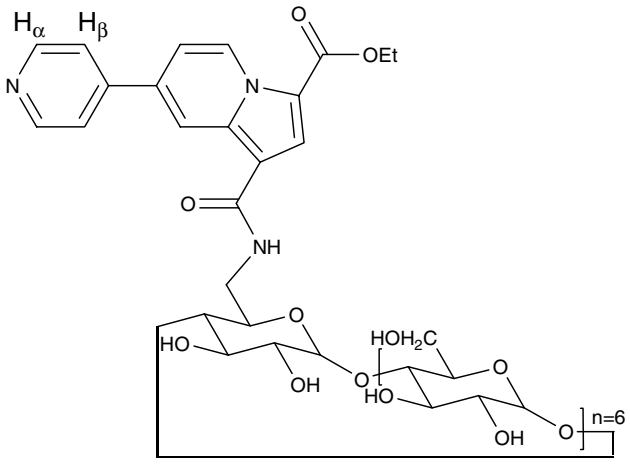

Figure 1.

Keywords: Molecular switch; Cyclodextrin; Fluorescence.
* Corresponding author. Tel.: +33 0328658246; fax: +33 0328658254; e-mail: delattre@univ-littoral.fr

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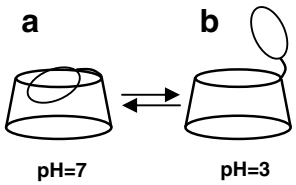

Scheme 1. Structures of pyridin-4-yl indolizin. β-Cyclodextrin **1** at pH 3 and pH 7.

The ground-state absorption and emission spectra of macrocycle **1** as a function of protonation level are shown in Figures 2 and 3, respectively. In neutral pH, the absorption spectrum exhibits an intense band at 283 nm assigned to $n\rightarrow\pi^*$ transition and a broadband in the near-UV region assigned to $\pi\rightarrow\pi^*$ pyridyl transition. As expected, upon addition of concentrated solution of HCl, we observed a red shift of the absorption bands with isobestic points (274 and 382 nm, respectively) indicating the presence of nonprotonated and protonated species[11] in neutral and acidic solution, respectively. The pK_a was determined by the Lachmann and Polster procedure[12] giving pK_a 5.01, which is more acid than free pyridine (pK_a 5.23).[13] Thus the pH-dependence of the emission was determined by acid titration between pH 6.5 and pH 2.5. The fluorescence emission of **1** was found to be 'switched off' after addition of an HCl solution (Fig. 3) and was accompanied by a large red shift of the maxima emission of the chemosensor **1** ($\lambda_{max} = 447$ nm to $\lambda_{max} = 527$ nm). Moreover, the fluorescence quantum yield decreased ($\varphi_F = 0.05$ at pH 3) 10-fold when the fluorescence was quenched by the protonation of pyridyl moiety. These results suggest that the quaternization of free pyridyl nitrogen induces an exclusion in the bulk water environment of chromophoric part caused by a loss of hydrophobicity.

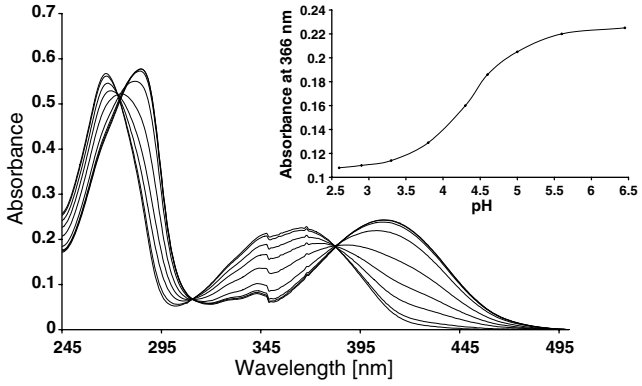

Figure 2. Reversible pH-dependence of the absorption spectra of **1** (5×10^{-5} mol L^{-1}) in H_2O at 298 K.

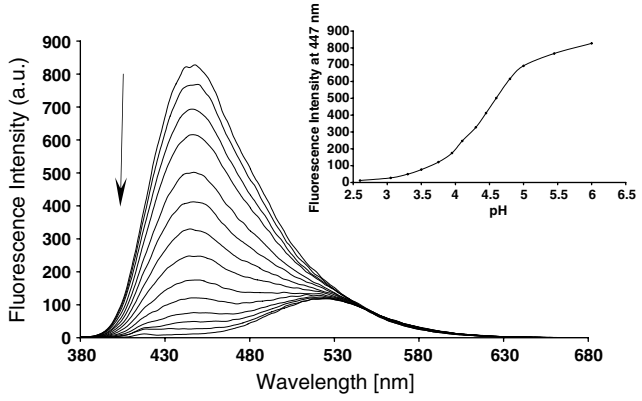

Figure 3. Reversible pH-dependence of the emission spectra of **1** (8×10^{-7} mol L^{-1}, $\lambda_{exc.} = 366$ nm) in H_2O at 298 K.

In order to confirm this environmental change, we carried out circular dichroism, ^1H and 2D NMR (ROESY) experiments under several pH conditions. Figure 4 shows the reversible CD spectral changes of **1** in aqueous solution upon addition of a concentrated solution of HCl. At slightly acidic pH, the dichroic signal shows two opposite intense bands at 262 and 283 nm whereas the bands are very weak and of negative signs under strongly acidic conditions. This result is in agreement with the exclusion phenomena of fluorescent moiety at low pH. Moreover, the comparison of ^1H NMR spectra (Fig. 5) shows that addition of 1 equiv D_2SO_4 causes a significant upfield shield of aromatic protons H_α ($\Delta\delta \approx +0.05$ ppm) and H_β ($\Delta\delta \approx +0.65$ ppm) which is consistent with pyridyl

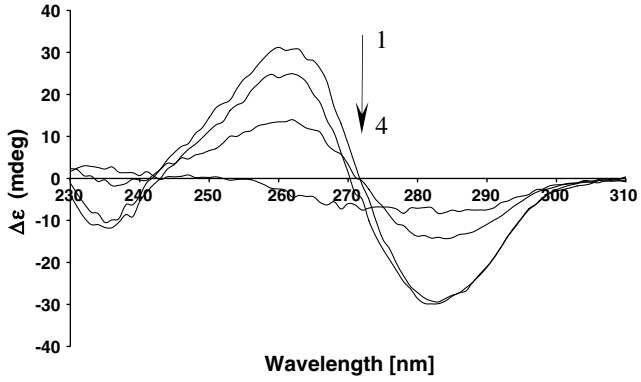

Figure 4. Circular dichroism spectra of **1** (5×10^{-5} mol L^{-1}) in H_2O at 298 K as a function of pH (1, 5.85; 2, 5.05; 3, 4.40; 4, 2.85).

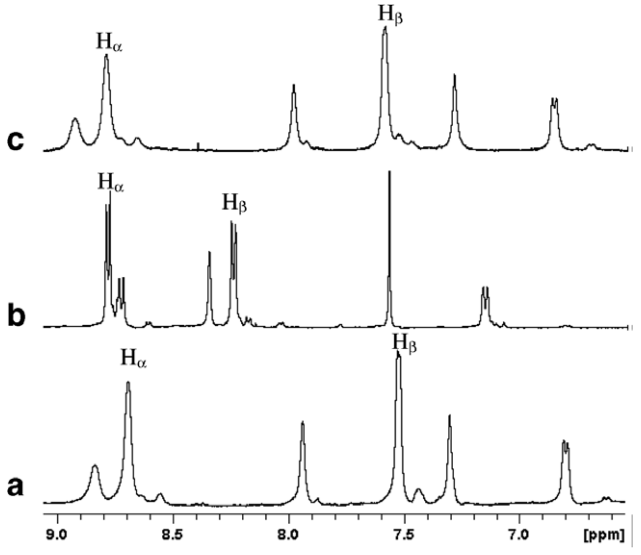

Figure 5. ^1H NMR spectra in D_2O: (a) at 25 °C of **1**; (b) +1 equiv D_2SO_4; (c) +2 equiv NaOD.

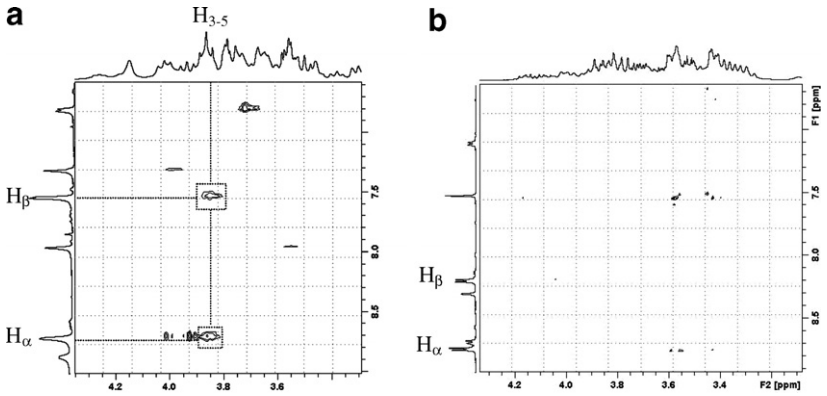

Figure 6. Partial ROESY NMR spectra of **1** (spin-lock time: 300 ms; $[\mathbf{1}] = 4$ mmol dm^{-3}) at 298 K (a) at neutral pH; (b) at acidic pH.

protonation. This latter was reversible by return to neutral conditions using 2 equiv of NaOD. It is obvious that nonambiguous proof regarding the reversible macrocycle exclusion of fluorophore was obtained from its 2D ROESY spectrum (Fig. 6). It is clearly observed that spectrum recorded at neutral pH displays strong dipolar interactions between the protons localized inside the β-cyclodextrin core and the $H_{\alpha/\beta}$ pyridinyl ones. These through space interactions disappeared on acidic pH and reappeared by using an alkaline deuterium solution. Thus these correlations clearly display the inside–outside molecular motion of fluorescent moiety, controlled by the protonation of free pyridyl nitrogen, inducing an extinction of fluorescence emission under acidic condition. This result is in agreement with the reversible pH-driven pyridin-4-yl indolizin unit appended to β-cyclodextrin and the fluorescence emission being 'switched off' when the enclosed chromophoric moiety is excluded toward the bulk water environment.

In conclusion, the experimental studies provide evidence of a pH-driven fluorescent molecular switch in water based on a β-cyclodextrin core and the protonation of the free nitrogen localized on the pyridyl group seems to be an efficient straightforward way to modulate the conformation and the fluorescent properties of sensor **1**. Further work will develop water soluble pH sensor to extend the system described here for the detection of relevant organic compounds.

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