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Effect of a hydroxyl group in an anthracene-labelled pyridine amide receptor in molecular recognition of α-keto and hydroxy monocarboxylic acids

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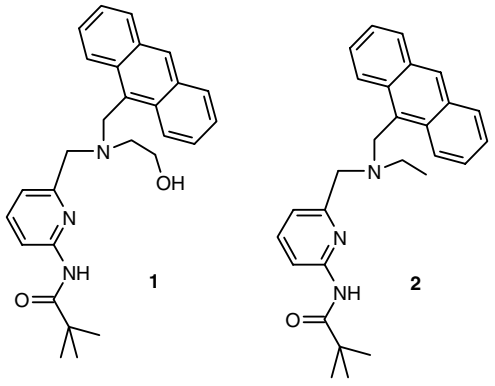
Abstract—To ascertain the role of a hydroxyl group in carboxylic acid recognition, anthracene-labelled pyridine amide sensor **1** was designed and synthesized. The sensor functions as an 'off–on' fluorescence switch for α-keto and hydroxy acids. The binding properties were studied using ^{1}H NMR, fluorescence and UV–vis spectroscopic methods. Sensor **1** is selective for pyruvic acid.

The development of chemosensors for biologically important species has recently emerged as a key research area in supramolecular chemistry.[1] In this regard, the transduction of recognition events into a fluorescent signal is of great importance. Over the past few years, considerable effort has been focused on the development of photoinduced electron transfer (PET) sensory systems for various guest species.[2] In designing such systems, the use of amide N–H,[3] urea/thiourea,[4] sulfonamides,[5] etc. as binding groups along with particular fluorophores is well documented. In this respect, a hydroxyl group as binding motif has been less studied[6] although a steroidal skeleton bearing a hydroxyl group,[7] urethane N–Hs and hydroxyl groups[8] and amino-alcohols[6c] were found to be promising in recognition of substrates ranging in nature from charged to neutral.

During the course of our ongoing program to develop receptors for molecular recognition of neutral substrates,[9] we report here the synthesis and photophysical behaviour of anthracene-labelled receptor **1** to examine the cooperative hydrogen bonding effect of the hydroxyl group in recognition of α-keto and hydroxy acids.

Receptor **1**, in which one anthracene substituent and a pyridine amide subunit are appended through $-CH_2-$ spacers to the nitrogen atom of an ethanolamine, has been synthesized according to Scheme 1 and characterized by ^{1}H NMR, ^{13}C NMR, and mass analysis.[10]



In receptor **1**, hydrogen bond donors (D) and acceptors (A) are arranged in a DAAD fashion and covalently linked to the 9-anthranilic position in order to generate the photoinduced electron transfer signal via the methylene ($-CH_2-$) bridge from the electron donor to electron acceptor (Fig. 1a). Molecular modelling[11a] revealed that receptor **1** (Fig. 1b; $E = 41.78$ kcal/mol) provides an open cavity into which the pyridine amide and alcoholic OH hydrogen bonding groups are well disposed for complexation.

The binding behaviour of **1** for benzoic, pyruvic, (*R*)-mandelic and 2-furoic acids was examined by ^{1}H

Keywords: Hydroxyl group; Off–on switch; Pyruvic acid; Mandelic acid; PET sensor.
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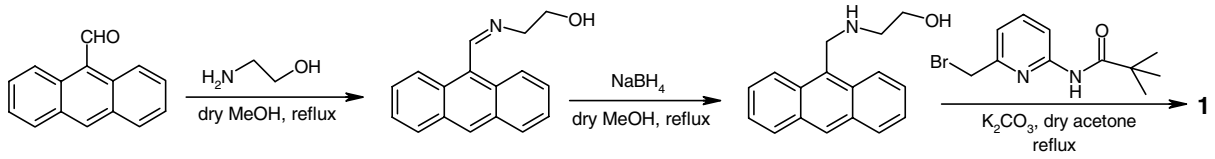

Scheme 1. Synthesis of receptor **1**.

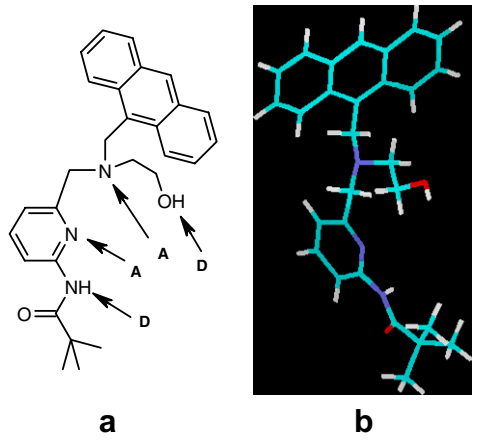

Figure 1. (a) Possible hydrogen bonding sites of **1** (A = hydrogen bond acceptor, D = hydrogen bond donor) and (b) energy minimized structure of **1**.

NMR titration, fluorescence and UV–vis methods. In dry $CDCl_3$ the signals of the OH and amide protons, which are D_2O exchangeable, appeared at 1.60 and 7.85 ppm, respectively (see Supplementary data). These two signals underwent significant downfield shifts upon addition of pyruvic, (*R*)-mandelic and 2-furoic acids suggesting that the hydroxyl group, along with the pyridine amide, serve as binding sites in complexation. The relatively smaller downfield shift of the amide proton compared to the hydroxyl proton is due to the steric nature of the pivaloyl group. As shown in Figures 2a and 2b, upon addition of pyruvic and (*R*)-mandelic acids, large changes in the chemical shift value of the OH protons ($\Delta\delta = 0.66$ ppm for pyruvic and 1.79 ppm for (*R*)-mandelic acids in their 1:1 complexes) were observed in the ^{1}H NMR spectra of **1**, while the signal of the amide proton shifted downfield by a smaller amount ($\Delta\delta = 0.36$ ppm for pyruvic and 0.49 ppm for (*R*)-mandelic acid in their 1:1 complexes). During complexation the $-CH_2-$ protons adjacent to the aliphatic nitrogen (a–d; see Fig. 3) also showed significant downfield shifts (Table 1) and suggest participation of the aliphatic nitrogen in complexation either in mode **A** or mode **B** as shown in Figure 3. Both forms **A** and **B** may exist in solution, in equilibrium, but we suggest that form **A** is more likely due to the six-centered hydrogen bonded structure as constituted by the carboxylic acid and alcoholic OH groups. The large downfield shift of the OH signal supports this proposition. During complexation in dry $CDCl_3$, the possibility of protonation of both the ring and aliphatic 3° nitrogens was neglected. This was proved by running ^{1}H NMR spectra in $CDCl_3$, but in the presence of the stronger acid HCl, which showed easy protonation by the appearance of a signal

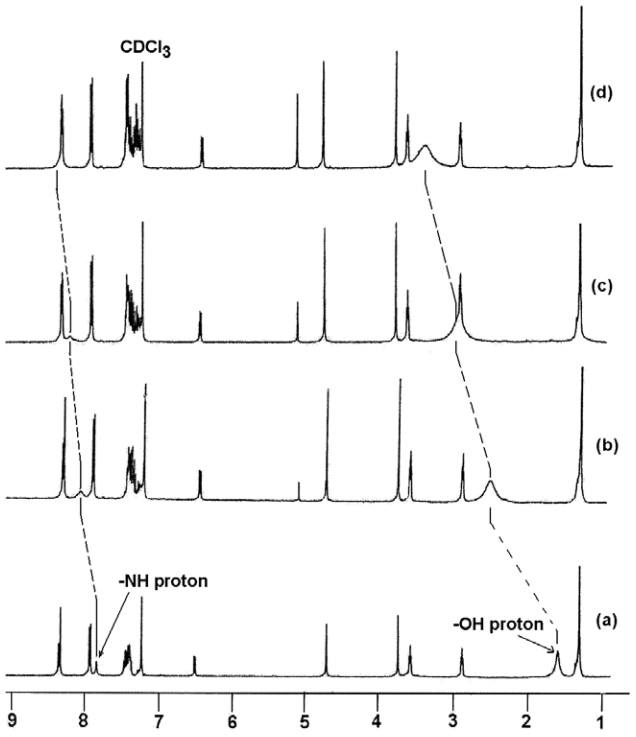

Figure 2a. ^{1}H NMR spectra on titration of **1** with (*R*)-mandelic acid in $CDCl_3$: (a) **1** ($c = 8.09 \times 10^{-3}$ M) only; (b) [G]/[H] = 0.29; (c) [G]/[H] = 0.57 and (d) [G]/[H] = 1.

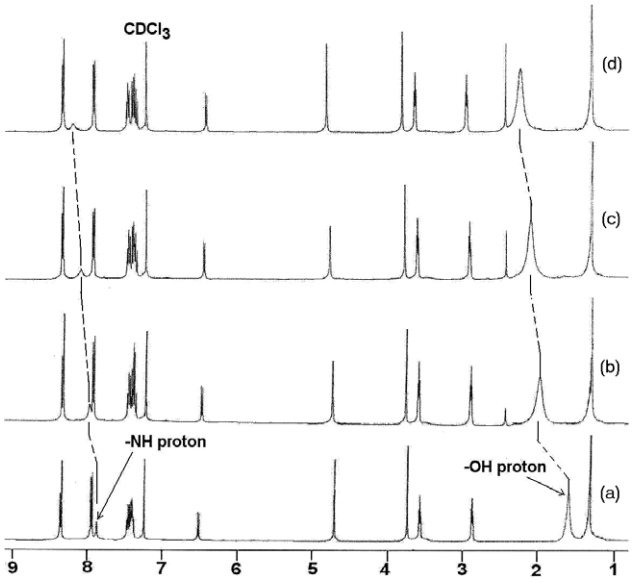

Figure 2b. ^{1}H NMR spectra on titration of **1** with pyruvic acid in $CDCl_3$: (a) **1** ($c = 7.77 \times 10^{-3}$ M) only; (b) [G]/[H] = 0.35; (c) [G]/[H] = 0.7 and (d) [G]/[H] = 1.