



A novel fluoride-sensing scaffold by a peculiar acid-promoted trimerization of 5,6-dihydroxyindole

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ARTICLE INFO

Article history:

Received 25 September 2008

Received in revised form 28 November 2008

Accepted 5 January 2009

Available online 8 January 2009

Keywords:

5,6-Dihydroxyindole

Fluoride

Sensor

Fluorescence

Rearrangement

ABSTRACT

An unusual rearranged trimer, 2-(2-amino-4,5-dihydroxybenzyl)-6,7-dihydroxy-3-(5,6-dihydroxyindol-3-yl)quinoline (**1a**), was obtained as the acetyl derivative (**1b**) by mild acid-promoted polymerization of 5,6-dihydroxyindole at pH 2. Compound **1b** proved to be a selective fluoride-sensing compound, transducing F⁻ binding into a distinct absorption at 414 nm and a marked fluorescence enhancement at 489 nm.

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1. Introduction

5,6-Dihydroxyindoles are a unique group of naturally occurring, catechol-containing heterocyclic compounds, which arise biogenetically by the oxidative cyclization of catecholamines and related tyrosine-derived metabolites. A marked facility to oxidation, leading to black insoluble polymeric materials, is the distinctive chemical feature underlying the biological importance of 5,6-dihydroxyindoles.¹ This is well illustrated by their role as primary building blocks of eumelanins,² the key components of the human pigmentary system.³ 5,6-Dihydroxyindoles have also been exploited in cosmetics and medicinal chemistry, e.g., as active moieties in antiviral agents and antibiotics.⁴

Recently, while pursuing a program aimed at designing novel 5,6-dihydroxyindole-based functional materials,⁵ we came across an unexpected behavior of this indole when left to polymerize under mildly acidic conditions. The noticeable outcome of this reaction was the formation of a rearranged trimer featuring an unusual 2-benzyl-3-indolylquinoline skeleton. Interestingly, the acetylated derivative of the trimeric product was found to exhibit selective binding properties toward fluoride anions, as revealed by

the marked F⁻-induced changes in the absorption and fluorescence spectra. This observation suggested a potential of the trimer as a novel prototype of fluoride-sensing scaffolds. Despite the vast literature that accumulated during the past few years, the quest for easily accessible and efficient fluoride-sensing molecular systems is still an active area of research⁶ because of the significant biological, medical, industrial, and environmental relevance of fluoride chemistry.

In this paper we report details of the acid-promoted trimerization of 5,6-dihydroxyindole and describe the selective effects of the fluoride anion on the chromophoric and fluorescence properties of the acetylated trimer.

2. Results and discussion

When 5,6-dihydroxyindole was dissolved in phosphate buffer at pH 2 and left at room temperature a smooth reaction occurred, leading after ca. 24 h to a main trimeric species (LC/MS analysis). This was obtained as the heptaacetyl derivative ([M+H]⁺ *m/z* 740) in 10% yield by a simple work-up procedure involving acetylation of the crude mixture followed by a chromatographic step, and was identified as 2-(2-acetamido-4,5-diacetoxybenzyl)-6,7-diacetoxy-3-(5,6-diacetoxyindol-3-yl)quinoline (**1b**) following complete spectral characterization (see [Supplementary data](#)). Inspection of the reaction mixture in the early stages showed the formation of dimer **2** and trimer **3a** as minor isolable products.⁷

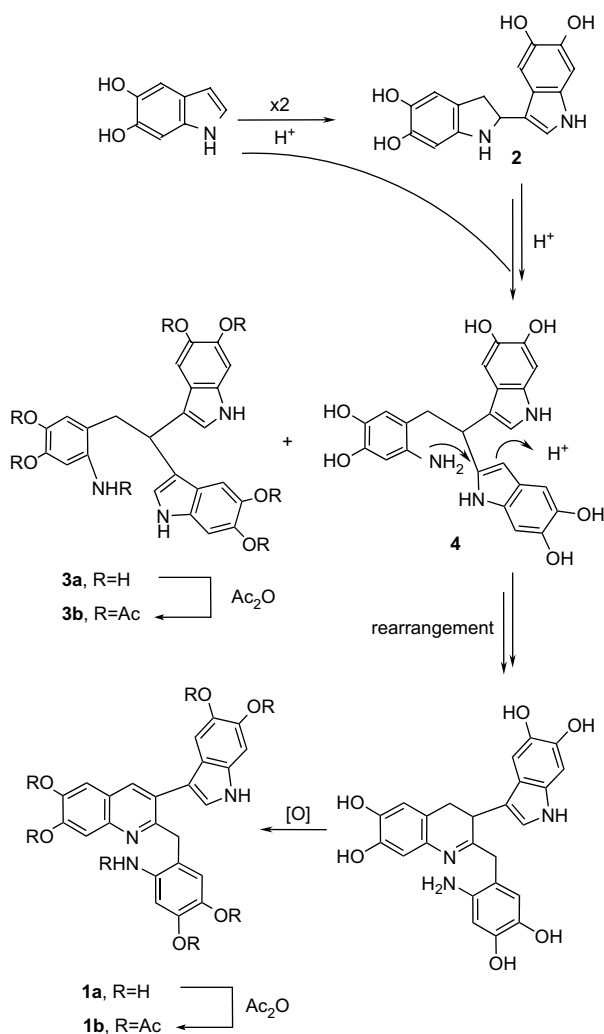
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A comparative study showed that none of the other indoles examined, i.e., indole, 5-hydroxyindole, 6-hydroxyindole, 5,6-dimethoxyindole, and 5,6-dihydroxy-*N*-methylindole, give the corresponding 3-(indol-3-yl)quinoline trimer under the same conditions. Use of stronger acids, e.g., HCl, or organic acids, e.g., acetic acid, was not productive, furnishing invariably ill-defined mixtures. The facile formation of **1a** from 5,6-dihydroxyindole is therefore attributed to the specific reactivity of this indole via the 2-position,⁸ steering in part the acid-promoted polymerization pathway through the usually less favorable 2-(2-amino-4,5-dihydroxyphenyl)-1-(5,6-dihydroxyindol-2-yl)-1-(5,6-dihydroxyindol-3-yl)ethane (**4**) (Scheme 1). Formation of the quinoline system of **1a** from **4** may proceed through a rearrangement step akin to that described for indole trimers in acidic media.⁹

The 2-(2-aminobenzyl)-3-(indol-3-yl)quinoline system featured by **1a** has previously been obtained only by harsh treatment of indole under Friedel–Crafts acylation conditions¹⁰ or in the presence of *p*-toluenesulfonic acid followed by complex work-up, extraction, and chromatographic separation steps.⁹

The absorption properties of **1b** are shown in Figure 1. The compound exhibited a distinct maximum at 330 nm in CH₃CN. Upon the addition of increasing concentrations of F⁻, a yellow coloration became apparent, due to the development of an absorption at 414 nm. Examples of colorless-to-yellow color changes associated with F⁻ binding to an organic compound have already been reported in the literature.¹¹ No clear isosbestic point is



Scheme 1.

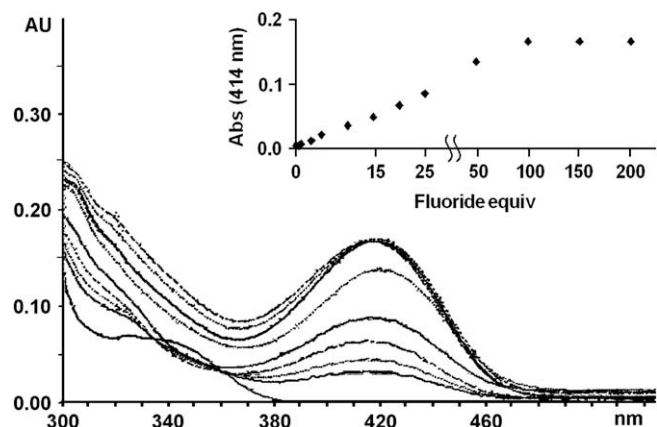


Figure 1. Changes in the UV/vis spectra of **1b** (1×10^{-5} M) in CH₃CN after addition of 0, 10, 15, 20, 25, 50, 100, 150, and 200 equiv of tetrabutylammonium fluoride (TBAF). Inset: Absorbance at 414 nm versus equiv of F⁻.

apparent from data in Figure 1, which suggests that color development involves more complex equilibria than a simple 1:1 substrate–anion binding process.

The acetylated derivative **1b** exhibited a remarkable fluorescence enhancement upon the addition of F⁻ (Fig. 2). The fluorescence response of **1b** (5×10^{-7} M) upon addition of up to 300 equiv F⁻ is shown in Figure 3. In the absence of F⁻, fluorescence of the free compound was weak and barely detectable. Addition of the anion to the solution caused the emergence of a distinct emission band at 489 nm following excitation at 414 nm. This effect is worthy of note since anion binding causes fluorescence quenching for most of the reported sensors,¹² with only a few exhibiting fluorescence enhancement.^{11c,13}

The recognition process was selective for F⁻ since in the presence of other anions, including Cl⁻, Br⁻, I⁻, AcO⁻, NO₂⁻, HSO₄⁻, no significant changes in the fluorescence spectra were observed. Complete fluorescence quenching was noted however in the presence of water (>20%). The stoichiometry of the fluoride–**1b** interaction was determined to be 2:1 from the Job's plot (Fig. 3).

In subsequent experiments, the effects of F⁻ binding on the parent 5,6-diacetoxyindole and the acetylated trimer **3b** were investigated. Trimer **3b** was a suitable model to identify the chromogenic and fluorogenic systems in **1b**, since it exhibited the

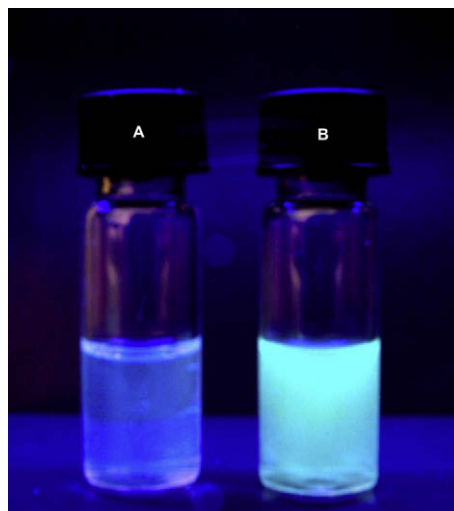


Figure 2. Fluorescence changes of **1b** (5×10^{-5} M) in CH₃CN upon addition of 25 equiv of TBAF. (A) no additive; (B) +TBAF (under a UV lamp at 366 nm).

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