Journal of Photochemistry and Photobiology A: Chemistry 326 (2016) 89–99

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology A: Chemistry

journal homepage: www.elsevier.com/locate/jphotochem

Dormant acceptor activation of 10-hydroxybenzoquinline derivatives by excited-state intramolecular proton transfer

Einat Kisin-Finfer, Ron Simkovitch, Doron Shabat, Dan Huppert*

Raymond and Beverly Sackler Faculty of Exact Sciences, School of Chemistry, Tel Aviv University, Tel Aviv 69978, Israel

ARTICLE INFO

Article history:
Received 24 February 2016
Received in revised form 26 April 2016
Accepted 30 April 2016
Available online 2 May 2016

Keywords:
ESIPT
10-HBQ
Photoacids
Fluorogenic-dye

ABSTRACT

We studied the excited-state intramolecular proton transfer (ESIPT) of two derivatives of hydroxybenzo[*h*]quinoline (10-HBQ). We used time-resolved and steady-state techniques for this purpose. These two compounds are water soluble and can be excited by visible light, thus they have a potential use in *in vitro* and *in vivo* imaging applications. We found that the ESIPT rate of ortho-indolium-10-hydroxybenzo[*h*]quinoline is greater than $10^{13}\,s^{-1}$, whereas for ortho-picolinium-10-hydroxybenzo[*h*]quinoline the rate constant is rather low ($k_{PT} = 7 \times 10^{12}\,s^{-1}$, $\tau_{PT} = 140 \pm 20$ fs). We also found a kinetic isotope effect of 1.5 ± 0.2 for ortho-picolinium-10-hydroxybenzo[*h*]quinoline. We observe in both compounds, a slower time component of 300 ± 50 fs with low amplitude of 0.05 ± 0.02 for the enol form decay. This slower component is also observed in the fluorescence-signal rise of the keto form, but with a higher amplitude of 0.2 ± 0.04. The fluorescence-signal rise of the keto forms of both compounds shows a third long-time component of several picoseconds. This time component in ortho-indolium-10-hydroxybenzo[*h*]quinoline is solvent-dependent and is assigned to solvation dynamics in protic solvents. We explain the relatively slow ESIPT rate of ortho-picolinium-10-hydroxybenzo[*h*]quinoline by the smaller enol-keto energy gap of this compound.

1. Introduction

Excited-state proton-transfer reactions occur in certain compounds and are quite common in photochemistry [1]. There are two classes of such photoprotolytic processes. The first class is excited-state intermolecular proton-transfer reactions (ESPT) [2–16], in which the proton is transferred to a solvent molecule, in most cases water. The molecules in this class are called photoacids. In their ground state, these molecules are weak acids with a pK_a in the range of 5–10. In the first excited state, their acidity changes and their pK_a^* is lower by about 7–11 orders of magnitude. The pK_a^* values of these photoacids range from 3 to about −8. The ESPT rate constants range from a k_{PT} value of $\sim 10^{13}\,s^{-1}$ ($\tau_{PT} \approx 100$ fs) for compounds with $pK_a^* \approx -8$ to about $10^7\,s^{-1}$ for compounds with a pK_a^* of 3.3.

Compounds of the second class undergo intramolecular proton transfer (ESIPT) [17–39]. The structure of these compounds consists of a proton donor and a proton acceptor in close proximity. Usually the proton donor is a hydroxyl group of a hydroxyaryl moiety and the proton acceptor is a heterocyclic nitrogen atom.

Two ESIPT compounds have received much attention in the literature, hydroxyphenylbenzothiazol (HBT) and 10-hydroxybenzo[h]quinoline (10-HBQ). In recent studies in which ultrashort laser pulses of 100 fs duration and even much shorter laser pulses of $\tau_{pulse} \approx 30$ fs, it was shown that ESIPT in both HBT and 10-HBQ in a protic solvent occurs within the time resolution of the laser apparatus, namely ~30 fs. Riedle and coworkers [19] reported that HBT undergoes ESIPT with a time constant of ~30 fs. Similar conclusions were drawn in the case of ESIPT of 10-HBQ by Takeuchi and Tahara [18].

We have recently synthesized new compounds based on the structure of 10-HBQ. This was done by a method described in a new study of fluorogenic dye-design [40] that provides molecular insight into an intramolecular hydrogen bond bridge, between a donor and a dormant acceptor. The fluorescence quantum yield (QY) of the two compounds is ~0.15, whereas that of 10-HBQ is only 0.03 [17]. By conjugation with an additional acceptor, the hydrogen bonding is harnessed to produce a long-wavelength fluorogenic dye. The general molecular structure of a dye activated through hydrogen bonding is illustrated in Scheme 1.

* Corresponding author.
E-mail address: dhuppert@post.tau.ac.il (D. Huppert).

http://dx.doi.org/10.1016/j.jphotochem.2016.04.021
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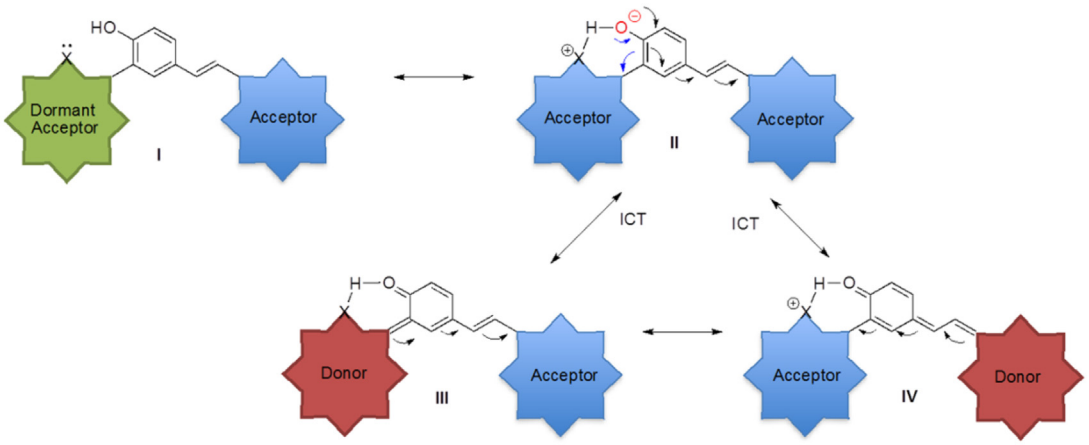


Scheme 1. Graphical illustration of a dormant acceptor activated by hydrogen bonding to produce a new long-wavelength emitting fluorochrome.

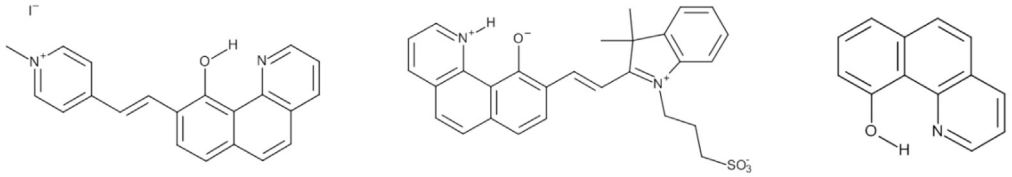
The dye is composed of a latent phenol donor conjugated at the *para* position to an active acceptor moiety and at the *ortho* position to a dormant acceptor (structure **I**). Upon formation of an intramolecular hydrogen bond between the donor and the dormant acceptor (structure **II**), three functions are achieved: (1) the dormant acceptor gains a positive charge enabling it to act as an active acceptor, (2) the phenol latent donor gains a negative charge allowing it to act as an active donor, and (3) the hydrogen bridge locks the molecule in a planar conformation. At the same time, an intramolecular charge transfer (ICT) from the phenol donor to either one of the two acceptors forms a new donor-acceptor pair with longer π-electron conjugation (structures **III** and **IV**). As a result, a long-wavelength emitting fluorochrome is formed.

By implementing a benzoquinoline skeleton in the design presented in Scheme 1, we significantly increased hydrogen bond strength. This also extended the conjugated π system and planarization of the dye molecule and, consequently, shifted the fluorescence to a longer emission wavelength in the NIR region. Due to the increased strength of the hydrogen bond (pK_a of 11.3) in the benzoquinoline molecule, the resulting dye strongly fluoresced under physiological conditions.

As illustrated in Scheme 1, the dormant acceptor activation mechanism of dye **I** relies on the hydrogen bridge formation between the phenol and the quinolone-nitrogen. Therefore, masking of the phenol by a protecting group should eliminate the hydrogen bridge and the corresponding fluorochrome. This approach is commonly used to construct turn-ON fluorescent probes, where the masking is performed with an analyte-responding group. We have demonstrated in the past that such a probe can be made by masking the phenol moiety by a benzyl-boronate-ester protecting group, which is known to undergo removal reaction by hydrogen peroxide. The probe was effectively activated by hydrogen peroxide to release its corresponded NIR fluorescent dye. Similarly other analyte/enzyme responsive substrates can be used to mask the phenolic dye in order to compose a turn-ON corresponded probe. We anticipate that the molecular insights provided by this design will assist in design of fluorescent dyes that can be used for *in vitro* and *in vivo* imaging applications.

In the current study we measured the spectroscopic properties of two of these newly synthesized compounds (called compound **1** and compound **2** in Scheme 2).

In compound **1** a methylpicolinium ion is attached to 10-HBQ (also shown in Scheme 2) via a conjugated bridge at the *ortho* position to the hydroxyl group. The absorption of compound **1** is red-shifted by ~50 nm to that of 10-HBQ, also shown in Scheme 2 and is therefore accessible to photoexcitation by visible light. Compound **2** is a similar analog but the picolinium is replaced by propyl sulfonate indolium ion and the absorption band of compound **2** is much more red-shifted than compound **1**. The



Compound **1**: ortho-indolium-10-Hydroxybenzo[*h*]quinoline

Compound **2**: ortho-picolinium-10-Hydroxybenzo[*h*]quinoline

10-hydroxybenzo[h]quinoline (10-HBQ)

Scheme 2. Molecular structure of the molecules studied.