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Red to near IR fluorescent signalling of carbohydrates

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Abstract: A novel symmetrical squaraine derivative with two phenylboronic acid functions has been synthesized. This compound detects carbohydrates in aqueous solutions with a fluorescence intensity increase. The emission maximum is at 645 nm with a γ-band shoulder at 695 nm, making this the first example of a near IR emitting carbohydrate chemosensor. © 1999 Published by Elsevier Science Ltd. All rights reserved.

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Reversible interaction of boronic acids with carbohydrates has long been recognized as a promising path for the development of novel carbohydrate sensing molecules.[1-3] The change in the pK_a of arylboronic acids on binding to a vicinal diol or carbohydrate is sufficient to induce a fluorescence signal for the interaction. Recent coupling of the boronic acid interaction with the PET[4] phenomena resulted in even more interesting sensory molecules for carbohydrates and derivatives.[5]

Recently, Shinkai and coworkers[6] synthesized porphyrin-boronic acid derivatives as carbohydrate sensitive long wavelength fluorophores, but carbohydrates caused aggregation leading to decreased fluorescence emission. Further alteration of the structure led to useful signals in circular dichroism, but not in fluorescence.[6b] In our own studies, we have been investigating the potential of squaraines as the fluorophore base in different sensing schemes.[7-12] Squaraines with their long wavelength excitation and emission proved to be highly amenable to modification yielding novel fluorescent chemosensors. Theoretical calculations suggested that the charge transfer in squaraines is mostly confined to the squaryl moiety,[13] and it is likely that squaryl oxygens can participate in interactions with the analyte being sensed, thus resulting in enhanced fluorescence. With these considerations in mind, we set out to synthesize compound **3**.

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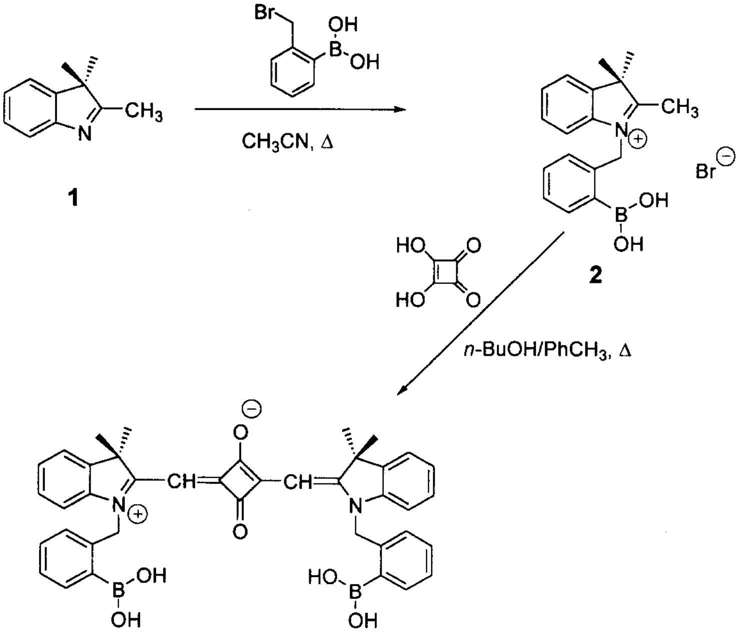
The synthesis is straightforward. The quaternization of 2,3,3-trimethylindolenine (**1**) has been carried out by refluxing an acetonitrile solution of 2-bromomethylphenylboronic acid and the indolenine derivative **1**. Protection of the boronic acid function proved to be unnecessary. The squaraine **3** is obtained by heating compound **2** with squaric acid in a n-BuOH/toluene mixture (50/50) in a Dean-Stark apparatus. Washing with methanol resulted in an analytically pure sample. The fluorescence response of this squaraine in EtOH/aqueous buffer solutions (pH 10.0, 50 mM carbonate buffer) is maximal for fructose. This is in line with observations suggesting a stronger binding interaction with fructose compared with other monosaccharides. There are clear signs of 1:2 squaraine/fructose stoichiometry at higher fructose concentrations.



Scheme 1. Synthesis of bis(phenylboronylmethyl)squaraine **3**.

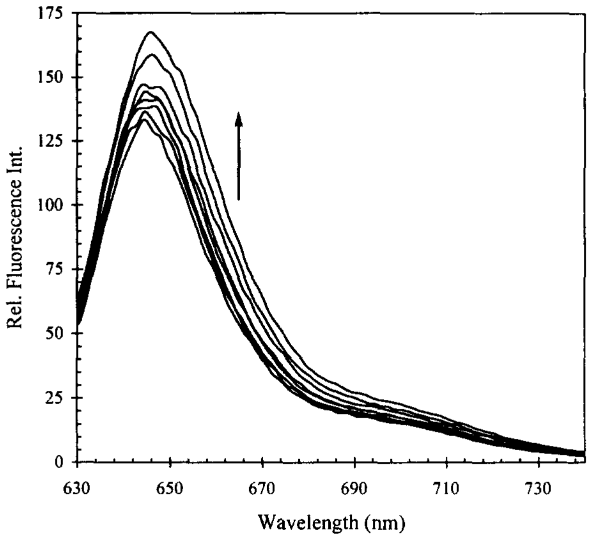


Figure 1. Relative fluorescence emission intensity change of compound **3** due to increasing concentrations of D-fructose. Intensity increases as the concentration increases in the following order: 0, 1, 5, 10, 25, 50, 100, 200 mM. The shoulder at 695 nm is due to the squaraine γ-band.[14]

Saturation is not reached at 200 mM fructose concentration. There is a 25 % increase in the emission intensity at the peak emission wavelength (645 nm). The increase could be partly due to rigidification of the squaraine skeleton, and partly due to a favorable interaction of squaryl oxygens with the carbohydrate in the form of additional H-bonding. This is evidenced by a small auxochromic effect in the absorption and emission spectra in fructose solutions. Comparable concentrations of D-galactose, D-glucose and D-mannose cause only about 8 % increase in the emission intensity.

Thus, we demonstrate that the versatile squaraine base can be modified to signal carbohydrate concentrations in aqueous solutions.

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