Dyes and Pigments 157 (2018) 305–313

Contents lists available at ScienceDirect

Dyes and Pigments

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

# A series of dual-responsive Coumarin-Bodipy probes for local microviscosity monitoring

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ARTICLE INFO

*Keywords:*
Fluorescent probes
Viscosity probes
Coumarin
Bodipy
Fluorescent molecular rotors

ABSTRACT

Local microviscosity monitoring in living cells is a powerful tool to determine their healthy status in either a specific organelle or in the cytosol. Here is presented the rational design of a new family of self-calibrating dual-microviscosity probes as a strategy to improve the probe response at low viscosity ranges. We found one of the probes is useful to determine low viscosity variations in living cells where subtle stiffening of the rotor group in the probe can increase its viscosity sensitivity. Further X-ray structure analysis, fluorescence anisotropic measurements, and quantum chemical calculations of the electronic excitation by means of a natural transition orbital (NTO) analysis confirmed the observed response. The present work demonstrates that small viscosity variations (0.01–0.1 cP) in cells require improved analytical sensitivity to be properly monitored.

## 1. Introduction

Local microenvironment sensing is an essential tool that relates the physical and chemical behavior of a molecule with its surrounding. Molecular microenvironment information includes polarity, polarizability, acidity, basicity, microviscosity, temperature and redox status [1–7], thus being implicated in many biological processes [8].

Fluorescence molecular rotors are molecules exhibiting excited-state intramolecular rotation capable of being calibrated either by physical (light), chemical (ionic species) or physicochemical (local microviscosity) inputs [9–11]. On the other hand, fluorescence polarization techniques can be used to estimate the rotor dynamics. These techniques, however, require the probes to fulfill as far as possible the following requirements: 1) minimum disturbance by the medium, 2) transition moment symmetry and direction such that rotations can be considered as isotropic (thus the molecular structure of the rotor needs to be non-planar), 3) minimum specific interactions with the surrounding molecules and 4) minimum sensitivity of the excited-state lifetime to the microenvironment when only steady-state anisotropy is measured.

Despite microviscosity measurements in living cells and/or specific organelles have been described previously, the analytical sensitivity of the molecular rotors remains poorly characterized. Most of the reported research focuses on instrumental sensitivity, time response, and the optical response nature. However, these probes have not been carefully designed nor evaluated for small microviscosity variations which comprises a crucial factor determining the intrinsic analytical sensitivity of the probe. In fact, most of the present literature describes a typical fluorophore calibration attained after extremely large changes in viscosity which do not occur in real biological samples [12–14].

On the other hand, monitoring of small microviscosity variations is a challenging enterprise since the probe needs to present a fluorescent response with only 0.1 cP variations. This subtle microviscosity variation can be achieved by an external perturbation such as temperature, pressure, and by the addition of chemical agents or drugs that induce cellular malfunction caused by structural changes or swelling [15–17].

In this contribution, we report a new family of probes with dual-emission band pattern containing a different rotor group, i.e. phenylene (**mVP1**), thiophenylene (**mVP2**), and a coumarin moiety directly connected to a Bodipy fragment (**mVP3**). The architecture of the probes belongs to the electron donor-acceptor family, featuring an electron-withdrawing boron-dipyrromethene (Bodipy) core and electron-

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https://doi.org/10.1016/j.dyepig.2018.05.009
Received 13 March 2018; Received in revised form 26 April 2018; Accepted 5 May 2018
Available online 07 May 2018