



Synthesis and characterization of new fluorinated tetrazines displaying a high fluorescence yield



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ABSTRACT

New tetrazines substituted with perfluorinated alkyl chains have been synthesized and their electrochemical and photophysical properties investigated under various conditions. Their fluorescence quantum yields in dichloromethane appear to be interestingly slightly higher than with classical tetrazines, placing these new derivatives among the most fluorescent tetrazines characterized to date.

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1. Introduction

s-Tetrazine chemistry has been known for more than a century [1], but for a long time their photophysical [2–4] and electrochemical [5] properties have been only briefly recognized. Meanwhile, *s*-tetrazines and their derivatives have been claimed to have a potential for biological activity and some of them were recently tested for their antitumor activity [6]. Some derivatives have also been tested as pesticides and herbicides [7]. However, their original physico-chemical, and especially fluorescence properties were extensively investigated only recently. Some of us have reviewed the properties of several substituted tetrazines [8], which display fully reversible electrochemical behaviour and an intense fluorescence, both in solution and in the solid state [9–14].

The introduction of fluorine atoms into heterocyclic compounds has led to the discovery of new bioactive products [15–18]. It also introduces electron-withdrawing atoms that may change the physical properties of compounds modified that way. We describe herein the synthesis of new tetrazines bearing perfluorinated alkyl

chains on one side, and on the other side, either a chlorine atom, or an allyloxy group (in order to access, if possible, active polymers). We have especially investigated the fluorescence characteristics of these tetrazines in different solvents. The results show that the emission properties of the new derivatives are noticeably solvent-dependent, contrary to previous findings with other tetrazines. Under standard conditions, for example in dichloromethane (DCM) solution, two of these new tetrazines display fluorescence quantum yields among the highest found to date.

2. Results and discussion

2.1. Synthesis

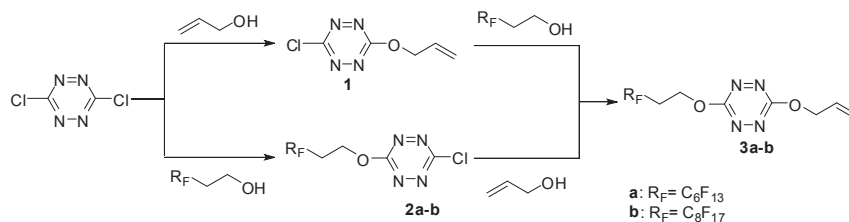
Fluorinated tetrazines **3** were prepared following two complementary pathways according to Scheme 1.

The monosubstitution of dichlorotetrazine was accomplished with the corresponding alcohol according to the standard procedure developed by some of us using *s*-collidine as an activator [11] to give **1** (pathway A) or **2 a-b** (pathway B) in good yields (Table 1). The second substitution by an alcohol on chloro-alkoxy-tetrazines is known to be less easy, but could be done by warming the reaction mixture at 100 °C in a sealed tube [19]. Better yields for tetrazines **3** have been obtained starting from **1** (pathway A) instead of **2**.

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Scheme 1. Synthetic pathways for the preparation of the new tetrazines.

Table 1
Synthetic yields and melting points for fluorinated tetrazines 2 and 3.

2:3	R _F	Yield (%)	mp (°C)
a	C ₆ F ₁₃	58:53	102:50
b	C ₈ F ₁₇	64:58	116:70

2.2. Physical chemistry

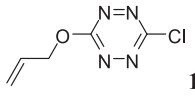
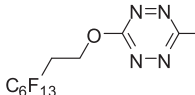
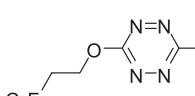
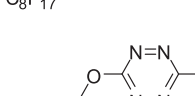
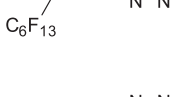
2.2.1. Spectroscopy

We have examined the absorption and fluorescence properties of the five new tetrazines in dichloromethane. Table 2 gathers the spectroscopic data (all spectra are given in the SI).

The wavelengths of the absorption and emission maxima are practically insensitive to the presence of a perfluorinated chain and similar to those of tetrazine derivatives substituted by an alkyloxy chain (see for example [8,9,11]). This confirms that the emission properties of the tetrazine core are preserved, while the fluorinated chain may play its water-protecting role for example.

A striking feature on these new tetrazines is that their fluorescence quantum yield is always higher than the equivalent bearing aliphatic chains [14], by about 10%. It goes from 30–35% to 40–45% in the case of the chlorinated examples, and from 8–10% to 16–18% in the case of the dialkoxytetrazines. This lies beyond the

Table 2
Spectroscopic data for all new tetrazines recorded in dichloromethane (for complete set of spectra see SI).

Molécule	$\lambda_{\max}^{\text{abs}}(1)$ (nm)	$\epsilon_{\lambda 1}$ (L mol ⁻¹ cm ⁻¹)	$\lambda_{\max}^{\text{abs}}(2)$ (nm)	$\lambda_{\max}^{\text{em. a}}$ (nm)	φ_F
 1	521	850	327	567	0.20
 2a	519	660	325	566	0.40
 2b	519	890	325	552	0.44
 3a	526	540	343	573	0.18
 3b	526	520	343	572	0.16

^a $\lambda_{\text{ex}} = \lambda_{\max}^{\text{abs}}(1)$.

experimental error, and is the first time that seemingly non-interfering substituents exert a noticeable influence on the fluorescence quantum yields. Actually compound **2b** is the tetrazine with the highest fluorescence quantum yield reported to date.

A possible explanation for the increase in the efficiency of fluorescence emission could be that the introduction of an additional dipole moment on the molecule, opposite in direction to the main moment of the tetrazine, may be the reason for this intriguing behaviour [20]. The origin of this effect may be electrostatic. There is a large permanent dipole moment at the bond linking the perfluoroalkane chain to the short alkane spacer, $D \approx 3$ Debye [21]. It generates a strong (and anisotropic) electric field on the tetrazine, only 5 to 10 Å away, a field stronger than usually applied external one. Its effect on the tetrazine orbitals will of course be dependent on the presence or absence of a permanent dipole moment on the solvent molecules (and their polarizability), so the actual situation is complex and a more quantitative discussion is beyond the scope of this paper.

Therefore we decided to also investigate the influence of the polarity of the solvent on the spectroscopy of these tetrazines. We examined the absorption and fluorescence of tetrazines **2a**, **2b**, and **3a**, along with the generic chloromethoxytetrazine into a fluorinated solvent, the highly polar trifluoroethanol. The results are comparatively summarized in Table 3.

It can be seen that in all cases, the fluorescence quantum yields are lower in the polar trifluoroethanol than in DCM. This seems in apparent contradiction with our former hypothesis. However, the solvent provides only an average random field which can have a different influence from a chain grafted on the tetrazine, whose orientation is collinear with the dipole moment of the heterocycle. In addition, the relatively acidic proton of the fluoroalcohol may also play a detrimental role on the fluorescence quantum yield by establishing a hydrogen bond with one of the tetrazine nitrogen.

Some behaviours are common to all four tetrazines, while some seem to be related to **2a** and **2b** (the **2** family) and other to **3a** and **3b** (the **3** family). All molecules have their fluorescence quantum yield almost doubled when compared to similar non-fluorinated analogues [9]. However, in going from DCM to trifluoromethanol, the fluorescence quantum yields decrease by a factor 2 in the case of the **2** family, while they are driven to almost zero in the case of the **3** family! Indeed, taking a closer look to all parameters, in the case of the **3** family (with a vinyl) this simply shows that the non-radiative rate constant (k_{nr}) considerably increases (by more than a factor 10) while the radiative constant (k_r) decreases only by a factor 2. However, the analogous examination of the results for the **2** family (the molecules with a chlorine on the other side of the perfluoroalkyl chain), shows that the lifetimes are virtually unaffected by the solvent change, and that the drops in quantum yields are essentially due to a twofold decrease of the radiative constant (k_r) accompanied by small increase of k_{nr} (see ESI for detailed values of k_r and k_{nr}).

To summarize, changing to a strongly polar and acidic solvent like trifluoroethanol leads to a slight decrease (twofold) of the

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