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Graphical Abstract

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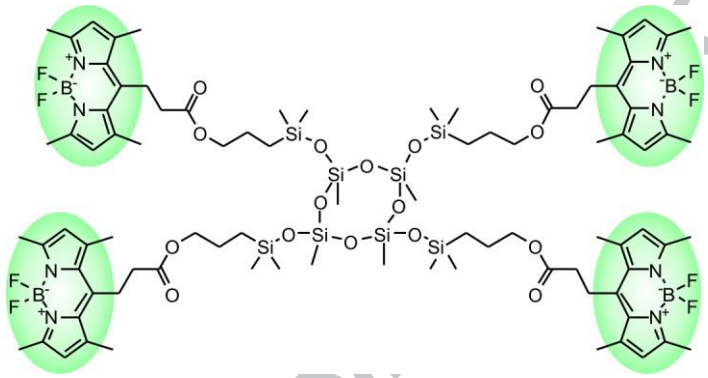

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Synthesis and photophysical properties of a new BODIPY-based siloxane dye

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ABSTRACT

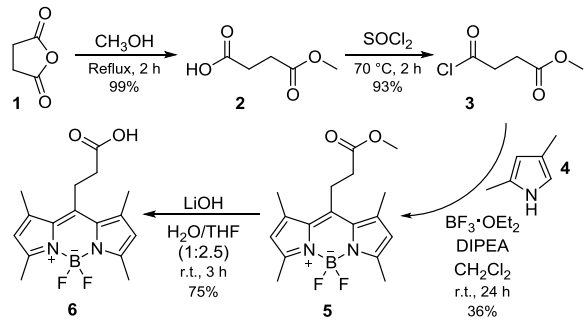
A fluorescent dye comprising of four BODIPY derivatives conjugated to a cyclotetrasiloxane core was synthesized by consecutive hydrosilylation and esterification reactions. Photophysical properties of the dye in various organic solvents were investigated. It was shown that due to a fourfold extinction coefficient increase and a moderate quantum yield decrease the brightness of the tetra-BODIPY dye in low-polarity solvents, calculated per molecule, increased 3 times when compared to mono-BODIPY. By contrast, in polar solvents there was a dramatic drop in brightness apparently associated with intramolecular interactions of the low-polar BODIPY chromophores.

Bright and photostable fluorescent compounds are of particular interest in the fields of modern photonics, photochemistry and molecular biology. Derivatives of 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) display outstanding photophysical properties and usually possess considerable light-absorbing capacity, high quantum yield, sharp absorption and emission bands, remarkable photostability and solubility in organic solvents.[1] Different BODIPY derivatives span most of the visible and near infrared spectrum and offer great potential for the development of biomolecular labels,[2,3] chemosensors,[4] energy transfer cassettes,[5,6] dye-sensitized solar cells (DSSC)[7] and can be used in photodynamic therapy.[8] BODIPYs were used as a base structure in the construction of fluorescent molecular rotors[9] and fluorescent liquid-crystalline dendrimers.[10] Herein, we have synthesized a carboxylic derivative of 1,3,5,7-tetramethyl-BODIPY (TMB) and conjugated it with cyclotetrasiloxane. Cyclic and polyhedral oligosiloxanes are known to be indispensable building blocks for the preparation of a variety of organic polymer materials[11, 12] improving their thermal and optical properties.[13, 14] Moreover, these compounds display high chemical inertness and biocompatibility.[15, 16] As might be expected, conjugation of several TMB fluorophores with the cyclosiloxane core structure would enhance the total brightness, which is proportional to the product of extinction (ε) and quantum yield (QY). Thus, combining four fluorophores at the cyclotetrasiloxane matrix might enhance the total brightness up to 4 times due to an extinction increase. On the other hand, raising of the local concentration of fluorophores may lead to the formation of nonfluorescent aggregates and in turn lead to a drop in quantum yield, which is the primary reason for fluorescence quenching of chromophore bearing dendrimers.[17] In the present work, we have attempted to design a multichromophore compound with the minimized effect of self-quenching. We presumed that the use of TMB would prevent aggregation-induced quenching owing to the BODIPY π-system being protected by four methyl groups.

A new tetra-BODIPY-substituted siloxane fluorescent dye was synthesized from two fragments: a siloxane ring and 3-(4,4-difluoro-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene-8-yl)-propionic acid (TMB-propionic acid). The latter was prepared analogously to the method described earlier.[13] Briefly, the reaction of succinic anhydride **1** with methanol followed by thionyl chloride chlorination yielded chloroanhydride **3** (Scheme 1). Product **3** was reacted with 2,4-dimethylpyrrole **4** in dry dichloromethane under argon at room temperature for 24 h followed by neutralization using DIPEA and subsequent reaction with boron trifluoride diethyl etherate. Addition of an extra equivalent of dimethylpyrrole **4** (3:1 instead of the commonly used 2:1) drastically improved the reaction yield. After purification, the resultant TMB ester **5** was saponified using LiOH in water-THF yielding TMB-propionic acid **6**.

The synthesis of hydroxyl-bearing cyclotetrasiloxane began from methyltriethoxysilane **7** (Scheme 2). The potassium *cis*-tetramethylcyclotetrasiloxanolate **8** was synthesized in good yield by the method previously reported by our group.[18] The reaction was carried out at room temperature in a mixture of ethanol and hexane. It should be noted that in this reaction only the *cis*-isomer can be formed, which was confirmed by X-ray analysis.[19]

At the next stage, modification of compound **8** by the dimethylsilyl

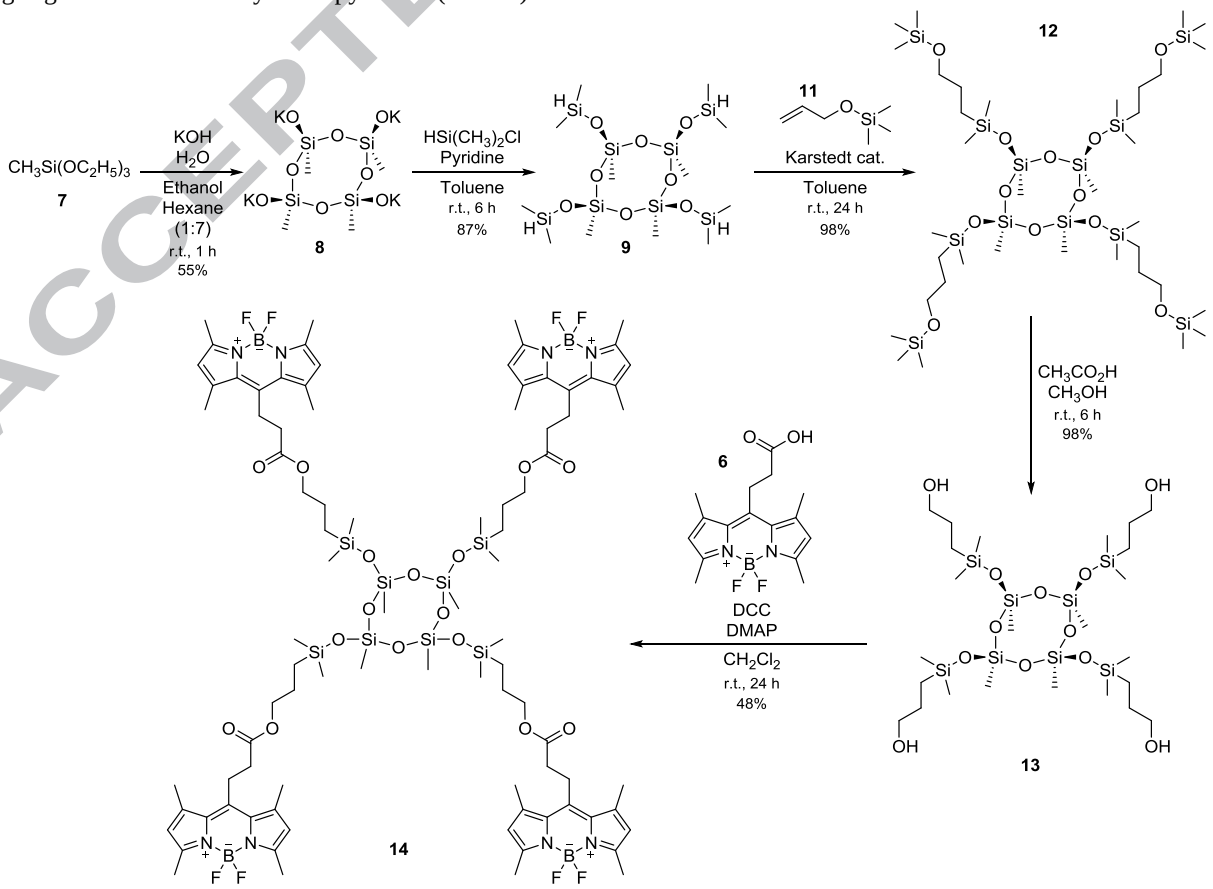


Scheme 1. Synthesis of TMB-propionic acid **6**.

group was accomplished. Reaction between salt **8** and chlorodimethylsilane was carried out in dry toluene at room temperature. The obtained compound **9** was used without further purification. Allyloxytrimethylsilane **11** was used to introduce the hydroxyl-bearing fragment into the siloxane ring. The hydrosilylation reaction was carried out in dry toluene under an inert atmosphere at room temperature. Product **12** was sufficiently pure and was used at the next stage without any purification. It should be noted that during the reaction only *β*-addition occurred which was confirmed by NMR. The trimethylsilyl protecting group was removed by stirring at room temperature in methanol with acetic acid. Thus, for the first time a hydroxyl-bearing *cis*-cyclotetrasiloxane **13** was prepared and characterized.

The final step of the synthesis of the star-shaped BODIPY-bearing siloxane fluorescent dye was Steglich esterification (Scheme 2). The reaction was carried out in dichloromethane at room temperature using dicyclohexylcarbodiimide (DCC) as condensing agent and 4-dimethylaminopyridine (DMAP) as catalyst. Product **14** was obtained in 48% yield and purified by silica column chromatography using toluene/ethylacetate (10:1) as eluent. It should be noted that during the reaction, isomerization of the siloxane ring with loss of the all-*cis* configuration takes place as evident from the ^{29}Si NMR spectrum (see ESI). Probably, isomerization of the all-*cis* compound is the result of DMAP base treatment. To verify this proposal we incubated *cis*-cyclotetrasiloxanolate **13** with DMAP and observed an analogous loss of the all-*cis* configuration. The obtained compounds were characterized by ^{1}H, ^{13}C, ^{19}F, ^{29}Si NMR, IR, MS and elemental analysis.

Spectral properties of the obtained mono-TMB ether **5** and tetra-TMB-siloxane **14** were studied in various solvents (Fig. 1). In the case of mono-TMB compound **5**, both absorbance and emission spectra showed a moderate hypsochromic shift upon increased solvent polarity (Table 1). The shape of the spectra did not vary upon solvent change and the molar extinction coefficient was constant, within the experimental error of determination. The quantum yield slightly changed from 0.85 to 0.95, which supported a lack of solvent quenching effect. Thus, there was no detectable specific interactions of the chromophore with the solvent. In the case of tetra-TMB siloxane **14**, the expected approximately fourfold molar extinction coefficient increase was detected, along with a moderate increase in the absorbance and emission bandwidths. The Stocks shift slightly increased in toluene, dichloromethane and tetrahydrofuran. A slight bathochromic shift and broadening of the fluorescence emission spectra could be explained by alterations in a solvate shell resulting from high density of intramolecular fluorophores in tetra-TMB-siloxane. There was a considerable change of the quantum yield, the most drastic decrease was observed in acetonitrile (up to 11-fold). Compared to other solvents, acetonitrile possesses the highest dielectric constant and dipole moment, followed by tetrahydrofuran and dichloromethane. The lowest reduction of the quantum yield was observed in toluene,



Scheme 2. Synthesis of star-shaped cyclotetrasiloxane with four terminal TMB fluorophores.

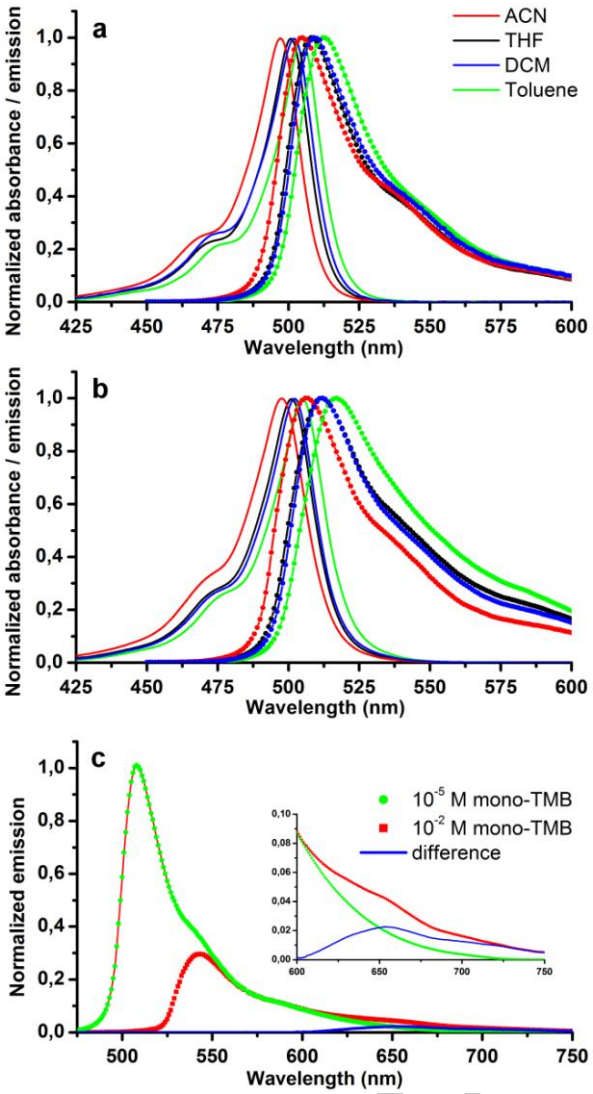


Figure 1. Normalized absorption (—) and fluorescence emission (-●-) spectra of mono-TMB **5** (a) and tetra-TMB cyclosiloxane **14** (b) in different solvents with fluorophore concentration 10^{-5} M. (c) Normalized emission spectra (at 570 nm) of mono-TMB **5** in THF at concentration 10^{-5} M (green ●), 10^{-2} M (red ■), full reconstructed spectrum of mono-TMB **5** at a concentration of 10^{-2} M (red —) and difference spectrum, which corresponds to excimer (blue —); insert shows magnification of 600-750 nm interval.

i.e. there was a correlation of QY with the dielectric constant and solvent polarity. Apparently, a quasi-concentration quenching takes place: in a polar solvent, TMB-groups attached by flexible spacers tend to move closer together to a distance equivalent to one at very high fluorophore concentrations. Generally, solvent properties have a significant influence on the formation of concentration-induced aggregates. To verify concentration-induced TMB interfluorophore aggregate formation, we prepared a solution of mono-TMB **5** in THF with a concentration of 10^{-2} M. The average distance between the fluorophores became close to that within tetra-TMB siloxane under these conditions. For spectra measurement we further used a 1 mm thin cuvette. In the absorption spectrum of the concentrated solution of mono-TMB **5** we observed off-scale readings of all bands and did not detect any new ones. In contrast, in the fluorescence emission spectrum we observed a new peak with a maximum at ~ 650 nm (Fig. 1c), that could be referred to excimer emission.[20, 21] We reconstructed the whole emission spectrum and estimated the QY of TMB in concentrated solution to be 47%, which was close to QY of tetra-TMB **14** in THF. In this way the formation of weakly fluorescent excimers can cause quenching of fluorescence both in a concentrated TMB solution and in tetra-TMB.

Thus, several BODIPY fluorophores combined together in a single molecule can exhibit considerable solvatochromism that is not characteristic for a single BODIPY molecule. Owing to a considerable brightness increase in nonpolar media and a fluorescence quenching effect in polar ones, TMB-siloxane conjugates can be used as microenvironment sensitive probes in real-time biomolecular imaging for monitoring biomolecular interactions with the cellular membrane and for the study of dynamic conformational transformations of biological molecules.[22] Another remarkable feature of tetra-TMB-siloxane **14** is its high solubility in organic solvents. Compared to the original TMB **5**, which is a crystalline powder, tetra-TMB **14** is an oil, which is readily mixed with organic solvents. Therefore, it is possible to generate TMB solutions of very high concentrations.

In summary, a fluorescent dye comprising of four BODIPY derivatives conjugated to the cyclotetrasiloxane core was synthesized. Analysis of the spectral properties of the dye showed that tetra-BODIPY cyclosiloxane remained fluorescent in low-polarity solvents, whereas in polar solvents, there was a considerable drop of the quantum yield due to intramolecular interactions of BODIPY chromophores. Compared to mono-BODIPY, the brightness of the dye in THF, DCM and toluene

Table 1. Spectral characteristics of mono-TMB **5** and tetra-TMB cyclosiloxane **14** in various solvents.

Compound	Solvent	λ_{max} abs (nm)	ε ($M^{-1}cm^{-1}$)	λ_{max} em (nm)	Φ_f (%)	$\Delta\lambda_{1/2}$[a] abs (cm^{-1})	$\Delta\lambda_{1/2}$[a] em (cm^{-1})	ε_a[b]	μ[c] (Db)
mono-TMB **5**	Toluene	505	79100	513	85	750	1190	2	0.36
	DCM	502	78300	509	94	800	1130	9	1.58
	THF	501	80200	508	95	760	1100	8	1.63
	ACN	497	75200	505	90	810	1220	38	3.2
tetra-TMB **14**	Toluene	505	337200	517	64	870	1730	2	0.36
	DCM	502	325200	512	50	840	1480	9	1.58
	THF	501	356000	512	49	880	1620	8	1.63
	ACN	498	300800	506	8	980	1480	38	3.2

[a] half-width of absorbance or emission peak.
[b] dielectric constant of solvent.
[c] dipole moment of solvent.

calculated per molecule was raised approximately 3 times due to a fourfold extinction increase and a moderate quantum yield decrease. Consequently, the TMB-siloxane conjugate may serve as a base structure in the design of compounds with high molar brightness, which is a prerequisite for single molecular spectroscopy[23] and in designing biomolecular fluorescent probes.[24] Further development of bright multichromophore BODIPY derivatives should be aimed at the minimization of aggregation induced fluorescence quenching.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/

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