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A Fluorinated Carbanionic Substituent for Improving Watersolubility and Lipophilicity of Fluorescent Dyes

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Abstract: Installation of a carbanionic substituent, that is strongly stabilised by two (trifluoromethyl)sulfonyl (Tf = SO_2CF_3) groups, into several fluorescence dyes including boron-dipyrromethenes (BODIPYs), fluoresceins, and aminocoumarins has been achieved by the 2,2-bis(triflyl)ethylation reaction of the dye frameworks with highly electrophilic Tf_2C=CH_2, followed by neutralisation with NaHCO_3. Despite the contradiction between water-solubility and lipophilicity, the carbanion-decorated dyes thus obtained showed significant enhancement of not only water-solubility but also lipophilicity. This work clearly demonstrates that the fluorinated, highly stabilised carbanionic substituent is a new option for controlling the macroscopic property of chemical materials.

Water-solubility (and aqueous solubility) is a key macroscopic property for chemical materials directed towards bio-relevant applications.^[1] The most common way to improve the water-solubility of less soluble compounds is introduction of ionic groups such as the sulfonato group into the molecular structure (Figure 1A). However, such ionic functionalities generally impair the lipophilicity of the compounds. Indeed, a strong correlation of water-solubility with lipophilicity parameters including log P_{olw} (an octan-1-ol/water-biphasic partition coefficient; where P_{olw} is a quotient of the concentrations of solute in each phase) has been demonstrated in a large set of compounds.^[2,3] In contrast, simple alkyl groups increase lipophilicity through reducing water-solubility and increasing liposolubility (Figure 1B).



Figure 1. Substituent-based Control of Water-solubility and Lipophilicity.

Although perfluoroalkyl groups usually make liposolubilitiv of the compounds lower (cf. poor solubility of fluorous compounds in organic solvents),^[4] structural decoration by such substituents enhances apparent lipophilicity of the compounds because lowering the water-solubility is more appreciable (Figure 1C). Such phenomenon implies that scientists still face with a problem on water-solubilisation methodology with keeping or enhancing lipophilicity.^[5] One of traditional approaches against this antinomy is the use of suitable hydrophobic linkers inserted between the hydrophilic functionalities and the core structure (Figure 1D).^[6] The linkers not only provide a chance to moderate the electronic and/or steric effects of the ionic groups on their molecular functions, but also, they relieve their substituent effects on the macroscopic properties of compounds. However, tiresome trial and error is necessary to discover compounds with the desired properties. Upon such background, we are interested in the use of a fluorinated carbanion as a novel substituent for water-solubilisation without impairing lipophilicity (Figure 1E). This idea may be outlandish because carbanions are, in most cases, reactive and strongly basic chemical species. However, recent progress on highly stable and isolable carbanion-containing salts motivated us.^[7,8] Among them, interor intramolecular salts bearing Tf_2C^- group(s), which is a chemically inert carbanionic substituent, were reported one after another.^[9] Utilisation of this carbanionic group is attractive in the context of controlling macroscopic properties because of its ionic character and trivalency of the carbon centre permitting to place a couple of triflyl groups and a linker to the functional moiety on it. During investigating water-solubilisation involving the carbanionic substituent, interesting observations were made regarding solubility and lipophilicity. Herein, we report that this fluorinated carbanionic substituent could serve as a new option for enhancing both water-solubility and lipophilicity.

Boron-dipyrromethene (BODIPY) constitutes an emerging class of heterocyclic scaffolds utilised for various applications including fluorescence bio-probes, which show sharp fluorescence emission spectra in several media, and photosensitisers for medical purposes.^[10] However, simple BODIPYs are insoluble in common aqueous solvents. Watersolubilisations of BODIPYs through the introduction of sulfonato group(s)^[11] or conjugation with water-soluble peptides, saccharides, and poly(oxyalkylene)s^[12] were examined. To investigate the effects of the fluorinated carbanionic substituent to the macroscopic properties of fluorescence dyes, we examined the reaction of BODIPY **2a** using 2-fluoropyridinium ethanide **1**,^[13,14] an effective reagent for in-situ generation of

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Scheme 1. Two-step synthesis of carbanion-decorated BODIPYs.



Scheme 2. Two-step decoration of fluorescein and aminocoumarin.

Tf₂C=CH₂ (Scheme 1).^[15] Fortunately, the reaction of **2a** with 2.1 equiv of 1 was quickly completed (<15 min) in acetonitrile at room temperature to give 2,6-dialkylated product 3a-H. Through neutralisation using NaHCO3, acid 3a-H was converted to sodium salt 3a-Na in 99% yield. Although the 1:1 reaction of 2a with 1 vielded a mixture of mono- and di-alkylated products, we failed to separate them despite various efforts including chromatographic methods. Similarly, more lipophilic 3,5dialkenyl-8-phenyl BODIPY 2b was converted to sodium salt 3b-Na in 95% overall yield. In contrast, all our efforts for the sulfonylation reaction of **2b** resulted in failure.^[11a,b] This two-step protocol to incorporate the carbanionic group was successfully applied to other classes of fluorescence dyes (Scheme 2). For example, fluorescein 4 was converted to sodium salt 5-Na in 89% yield. Likewise, blue fluorescent aminocoumarin 6 gave sodium salt 7-Na in 91% yield. The carbanion-decorated dyes 3a-Na, 3b-Na, 5-Na, and 7-Na, thus obtained, were easy-tohandle (non-fuming and non-hygroscopic) and could be stored for at least a few months in light-shielding vials without detectable decomposition.

Scheme 3 shows the scope of the BODIPY modification. High-yield incorporation of the carbon acid moiety at two positions (**3c**-j) and one position (**8a**-c) was attained by employing 2 equiv or 1 equiv of 2-fluoropyridinium salt **1**, respectively. It is noteworthy that the reactions of the 3,5,8-tri-



Scheme 3. 2,2-Bis(triflyl)ethylation reaction of BODIPYs.



Scheme 4. 2,2-Bis(triflyl)ethylation reaction of BODIPY dimer 9.

substituted BODIPYs selectively occurred at the 2,6-positions (3g-j). Moreover, several functionalities including ester (3e), carboxylic acid (3f), aldehyde (8b), and bromine atom (8c) were well tolerated during the reaction. Likewise, tri-acid 10 was obtained by the reaction of BODIPY dimer 9 with 3 equiv of 1 (Scheme 4).

Next, the photochemical and macroscopic properties were evaluated (Table 1 and Figure 2). BODIPY sodium salt 3a-Na showed the wavelength maxima of UV-Vis absorption and photoluminescence emission (PLE) bands ($^{abs}\lambda_{max}$ and $^{PLE}\lambda_{max}$) in EtOH at 519 and 541 nm, respectively (entry 1). These values were close to those of acid 3a-H (entry 2). Compared with 2,6unsubstituted BODIPY 2a (entry 3), both the UV-Vis absorption and PLE bands of 3a-Na were slightly red-shifted. In addition, in phosphate buffers, the PLE profile of 3a-Na was less sensitive to pH changes (Figure 2A and Supporting Information).^[16] These data suggest that protonated species of 3a-Na are negligibly minor components in slightly acidic buffers as well as EtOH. The electron-donating ability of the anionic CH₂C⁻Tf₂ group on the fluorophore was estimated to be similar in magnitude to that of the ethyl group in 11 (entry 1 vs. entry 4; also see, Figure 2B). The structural decoration of the BODIPYs by this substituent did not impair the fluorescence quantum yields Φ_{PLE} (entry 1 vs. entries 3 and 4) as well. These facts evidence that the benzylic methylene moiety separating the π system from a lone electron pair on the anionic carbon atom mitigated the electronic effects on the photophysical properties.



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Table 1. Photophysical Data, Water-solubility, and log D of PLE Dyes.[a]



Entry		$^{\mathrm{abs}}\lambda_{\mathrm{max}}$ (nm)	ε (M ⁻¹ cm ⁻¹)	$^{\text{PLE}}\lambda_{\text{max}}$ (nm)	Stokes shift (cm ⁻¹)	$arPhi_{PLE}$ [b]	Water-solubility (mg L ⁻¹)	log D ^[c]
1	3a-Na	519	74,400	541	784	0.77	>10,000	6.8
2	3a-H	518	84,400	540	787	0.76	300	7.6
3	2a	494	89,400	506	480	0.76	<1	4.1
4	11	517	81,000	536	686	0.77	<1	4.6
5 ^[d]	12	497	98,400	525	1,070	0.71	>10,000	-0.9
6 ^[e]	3a-Na	511	63,000	533	808	0.80		
7 ^[e]	12	491	87,800	519	1,100	0.76		
8 ^[f]	5-Na	518	87,800	541	821	0.47	>10,000	6.6
9 ^[f]	4	502	88,800	524	836	0.93	110	-1.2
10	7-Na	359	20,600	443	5,280	0.70	3,600	6.5
11	6	366	23,000	447	4,950	0.71	<1	2.5

[a] Measurements were conducted by using 5.0 x 10⁻⁶ mol L⁻¹ solutions for UV-Vis and 1.0 x 10⁻⁶ mol L⁻¹ solutions for fluorescence in EtOH, respectively. [b] Φ_{PLE} values were obtained by using a solution of rhodamine 6G in EtOH as a reference ($\Phi_{PLE} = 0.95$). [c] Calculated by distribution coefficient in a biphasic system prepared by MeCN / pH 7.4 phosphate buffer / octan-1-ol (25:25:4 v/v/v). See, ref. 17. [d] In MeOH. [e] In H₂O. [f] In 0.1 M NaOH (*aq.*).



Figure 2. (A) UV-Vis absorption and PLE spectra of **3a-Na** in pH 6.0-8.0 phosphate buffers. (B) PLE spectra of BODIPY derivatives in EtOH (1.0×10^{-6} mol L⁻¹ solutions) in EtOH. Due to poor solubility, the spectrum of **12** was measured in MeOH instead of EtOH. (C) PLE spectra of sodium salts **3a-Na**, **3b-Na**, **5-Na**, and **7-Na** in aqueous solvents.

Notably, the water-solubility (>10,000 mg L⁻¹) of carbaniondecorated BODIPY **3a-Na** was over 10,000 times greater than that of simple BODIPYs **2a** and **11** (<1 mg L⁻¹). Also, we found that the log *D* (distribution coefficient in an octan-1-ol/pH 7.4 phosphate buffer biphasic system) of **3a-Na** was 6.8 by applying Yanagida's protocol^[17] using a biphasic system containing acetonitrile, 0.1 M phosphate buffer, and octan-1-ol in a ratio of 25:25:4 v/v/v (see, SI). In contrast, a known water-soluble BODIPY **12**^[10a] bearing two sulfonato groups showed remarkable hydrophilic character with –0.9 of log *D* (entry 5). As shown in Figure 3, such a notable difference in the distribution

properties in the biphasic system containing acetonitrile was visible as a macroscopic phenomenon. Even in water, **3a-Na** showed a PLE band maximum of 533 nm with 0.80 of Φ_{PLE} (entries 6 and 7). Similar substituent effects by the carbanionic substituent towards water-solubility and log *D* were observed not only in the series of BODIPYs but also in fluorescein and aminocoumarin dyes (entries 8–11). That is, **5-Na** and **7-Na** showed significant enhancement of lipophilicity as well as water-solubility. These results evidence a wide range of generality in the present water-solubilisation with enhancement of lipophilicity by the highly fluorinated carbanionic substituent. As a result, we



Figure 3. Distribution of BODIPY Derivatives in a Biphasic System Containing Acetonitrile, pH 7.4 Phosphate Buffer, and Octan-1-ol (25:25:4 v/v/v). Upper layers are organic phases and lower layers are aqueous phases. (A) Carbanion-decorated BODIPY **3a-Na**, (B) 2,6-unsubstituted BODIPY **2a**, (C) 2,6-disulfonato-BODIPY **12**, (D) Solubility of **3a-Na** in pH 7.4 phosphate buffer. Red crystals of **2a** float on the aqueous phase.

successfully developed several PLE dyes, which can accommodate a wide range of PLE wavelengths (Figure 2C). The effective charge-dispersion nature and steric bulkiness of the carbanion moiety by two triflyl groups^[15a,18] allow to give a molecular interpretation on such macroscopic properties. The carbanionic substituent can make relatively weak, but still effective hydrogen bonds with water molecules in aqueous solutions. In the solid phase, such properties might contribute to reducing the lattice energy. Therefore, the carbanion-decorated compounds exhibit a considerable level of water-solubility. However, considering that hydrogen bond acceptor ability of the carbanion moiety should be weaker than those of common anionic groups including the sulfonato group, it is not surprising that this event also contributed to the thermodynamic distribution property in the biphasic system. That is, the carbaniondecorated dyes favourably distributed in the organic phase, likely because of the insufficient stabilisation by hydration in the aqueous phase in addition to the hydrophobic character endowed by the CF₃ moieties in the triflyl group positioned outside of the molecular structure.

To reveal the electronic effects of the carbon-acidic and carbanionic substituents on the π -system of the boradiazaindacene framework, we computed the molecular orbitals and energies of acid **3a-H**, mono-carbanion [**3a**]⁻, and dicarbanion [**3a**]²⁻ using time-dependent density functional theory (TD-DFT) with the B3LYP functional^[19] and the cc-pVTZ basis set (see, SI).^[20] The HOMO/LUMO shapes of acid **3-H** itself and its ionised derivatives [**3a**]⁻ and [**3a**]²⁻ were similar to those of 2,6-unsubstituted BODIPY **2a**. Although both HOMO and LUMO

levels increased by raising negative charge, the energy gaps between HOMO and LUMO of them were in a narrow range from 2.92 eV to 3.07 eV. Likewise, the HOMO/LUMO gap of **2a** was 3.07 eV. These results were consistent with the observed experimental photochemical signatures of BODIPY derivatives.

In conclusion, we developed a unique water-solubilisation method for hydrophobic BODIPY derivatives through incorporating the fluorinated carbanionic group. This protocol was successfully applied to other fluorescence dyes including fluorescein and aminocoumarin derivatives. Although this substituent did not impair the photophysical properties of the parent fluorophores, the macroscopic properties of the compounds were dramatically affected. That is, the enhancement of both their water-solubility and lipophilicity was observed. As the incorporation of conventional ionic substituents reduced the lipophilicity, the present group may be regarded as a new candidate to tune the macroscopic properties.

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Fluorinated carbanionic substituent enhanced both water-solubility and lipophilicity of organic fluorescence dyes, including BODIPYs, fluorescein, and aminocoumarin, without impairing the photophysical properties of the parent fluorophores. Considering that incorporation of conventional ionic substituents reduces the lipophilicity, the present carbanion structure is a new and promising candidate to tune such macroscopic properties.