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4-(*N*,*N*-Dimethylamine)benzonitrile (DMABN) derivatives with boronic acid and boronate groups: new fluorescent sensors for saccharides and fluoride ion†

Wei Tan, Deqing Zhang,* Zhuo Wang, Caiming Liu and Daoben Zhu*

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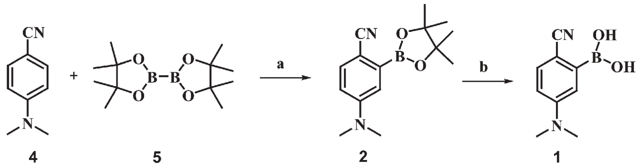
Two DMABN derivatives with boronic acid/boronate groups **1** and **2** were designed and synthesized for sensing saccharides and F^-, respectively. Fluorescent spectral changes were observed for **1** after reaction with fructose, galactose, mannose and glucose, and the corresponding binding constants were estimated. The results show that compound **1** can bind fructose more strongly than other saccharides tested. Interestingly, both absorption and fluorescence spectral changes occurred for compound **2** after addition of F^-, indicating that compound **2** is a potentially selective sensor for F^-.

Introduction

4-(*N*,*N*-Dimethylamino)benzonitrile (DMABN) and its derivatives represent a class of organic donor–acceptor compounds that exhibit dual fluorescence, one related to the local excited state ("B" band) and the other ascribed to the twisted intramolecular charge-transfer (TICT) state ("A" band).[1] Since the first observation by Lippert *et al.*,[1a] the phenomenon of dual fluorescence for DMABN has led to numerous studies of the TICT mechanism.[2,3] These results indicated that the dual fluorescence behavior is influenced by the substituents incorporated into the benzene ring of DMABN. However, to the best of our knowledge, DMABN has seldom been employed as the fluorophore in the design of new chemical sensors.[3j–k]

Boronic acid is known to bind with saccharides *via* covalent interactions to form the corresponding boronate; furthermore, the electron accepting ability of boronate is enhanced compared to boronic acid.[4] A number of saccharide sensors have been described based on boronic acid.[5] For instance, Shinkai *et al.*[6] and James *et al.*[7] have reported a series of three-component saccharide sensors based on the photoinduced electron transfer (PET) mechanism: a fluorophore, an amine group and a boronic acid group. More recently, Wang *et al.*[8] have designed saccharide sensors also featuring boronic acid groups by employing an intramolecular charge-transfer (ICT) mechanism. We have recently reported a new saccharide sensor combining the tetrathiafulvalene–anthracene dyad with a boronic acid group.[9] In addition, the boronate is able to bind F^- strongly to generate the corresponding boronate anion with sp^3 configuration, and consequently the electron accepting ability would be largely reduced.[10] In this context, several selective fluorescent sensors for F^- containing a boryl moiety have been reported.



Scheme 1 Synthesis of **2** and **1**: (a) $[Ir(OMe)(COD)]_2$, dtbpy, THF, 60%; (b) acetone–H_2O, HCl (12 M), 30%.

These considerations lead us to design a new DMABN derivative **1** (Scheme 1) by incorporating a boronic acid group into DMABN, aiming at developing new saccharide sensors. Alternatively, compound **2** (Scheme 1), the precursor to compound **1**, is expected to be able to detect F^- selectively. The design rationale is described as follows: in comparison with DMABN, compound **1** possesses one boronic acid group as an additional electron acceptor unit in **1**. As reported previously, the boronic acid can bind saccharides and transform into the corresponding boronate, which shows enhanced electron accepting ability. Consequently, the intramolecular charge-transfer extent in **1** would be altered after the binding of the boronic acid group with saccharides. Therefore, it is anticipated that the fluorescence spectrum of **1** would be changed accordingly. Similarly, the absorption and fluorescence spectral variation is expected for compound **2** after the binding of the boronate group with F^-, since the electron accepting ability of the boryl moiety would greatly decrease, as discussed above.

In this paper, we will report the synthesis of compound **1** and crystal structure of compound **2**,‡ the fluorescent spectral variation of **1** after binding with saccharides, and both the absorption and fluorescent spectral changes of **2** in the presence of F^-. The results show that compounds **1** and **2** can function as new fluorescent sensors for fructose and F^-, respectively.

Beijing National Laboratory for Molecular Sciences, Organic Solids Laboratory, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, China. E-mail: dqzhang@iccas.ac.cn

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‡ CCDC reference number 629770. For crystallographic data in CIF format see DOI: 10.1039/b618183j

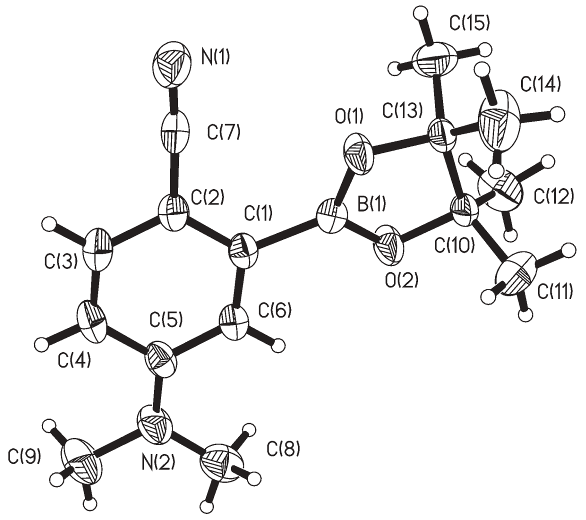

Fig. 1 The ORTEP diagram for compound **2**; thermal ellipsoids are 30% probability.

Results and discussion

Synthesis of compound 1 and crystal structure of compound 2

Compound **2** was synthesized according to the reported procedure, by borylation of DMABN with $[Ir(OMe)(COD)]_2$ as the catalyst.[11] Compound **1** was obtained through deprotection of compound **2** in a mixture of acetone and aqueous HCl in 30% yield after purification in a silica gel column.

Crystals of compound **2** suitable for single crystal structural analysis were successfully grown, and its structure was determined.‡[12] Fig. 1 shows the molecular structure of **2**, and all the bond lengths and angles are in the normal range. The benzene, dimethylamine and cyano moieties are almost co-planar. Also, the benzene ring forms a small dihedral angle of 14.7° with the plane defined by B1–O1–O2.

Fluorescent spectra of 1 after binding with saccharides

Fig. 2 shows the fluorescence spectrum of **1** and those in the presence of different concentration of fructose. Unlike DMABN, only one broad emission band centered at 393 nm was observed for **1**. This was probably due to the introduction of the boronic acid group, which would enhance the intramolecular charge transfer extent. As shown in Fig. 2, the fluorescence intensity of **1** decreased after reaction with fructose. The fluorescence quantum yield of **1** in THF–H_2O (1 : 1 v/v)[13] buffer containing 0.033 M phosphate (pH 7.3) was reduced from 0.36 in the absence of fructose to 0.11 in the presence of 10 mM of fructose.[14] Interestingly, the decrease of fluorescence intensity at 393 nm was accompanied by the appearance of two broad emission bands around 334 and 505 nm. The variation of the fluorescence spectrum of **1** may be understood as follows: the binding of the boronic acid group in **1** with fructose led to the transformation into the corresponding fructose boronate which is bulky and has enhanced electron accepting ability. Such structural variation would alter the behavior of **1** in the excited state, and result in the observed fluorescent spectral change after reaction with fructose.

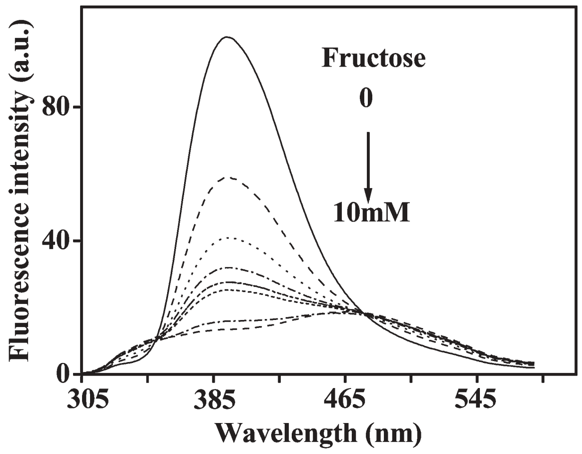

Fig. 2 Fluorescence spectrum of **1** (5.0×10^{-5} M) and those in the presence of different concentrations of D-fructose (0–50 mM) at pH 7.3 adjusted by 0.033 M phosphate buffer in THF–H_2O (1 : 1, v/v); the excited wavelength is 295 nm.

The fluorescence spectra of **1** containing fructose (10 mM) were measured in solutions of different pH values. As shown in Fig. 3, where the plot of the relative fluorescence intensity (393 nm) *vs.* the pH value is displayed, a large fluorescence intensity change occurred in the pH range of 6.0–7.6 for **1** after reaction with fructose.

The fluorescence spectra of **1** were also measured after reactions with other saccharides such as galactose, mannose and glucose at pH 7.3 adjusted by 0.033 M phosphate buffer in THF–H_2O (1 : 1, v/v). Similar spectral variation was observed. Fig. 4 shows the variation of the fluorescence intensity at 393 nm *vs.* the concentration of saccharides. Among the four saccharides tested, the largest fluorescence intensity variation occurred with **1** after reaction with fructose. Based on the data shown in Fig. 4, the apparent association constants (K_a) between **1** and these four saccharides were estimated assuming the formation of a 1 : 1 complex.[15] The affinity of **1** with these

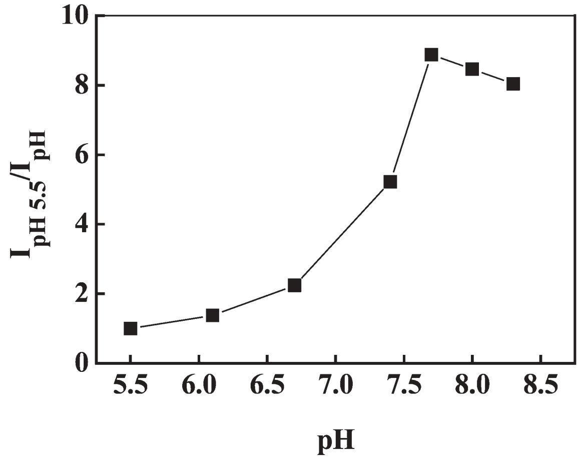

Fig. 3 Relative fluorescence intensity profiles *vs.* pH for **1** in the presence of fructose (10 mM) in THF–H_2O (1 : 1, v/v) adjusted by 0.033 M phosphate buffer; $I_{pH\ 5.5}$ is the fluorescence intensity of **1** at pH = 5.5; λ_{ex} = 295 nm.

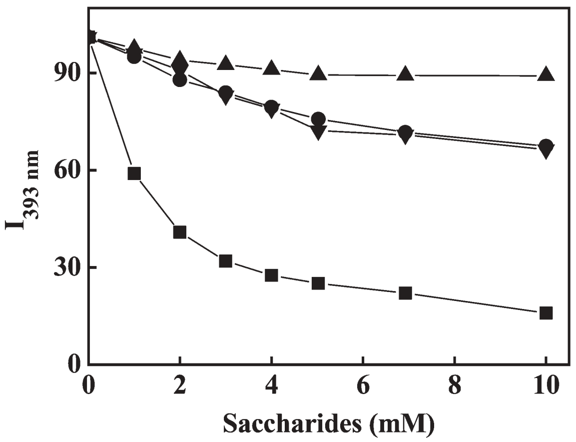

Fig. 4 Variation of the fluorescence intensity at 393 nm *vs.* the concentrations of D-fructose (■), D-galactose (▼), D-mannose (●), D-glucose (▲); the fluorescence spectra of **1** (5.0×10^{-5} M) were recorded at pH 7.3 adjusted by 0.033 M phosphate buffer in THF–H_2O (1 : 1, v/v); the excitation wavelength was 295 nm.

four saccharides followed the order: fructose > galactose > mannose > glucose (see Table 1). The association constants between **1** and these four saccharides are larger than those of phenylboronic acid with the four saccharides.[4]

Fluorescence spectra of 2 after binding with F⁻

As discussed above, F^- can bind boronate to generate the corresponding boronate ion with sp^3 configuration, and concomitantly the electron-accepting ability of boronate would be significantly diminished. Therefore, it is anticipated that both the absorption and fluorescence spectra of **2** would be altered after binding with F^-. Fig. 5 shows the absorption spectra of **2** in the presence of different amounts of F^-. The absorption bands in the range of 270–320 nm were blue-shifted by *ca.* 10 nm after 1.2 eq. of F^- was added to the solution. This may be well understood by considering the fact that the electron accepting ability of the boronate group would be largely reduced after binding with F^- and as a result the intramolecular charge transfer extent would decrease accordingly. The inset of Fig. 5 displays the plot of the variation of the absorption intensity at 285 nm *vs.* the molar ratio between F^- and **2**. The result indicates that the reaction stoichiometry between **2** and F^- is *ca.* 1 : 1. Based on the absorption variation, the binding constant of **2** with F^- was estimated to be $(3.4 \pm 0.2) \times 10^5$ M^{-1} in THF.[16]

Table 1 Association constants (K_a) and maximal fluorescence intensity changes (I/I_0) of **1** at 334 and 393 nm with four saccharides[15]

Sugar	K_a/M^{-1}	I/I_0 (0.01 M) 334 nm	I/I_0 (0.01 M) 393 nm	$\Delta I_{334\ nm}/\Delta I_{393\ nm}$
Fructose	794 ± 11	2.17	0.13	16.7
Galactose	149 ± 5.5	1.3	0.66	1.97
Mannose	118 ± 2.7	1.0	0.67	1.49
Glucose	40.3 ± 0.9	0.6	0.88	0.68

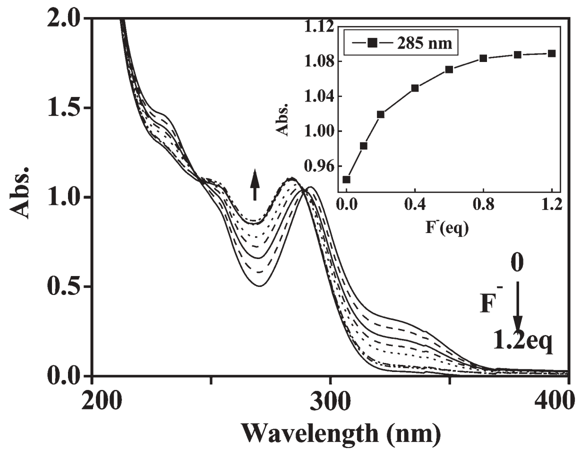

Fig. 5 UV/vis spectra of **2** (5.0×10^{-5} M) in the presence of different amounts of F^- in THF; inset shows the plot of the variation of the absorption intensity at 285 nm *vs.* the molar ratio between F^- and **2**.

Fluorescence spectral changes also occurred with **2** after addition of F^- (Fig. 6). The fluorescence quantum yield of **2** was reduced from 0.32 in the absence of F^- to 0.092 in the presence of 1.6 eq. of F^- in THF.[14] The emission band around 402 nm became gradually weaker, while a new emission band around 343 nm appeared, the intensity of which increased upon addition of F^-. Thus, ratiometric fluorescence intensity changes were observed for **2** after addition of F^-. The inset of Fig. 6 displays the variation of the fluorescence intensities at 343 and 402 nm *vs.* the concentration of F^-. Interestingly, almost linear relations were observed for the plots I_{402} and I_{343} *vs.* the concentration of F^-. Similar fluorescence spectral changes were also detected for **2** in other solvents, such as DMF, when F^- was introduced (see Fig. 7). It should be noted that no absorption and fluorescent spectral changes were detected for **2** when other halogen anions such as Cl^-, Br^- and I^- were added. These results indicated that compound **2** can be employed as a selective sensor for F^-.

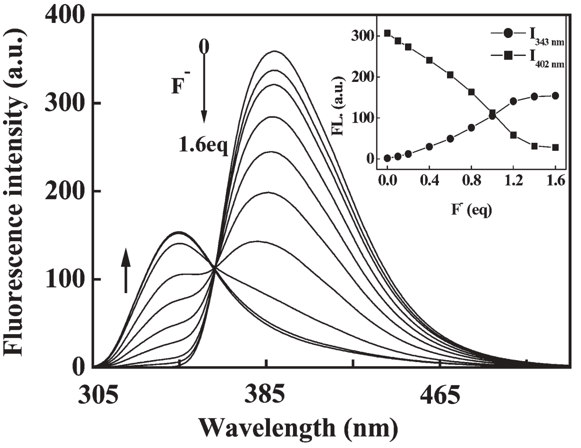

Fig. 6 Fluorescence spectra of **2** (5.0×10^{-5} M) in the presence of different amounts of F^- in THF; inset shows the variation of the fluorescence intensity at 343 (●) and 402 nm (■) *vs.* the concentration of F^-; λ_{ex} = 295 nm.

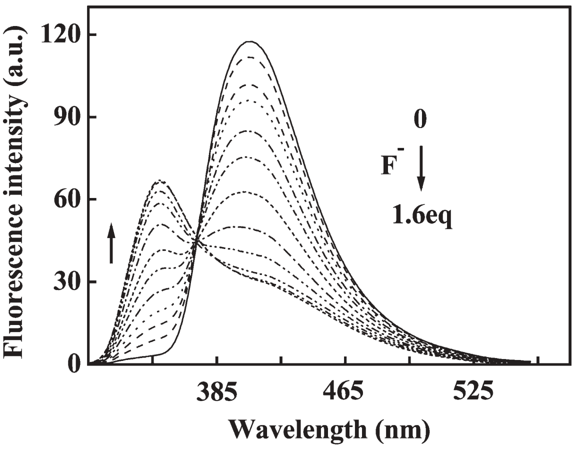

Fig. 7 Fluorescence spectra of **2** (5.0×10^{-5} M) in the presence of different amounts of F^- in DMF; $\lambda_{ex} = 295$ nm.

Summary

By coupling the features of DMABN and boronic acid (and boronate), compounds **1** and **2** were designed and synthesized for sensing saccharides and F^-. Fluorescent spectral changes were observed for **1** after reaction with fructose, galactose, mannose and glucose, and the corresponding binding constants were estimated. The results show that compound **1** can bind fructose more strongly than other saccharides tested. Interestingly, both absorption and fluorescence spectral changes occurred for compound **2** after addition of F^-, but not with Cl^-, Br^- or I^-. These results indicate that compound **2** is a potentially selective sensor for F^-.

Experimental

General

Melting points were measured with an XT4-100X microscope apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on BRUCK300 MHz and BRUCK400 MHz instruments. EI-MS was determined with AEI-MS 50. ESI-MS spectra were determined with LCMS-2010 instruments. Fluorescence spectra were recorded on a JASCO FP6000 spectrofluorometer in a 1-cm quartz cell. Absorption spectra were recorded on JASCO V-570 UV/VIS/NIR spectrometer. Column chromatography was performed with silica gel (200–300 mesh). THF was distilled from Na and benzophenone before use.

Compound **2** was prepared according to the reported procedure as a white solid (yield 66%).[11] Single crystals of **2** were obtained by recrystallization from CH_2Cl_2–cyclohexane.‡

Compound 1

To the solution of compound **2** (100 mg, 1.2 mmol) in acetone–water (9 : 1) (3 ml) a drop of 12 M HCl was added, and the mixture solution was stirred at room temperature for 4 h. After evaporation of solvent, the mixture was dissolved in CH_2Cl_2 (10 ml), followed by washing with 5% $NaHCO_3$ (2×5 ml). Then, the organic solution was dried over Na_2SO_4. The crude product was purified on a silica gel column with CH_2Cl_2–MeOH (40 : 1) as the eluants, to give **1** as a white powder (21 mg, 30%): mp 226–227 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ =3.07 (s, 6H), 6.72 (dd, J = 8.7, 2.4 Hz, 1 H), 7.29 (d, J = 2.6 Hz, 1 H), 7.52 (d, J = 8.7 Hz, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 40.1, 101.8, 109.0, 112.3, 120.6, 123.0, 135.1, 152.0; ESI-MS: 191.2 (M^+); HRMS (ESI): calcd for ($C_9H_{11}BN_2O_2\cdot 2NBA\cdot 2H_2O$): 460.1554; found: 460.1577.

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12 Crystal data: $C_{15}H_{21}BN_2O_2$, M = 272.15, orthorhombic, $P2(1)2(1)2(1)$, a = 7.3178(14) Å, b = 10.551(2) Å, c = 20.587(4) Å, V = 1589.5(5) Å^3, Z = 4, D_c = 1.137 g cm^{-3}; $F(000)$ = 584, μ(Mo Kα) = 0.075 mm^{-1}. 8938 reflections of which 1637 are unique (R_{int} = 0.0490) were collected to a θ limit of 1.98–25.05° on a Bruker CCD instrument at 296(2) K. The structure was solved by direct methods and refined by a least-squares matrix method. The final cycle of full-matrix least-square refinement was based on 1637 observed reflections [$I > 2\sigma(I)$] and 183 variable parameters and converged to $R1$ = 0.0701, $wR2$ = 0.1570 (R indices for all data: $R1$ = 0.0900, $wR2$ = 0.1682), $GooF$ = 1.094‡.

13 Since compound **1** shows rather low solubility in water, a mixture of THF–H_2O was used for the spectroscopic measurement. Replacing the two methyl groups of **1** with ionic groups may afford the analogue of **1** which can be dissolved in water.

14 The quantum yields were measured by standard technique by using 9,10-diphenylanthracene as a reference compound.

15 The association constants were estimated based on the variation of fluorescence intensity at 393 nm upon binding with saccharides by following the procedure reported previously: Y. Nagai, K. Kobayashi, H. Toi and Y. Aoyama, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 2965–2971.

16 The binding constant was estimated based on the absorbance variation at 285 nm by employing the Benesi–Hildebrand equation: H. Benesi and J. H. Hildebrand, *J. Am. Chem. Soc.*, 1949, **71**, 2703–2707.