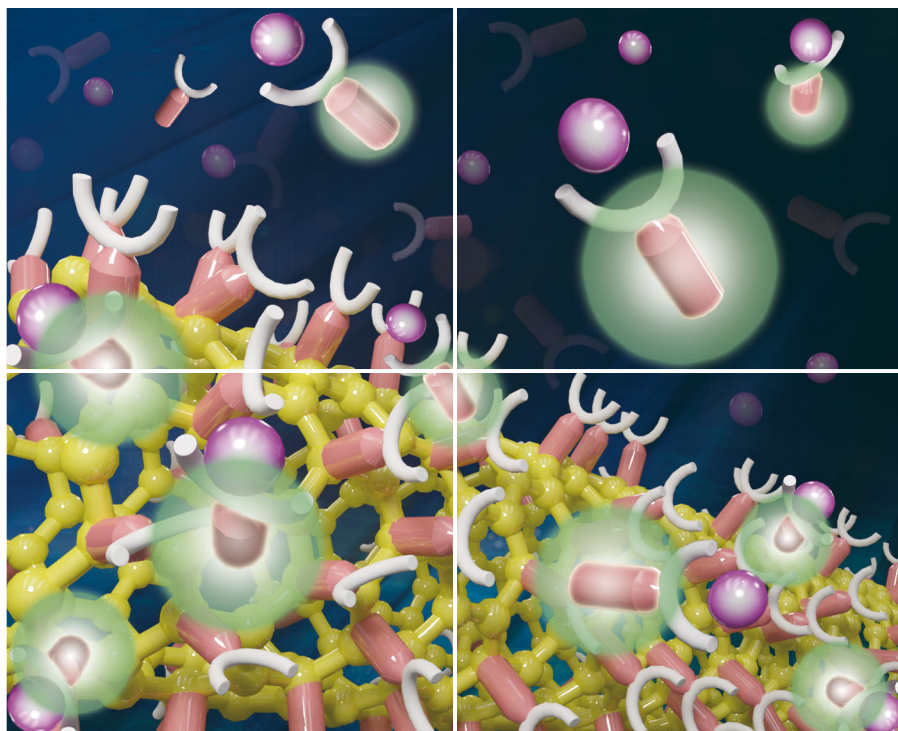




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Low-dimensional materials facilitate the conjugation between fluorogenic boronic acids and saccharides†

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Here we demonstrate that low-dimensional materials (LDMs) enhance the conjugation between fluorogenic boronic acids (BAs) and saccharides. Among the LDMs investigated, 1D carbon nanotubes significantly lower the limit of detection and enhance the binding of the BA with D-fructose.

The development of synthetic receptors capable of imitating the active sites of natural biological receptors are of particular interest in the advancement of sensor development.^{1–6} Fluorophore-tagged boronic acids (fluorogenic BAs) are artificial receptors that are synthesized extensively for sensing biologically important diols such as saccharides, glyco/glycated proteins and dopamine by fluorescence and electrochemical techniques.^{7–11} In addition, many other types of BAs have been developed for building polymeric materials, separation systems and imaging probes.^{9–11} However, due to the moderate affinity in forming cyclic boronate esters with diols, the sensitivity of BAs for complex saccharides remains unsatisfactory.

With the rapid advancement of materials science and technology, a number of new functional materials have been produced over the past few decades. Among them the low-dimensional materials (LDMs) including the one-dimensional (1D) carbon nanotube (CNT), the 2D graphene and 2D graphene analogues have been the most attractive because of their exceptional optical, electronic and mechanical properties. Recently there has been an emerging trend to employ these LDMs (especially graphene oxide [GO] with good water solubility and biocompatibility) for biomedical applications.^{12–19} While, graphene analogues such as 2D transition metal dichalcogenides and oxides have also been shown to be useful in the construction of biosensors, drug

delivering platforms and theranostic materials.^{12–19} We have shown in a recent study the possibility of constructing a BA/GO composite material for sensing saccharides.²⁰ Here we demonstrate that the presence of a proper amount of LDMs can enhance fluorogenic BA–saccharide conjugation.

Two fluorophore-tagged phenylboronic acids (**BA1**²⁰ and **BA2**) were synthesized (Fig. 1). We employed typical donor– π –acceptor (D– π –A)²¹ chromophores, 1,8-naphthalimide and dicyanomethylene-4H-pyran (DCM), to couple with BA for the construction of the fluorogenic probes (Scheme S1, ESI†). Herein, we demonstrate

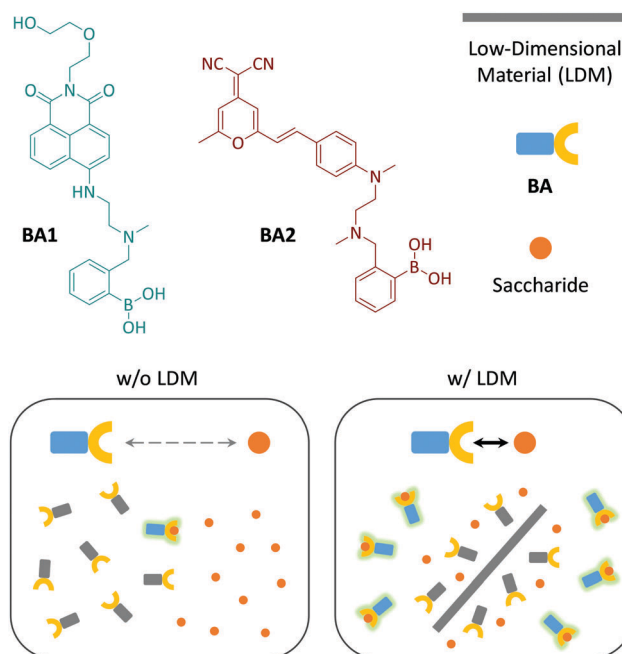


Fig. 1 Structures of the fluorogenic boronic acids (**BA1** and **BA2**) used in this study and schematic illustration of the low-dimensional material (LDM) enhanced conjugation between BA and saccharides.

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that the fluorescence emission produced as a result of the BA-saccharide conjugation is enhanced in the presence of a small amount of LDMs including: 1D CNT, 2D GO, 2D molybdenum disulphide (MoS_2) and 2D manganese dioxide (MnO_2).

The carbon materials (single-walled CNT and GO) were purchased and the 2D MoS_2 ²⁴ and 2D MnO_2 ²⁵ prepared according to previous reports. The LDMs were characterized using transmission electron microscopy (TEM), dynamic light scattering (DLS), Raman spectroscopy and UV-vis spectroscopy. While tube-like objects were observed for CNT, GO appeared to be flakes of atomic-thickness (Fig. 2a). Meanwhile, thin-layer sheets were observed for 2D MoS_2 and 2D MnO_2 (Fig. 2a), and the morphology is in agreement with those observed in previous reports.^{24,25} DLS indicates that 2D GO and 2D MoS_2 have a similar size distribution, whereas the particle size of 1D CNT was larger and that of 2D MnO_2 , and was slightly smaller than GO (Fig. 2b).

While typical absorbance peaks were observed for the LDMs (272 nm for 1D CNT,²⁶ 230 nm for GO,²⁷ 687/617 nm for 2D MoS_2 ,²⁴ and 370 nm for 2D MnO_2 ²⁵) (Fig. S1, ESI[†]), Raman spectroscopy also suggests the formation of the LDMs (Fig. S2, ESI[†]). For example, in-plane stretching of sp^2 -carbon atoms (G band) were observed for the LDM carbon materials (1593 cm^{-1} for CNT and 1604 cm^{-1} for GO).²⁸ The E_{12g} and A_{1g} vibration modes corresponded to the in-plane (382.6 cm^{-1}) and out-of-plane (406.6 cm^{-1}) vibrations of Mo and S atoms, proving the formation of thin-layer MoS_2 sheets.²⁹ In addition, a specific

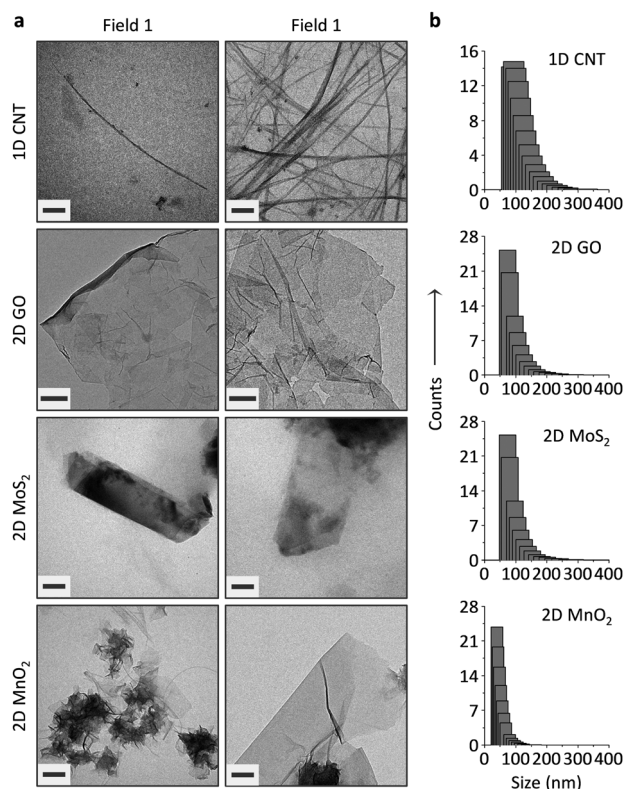


Fig. 2 (a) Transmission electron microscopy (scale bar: 200 nm) and (b) dynamic light scattering of low-dimensional materials including 1D carbon nanotube (CNT, $0.5\text{ }\mu\text{g mL}^{-1}$), 2D graphene oxide (GO, $3\text{ }\mu\text{g mL}^{-1}$), molybdenum disulphide (MoS_2 , $0.45\text{ }\mu\text{g mL}^{-1}$) and manganese dioxide (MnO_2 , $2\text{ }\mu\text{g mL}^{-1}$).

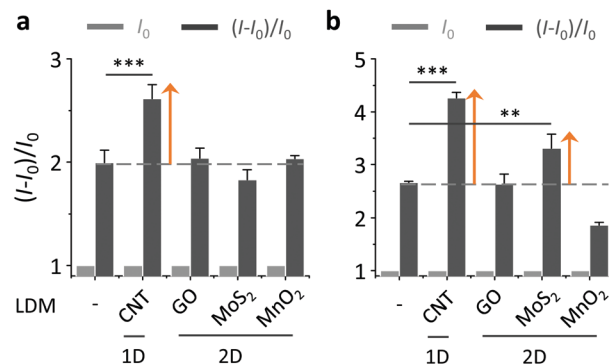


Fig. 3 Fluorescence enhancement of (a) BA1 ($20\text{ }\mu\text{M}$) and (b) BA2 ($20\text{ }\mu\text{M}$) with D-fructose (30 mM) in the absence (–) and presence of a low-dimensional material (LDM) including carbon nanotube (CNT, 1.25 and $0.8\text{ }\mu\text{g mL}^{-1}$ for BA1 and BA2, respectively), graphene oxide (GO, 0.625 and $0.6\text{ }\mu\text{g mL}^{-1}$ for BA1 and BA2, respectively), molybdenum disulphide (MoS_2 , 2.5 and $10\text{ }\mu\text{g mL}^{-1}$ for BA1 and BA2, respectively) and manganese dioxide (MnO_2 , 2.5 and $2.0\text{ }\mu\text{g mL}^{-1}$ for BA1 and BA2, respectively) in Tris-HCl (0.01 M , pH 7.4) (** $P < 0.001$; ** $P < 0.05$; two-tail P values were calculated by GraphPad software). Excitation wavelength: 450 and 470 nm for BA1 and BA2, respectively.

fingerprint of the Mn–O vibration in the MnO_2 framework was observed at 572 cm^{-1} .³⁰

With the LDMs prepared, we then evaluated their ability to enhance the BA-saccharide conjugation (Fig. 3). As expected, we first determined that the fluorescence of both BA1 and BA2 increased in a concentration-dependent manner with D-fructose (fru) in a Tris-HCl buffer (Fig. S3, ESI[†]).²⁰ A blue shift was observed for BA2 after conjugation with D-fructose. DCM has a typical D- π -A structure with a broad absorbance band because of an intramolecular charge transfer (ICT) process, therefore saccharide conjugation could compromise the planarity due to enlarged steric demand, resulting in a blue-shifted emission spectrum.²¹ Subsequently, with their initial fluorescence (I_0) normalized, we tested the fluorescence enhancement $[(I - I_0)/I_0]$ of the BAs with or without LDMs. Interestingly, we determined that the presence of 1D CNT rather than other 2D LDMs led to an additional fluorescence enhancement of BA1 with fru (with respect to BA1 with fru alone) (Fig. 3a). In contrast, the additional fluorescence enhancement was produced by both 1D CNT and 2D MoS_2 for the conjugation between BA2 and fru (Fig. 3b).

Subsequently, we investigated the effect of loading concentration with LDMs towards the BA-fructose conjugates. We calculated the limit of detection (LOD) for the fluorogenic BAs with D-fructose ($3\sigma/k$). The LODs of BA1 and BA2 in the absence and presence of the different LDMs are shown in Fig. 4. With low concentrations of CNT the LOD of BA1 for D-fructose was lowered (which means an improved sensitivity). Likewise the LOD of BA2 for D-fructose could also be lowered when using low concentrations of CNT and 2D MoS_2 . However, a further increase of the material loading reduces the sensitivity. According to our previous study,^{20a} we also determined that the fluorescence of both BAs decreased in a concentration-dependent manner with the LDMs and that the quenched

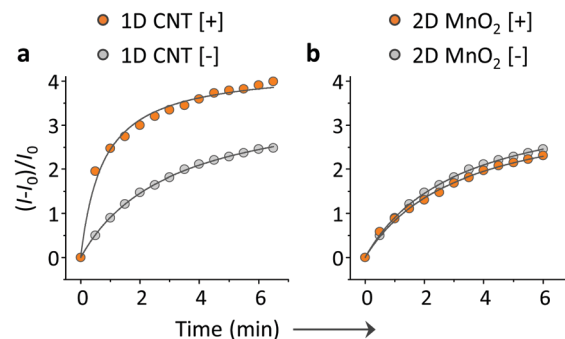


Fig. 5 Plotting the fluorescence enhancement of **BA2** (20 μM) with D-fructose (40 mM) in the absence and presence of (a) carbon nanotube (CNT, 1 $\mu\text{g mL}^{-1}$) and (b) (MnO_2 , 1.25 $\mu\text{g mL}^{-1}$) as a function of time in Tris-HCl (0.01 M, pH 7.4). Excitation wavelength: 470 nm.

a

BA1/
1D CNT

$(I-I_0)/I_0$

Fru Gal Glc Man Lac Mal

b

BA2/
1D CNT

Fru Gal Glc Man Lac Mal

Fig. 6 Fluorescence enhancement of (a) **BA1** (20 μM) with carbon nanotube (CNT, 1.25 $\mu\text{g mL}^{-1}$) and (b) **BA2** (20 μM) with carbon nanotube (CNT, 1 $\mu\text{g mL}^{-1}$) in the presence of different saccharides (Fru = D-fructose; Gal = D-galactose; Glc = D-glucose; Man = D-mannose; Lac = D-lactose; Mal = D-maltose) (30 mM) in Tris-HCl (0.01 M, pH 7.4). Excitation wavelength: 450 and 470 nm for **BA1** and **BA2**, respectively.

To conclude, we have demonstrated, for the first time that BA-saccharide conjugation can be improved by LDMs when loaded at an appropriate concentration. This unique feature of LDMs enables the development of other types of BA/LDM composite materials with enhanced diol binding properties for a wide range of biomedical applications.

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