Communication to the Editor

Fluorescent-Oxaboroles: Synthesis and Optical Property by Sugar Recognition

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The optical property of fluorescent unit-conjugated aliphatic oxaboroles has been investigated. The oxaboroles provide good fluorescence quantum yields and selective recognition toward D-ribose and D-ribose containing molecules. The molecular recognition induced significant fluorescence quenching. The property of the boroles showed the possibility of the boron-based nicotinamide adenine dinucleotide (NAD) sensor probe.

Key words oxaborole, recognition, nucleic acid, photoquenching

Introduction

Organoboron-diol recognition is highly specific, reversible, but robust and formable even in physiological environments.1,2) This property has been studied for decades and applied in various fields, as bioactive molecules,3) chemosensors,4) supermolecular components,4,5) and bio-imaging tools.2) In particular, saccharides are vital polyol molecules involved in antigen-antibody reactions, cell differentiation, immunity, morphological maintenance/protection within organisms.6,7) Thus, the selective polyol including sugar recognition under physiological conditions leads to drug therapy,8) the fostering of cellular uptake,9,10) and the imaging of the biological events.11) In this context, the polyol-affinity property of aryl boronic acids has been harnessed as the recognition tool and used to develop numerous chemical sugar-sensors (Fig. 1A).

Results

Notably, cyclic aryl boronic acid, benzoxaboroles, emerged as an excellent recognition unit because of the polyol-affinity based on the high Lewis acidity.12) Some of them have been approved as the drugs, Crisaborole,13) and Tavaborole.14) We recently designed 5-membered ring aliphatic oxaboroles and found their high diol-recognition ability involving Alizarin Red S (ARS) comparable to benzoxaborole15) (Fig. 1B). Aliphatic oxaboroles allowed the attachment of molecular functionality adjacent to the boron center, such as the construction of the chiral environment. Herein, we report the synthesis of oxaboroles bearing the fluorescent unit and optical property behavior by sugar-recognition. The oxaboroles enabled selective recognition of D-ribose, the component of RNA, concomitant with observing the significant quenching of fluorescence by the complexation to borate form which can be expected as a boron-based oxidized form of nicotinamide adenine dinucleotide (NAD +) imaging probe16) (Fig. 1C).

We have begun to synthesize a variety of oxaboroles originally developed two synthetic pathways (Fig. 2). Both routes pass through the common building block, gem-aryl boryl(E)-acrylate derivatives via phosphine-catalyzed E-selective hydroboration of electron-deficient alkyne17,18) (path A) or...
boron-selective Suzuki–Miyaura coupling from diborylalkene (path B). While the diborylalkene was useful feedstock for diverse synthesis, diarylation often occurred to drop the total yield. The reduction of common building blocks by reduction with NaBH₄ afforded to the corresponding 3-aryl substituted oxaborole via cyclization and boron-deprotection. These methods allowed the synthesis of diverse oxaboroles summarized in Table 1. We confirmed the structures of oxaboroles 3a and 3b by X-ray crystal structure analysis.

The photophysical properties, including UV/vis, fluorescence, and fluorescence quantum yields of synthesized oxaboroles, were investigated. The naphthyl-substituted oxaboroles, 3a–3e, showed relatively high quantum yields (Table 1, entries 1–4). The smaller Stokes shifts were observed in the heteroarene-substituted oxaboroles 3f and 3g, especially a quantum yield of benzothiophene was dramatically decreased (entries 5 and 6). While more π-extended arene, such as anthracene, phenanthrene, and pyrene-substituted oxaboroles 3h–3j afforded longer absorption and emission wavelengths, the meager quantum yields were obtained (entries 7–9).

We subsequently evaluated the sugar recognition ability of 2-naphthyl group-substituted oxaboroles 3a–3d because they showed good fluorescent quantum yields, appropriate Stokes shifts, and relatively longer fluorescent wavelengths (Fig. 3). Interestingly, the fluorescence of these boroles were quenched by sugar concentration-manner. Thus, we analyzed the relative fluorescence intensity (F/F₀) with various sugars (200 µM) for each borole (10 µM). In all boroles, the largest quenching was observed with d-ribose, pentose having a cis-diol unit, compared to other sugars. The borole 3c showed the highest d-ribose selectivity toward various sugars and significant quenching with d-ribose than the other boroles.

We focused on ribose derivatives, as d-ribose showed high selectivity. Since ribose is a structural component of biological molecules such as nucleic acids, their recognition with the fluorescent change is highly attractive. The fluorescence intensity ratio of oxaborole was similarly measured in the presence/absence of various ribose-containing intrinsic molecules, and the quenching was confirmed in most of the ribose derivatives (Fig. 4). Similar to the sugars, oxaborole 3c showed the largest quenching in all cases. Intriguingly, among the ribose derivatives used, the degree of quenching varied greatly depending on the structure. Especially, ATP, guanosine 5'-triphosphate (GTP), cytidine 5'-triphosphate (CTP), and uridine 5'-triphosphate (UTP) bearing triphosphate unit showed only slight quenching. For all four nucleotides, Tri-, Di-, and Mono-, the quenching (F/F₀) was more remarkable in the order of Tri-, Di-, and Mono-, suggesting that the polyphosphate group either inhibits molecular recognition or the quenching mechanism. Contrastingly, nicotinamide adenine dinucleotide (NAD), consists of nicotinamide mononucleotide and adenosine bridged with phosphate groups, showed significant quenching, which is higher than d-ribose (Fig. 3). Unfortunately, reduced nicotinamide adenine dinucleotide (NADH), a reduced form, was unavailable to the quenching analysis because the absorption spectra were overlapped with oxaboroles.

The ground state highest occupied molecular orbital/lowest
Table 2. Calculated HOMO and LUMO Energies of Optimized Oxaboroles 3a–d, k.

| R  | HOMO (eV) | LUMO (eV) |
|----|-----------|-----------|
| H  | -5.573    | -1.270    |
| OMe| -5.215    | -0.998    |
| CO2Me | -5.792  | -1.638    |
| F  | -5.648    | -1.203    |
| CN | -6.084    | -1.884    |

Calculation method: B3LYP/6-31G (d) for energies.

unoccupied molecular orbital (HOMO/LUMO) energy levels of oxaboroles 3a–d were calculated (Table 2). The LUMO levels reflect the Lewis acidity of these oxaboroles. Comparing the LUMO levels of the oxaboroles 3a–d, the fluorescence intensity ratio of the oxaboroles to α-ribose were in significantly agreement with the order of the LUMO levels.

We calculated the HOMO/LUMO level of cyano group-containing oxaborole, 3k, to design more electron-deficient oxaborole. The LUMO energy of 3k has the lowest level, as −1.884 eV, which is expected to higher recognition ability. Therefore, we have synthesized 3k and evaluated the recognition ability of sugars and sugar derivatives. Consequently, the oxaborole 3k showed the highest recognition ability, which corresponds to the density functional theory (DFT) calculation analysis (Fig. 5). Additionally, mass peak corresponding to the borate complex from oxaborole 3k with α-ribose was observed.

In summary, the fluorescent unit-pendant oxaboroles were synthesized and investigated their photophysical properties. The oxaboroles provided good fluorescence quantum yields and selective recognition toward α-ribose and α-ribose containing molecules. The molecular recognition induced significant fluorescence quenching, which has potential for the boron-based NAD sensor probe.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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22) The details for synthetic method and the optical property of 3k was also reported in Supplementary Materials.