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Novel benzimidazolium–urea-based macrocyclic fluorescent sensors: synthesis, ratiometric sensing of $H_2PO_4^-$ and improvement of the anion binding performance *via* a synergistic binding strategy†

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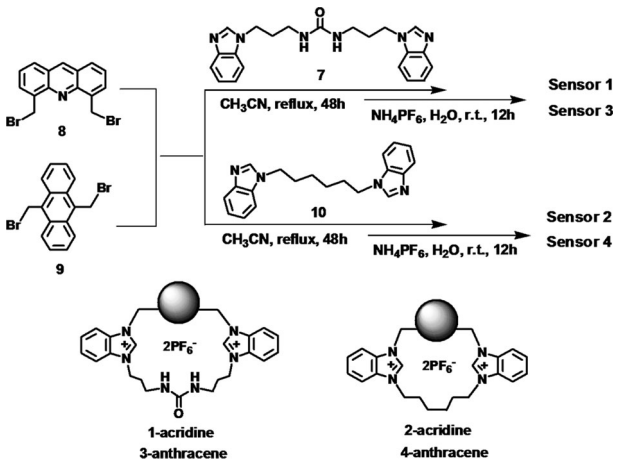
A modular approach to obtain benzimidazolium–urea-based, fluorophore-appended macrocyclic receptors was developed. This class of receptors could be used as selective ratiometric fluorescent sensors for $H_2PO_4^-$ due to the synergistic binding effect of benzimidazolium and urea moieties.

The sensing of anions by fluorescent sensors is an expanding area of molecular recognition,[1] especially for the biologically important $H_2PO_4^-$.[2] A number of fluorescent sensors for $H_2PO_4^-$ have been reported *via* fluorescence quenching or enhancement.[3] However, the ratiometric sensing of $H_2PO_4^-$ is still a challenging task.[4] Apart from the fluorescence-response behavior towards the anions, the binding site and structure of the sensors are also important. It is known that imidazolium/benzimidazolium and urea groups are effective hydrogen bond donors through formation of $(C–H)^+\cdots X$ and $N–H\cdots X$ hydrogen bonds with anions respectively.[5] Even though a few efficient imidazolium/benzimidazolium-based[3a,4c,6] macrocyclic receptors have been reported, there is no reported macrocyclic sensor simultaneously involving benzimidazolium and urea moieties. Nevertheless, it could be expected that with the assistance of urea, the benzimidazolium-based macrocyclic sensors would exhibit an improved anion binding performance due to their well defined cavities bearing multiple hydrogen binding sites. Hence, it is highly desirable to develop a facile method for synthesizing benzimidazolium–urea-based macrocyclic sensors and investigate the synergistic binding effect of benzimidazolium and urea moieties.

Recently, our group reported a class of benzimidazolium–acridine-based macrocyclic fluorescent sensors, such as sensor **2** (Scheme 1), which achieved ratiometric detection of $H_2PO_4^-$ *via* an anion-induced assembly mechanism.[4c] Bearing in mind the above concept, herein, we reported a new class of macrocyclic sensors (**1** and **3**) which contain two building blocks: benzimidazolium–urea linkage (**7**) and the model fluorophore (Scheme 1). Acridine and anthracene were, respectively, chosen as model fluorophores. Hence, this work provided an unprecedented opportunity to combine the benzimidazolium and urea moieties in the same macrocyclic molecule to strongly improve the recognition properties toward $H_2PO_4^-$.



Scheme 1 Synthesis of fluorescent sensors **1–4**.

The synthetic routes to obtain sensors **1** and **3** are illustrated in Scheme 1 and Scheme S1 (ESI†). 1,3-Bis-(3-hydroxyl-propyl)-urea **5** was reacted with $SOCl_2$ in $CHCl_3$ at r.t. to achieve 1,3-bis-(3-chloro-propyl)-urea **6** in 34% yield. Then **6** underwent a substitution reaction with benzimidazole in the presence of NaH in DMF resulting in 1,3-bis-(3-benzoimidazol-1-yl-propyl)-urea **7** in 39% yield. A [1+1] macrocyclization between **8**/**9** and **7** occurred in CH_3CN under high dilution conditions to afford the bromide salt of **1**/**3** in 85%/75% yield. Finally, the $[PF_6]^-$ salts of **1** and **3** were obtained by counterion exchange reaction using NH_4PF_6 in water. For comparison, sensors **2** and **4** bearing only benzimidazolium moieties were also prepared (see ESI†).

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† Electronic supplementary information (ESI) available: ^1H–^{13}C NMR spectra of sensors **1–4**, a summary of the crystallographic data, fluorescence titrations and Job's plots *etc*. CCDC 914122. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc43184c

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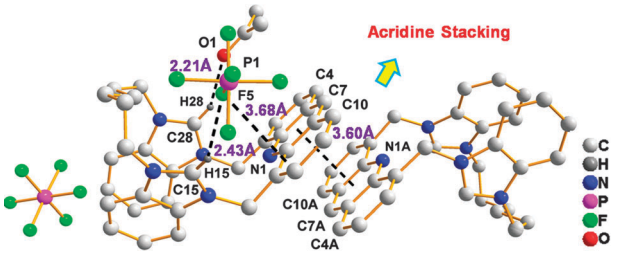


Fig. 1 Crystal structure of **2**·2(PF_6^-)·(CH_3COCH_3). Nonacidic hydrogen atoms, some PF_6^- counterions, some CH_3COCH_3 solvent molecules and one of the two sets of disorders in the sensor molecule are omitted for clarity. Dashed lines represent hydrogen bonds, anion–π and π–π interactions. Symmetry codes: $A = 2 - x, 1 - y, -z$.

The single crystal of sensor **2** revealed the self-assembly nature of the benzimidazolium-based sensors, as shown in Fig. 1 and Fig. S5 (ESI†). Hydrogen bonds formed by benzimidazolium C(2)–H and PF_6^-/CH_3COCH_3, π–π interactions between two benzimidazoliums and between two acridines were the main driving forces for the assembly behavior. It is worth mentioning that the formation of the assembled acridine dimer shown in Fig. 1 could also be induced by $H_2PO_4^-$ in solution and resulted in bathochromic-shifted fluorescence emission, as we reported previously.[4c]

Binding performance of sensors **1–4** toward $H_2PO_4^-$ was then evaluated by the fluorescent changes of the 5 μM sensor in CH_3CN upon addition of the tetrabutylammonium $H_2PO_4^-$ salt. As shown in Fig. 2a and Fig. S6a (ESI†), a significant decrease in the fluorescence emission at 430 nm and increase in emission at 501 nm with clear isoemission points at 459 and 476 nm, respectively, were observed upon addition of $H_2PO_4^-$ to the solution of sensors **1** and **2**. Adding 3.0 equiv. of $H_2PO_4^-$ to the solution of sensor **1** resulted in quenching of fluorescence by 68% at 430 nm and enhancement of fluorescence by 4.3-fold at 501 nm, changing the fluorescent color from blue to green. However, 4 equiv. of $H_2PO_4^-$ only caused 2.6-fold fluorescence enhancement at 501 nm of sensor **2**. The new fluorescence peaks of sensors **1** and **2** at 501 nm could be assigned to the anion-induced acridine excimer.[4c] Interestingly, such a $H_2PO_4^-$-induced fluorophore dimer displayed by acridine derivatives **1** and **2** was also exhibited by the anthracene derivative **3**. Similarly, a significant decrease in the monomer peak at 428 nm and increase in the excimer peak at 500 nm with a clear isoemission point at 479 nm were observed upon addition of $H_2PO_4^-$ to the solution of sensor **3** (Fig. 2b). It seems to be a versatile principle for the class of benzimidazolium–urea-based receptors that they could be used as ratiometric fluorescent sensors for $H_2PO_4^-$ even with the varying fluorophores. In contrast, the excimer peak of the anthracene derivative **4** induced by $H_2PO_4^-$ was not so obvious upon addition of $H_2PO_4^-$, since only a feeble fluorescence enhancement at longer wavelength was observed (Fig. S6b, ESI†).

In order to further evaluate the $H_2PO_4^-$ ratiometric sensing performance of sensors **1–4**, ratiometric curves of $I_{excimer}/I_{monomer}$ as a function of $H_2PO_4^-$ concentration were studied. As shown in Fig. S7a (ESI†) sensor **1** could achieve ratiometric sensing of $H_2PO_4^-$ at a much lower concentration than sensor **2** (1.0 *vs.* 6.5 μM). In addition, the curve with a good linear relationship from 1.0 to 7.5 μM $H_2PO_4^-$ could serve as the calibration curve of sensor **1** for the detection of $H_2PO_4^-$. Fig. S7b (ESI†) indicates that the linear range for $H_2PO_4^-$ of sensor **3** was 5.0–15 μM. However, the ratiometric

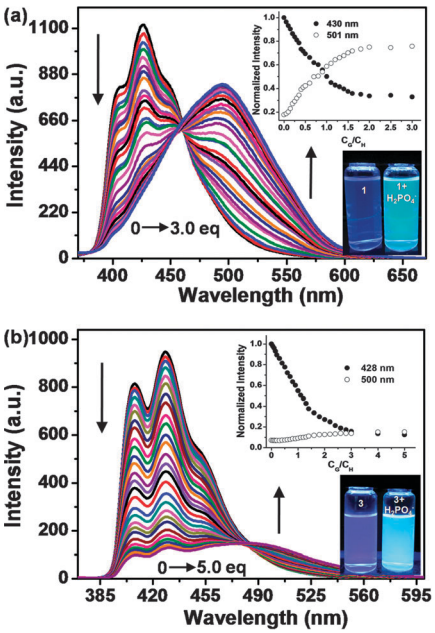


Fig. 2 Fluorescence titrations of 5 μM sensor **1** excited at 357 nm (a) and sensor **3** excited at 362 nm (b) with $H_2PO_4^-$ in CH_3CN. Insets: normalized emission developments at the wavelength of monomer and excimer peaks as a function of $H_2PO_4^-$ equivalents, and the fluorescent color of sensor **1**/**3** in the absence or presence of $H_2PO_4^-$ under a UV lamp excited at 365 nm.

curve of sensor **4** was much gentler and lower than that of sensor **3** (Fig. S7b, ESI†). Job's plots demonstrated the 1 : 1 complexes of sensors **1–4** with $H_2PO_4^-$ (Fig. S8, ESI†). Binding constants of sensors **1**, **3** and **4** with $H_2PO_4^-$ were 2.9×10^6, 2.6×10^5 and 1.6×10^5 M^{-1} respectively (Fig. S9, ESI†). The binding constant of sensor **2** with $H_2PO_4^-$ could not be calculated because of the two-step process of the titration profile (Fig. S9, ESI†).[4c] All these results indicated that compared with sensors **2** and **4**, sensors **1** and **3** which bear both benzimidazolium and urea binding sites exhibited better anion binding performance toward $H_2PO_4^-$ owing to the urea-assisted synergistic binding effect.

In order to check the sensing selectivity of **1** and **3** as $H_2PO_4^-$ ratiometric fluorescent sensors, the fluorescence responses of sensors **1** and **3** toward other common anions, such as F^-, Cl^-, Br^-, I^-, HSO_4^-, AcO^-, SCN^- and ClO_4^-, were evaluated, as shown in Fig. S10 (ESI†). Obviously, sensor **3** displayed excellent selectivity towards $H_2PO_4^-$ since only $H_2PO_4^-$ resulted in the unique excimer emission output at 500 nm. However, in terms of this view, both $H_2PO_4^-$ and HSO_4^- could give rise to the excimer peak of sensor **1** at 501 nm. Hence, special attention was paid to $H_2PO_4^-$ selectivity of sensor **1** in the presence of other competing anions. As shown in Fig. 3 and Fig. S11 (ESI†), no significant variations in the intensity ratio (I_{501}/I_{430}) and the excimer wavelength were found for the detection of 2 equiv. of $H_2PO_4^-$ when in the presence of 20 equiv. of other background anions. Sensor **1** has the ability to ratiometrically sense $H_2PO_4^-$ with high selectivity even in the mixture containing other competing anions.

To fully explore the interaction modes between sensor **1**/**3** and $H_2PO_4^-$, the ^1H NMR titration experiments were carried out in DMSO-d_6 due to the precipitation in CD_3CN. As shown in Fig. 4, effective binding between sensor **3** and $H_2PO_4^-$ occurred in DMSO-d_6 which can be confirmed by the vivid fluorescent color

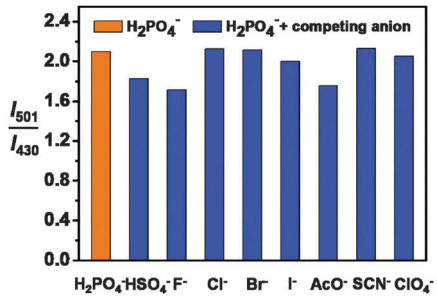


Fig. 3 Fluorescence responses of sensor **1** (5 μM) upon addition of 2 equiv. of $H_2PO_4^-$ and subsequent addition of 20 equiv. of other anions.

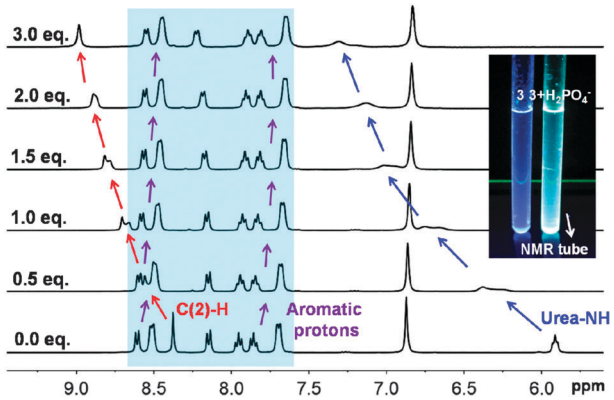
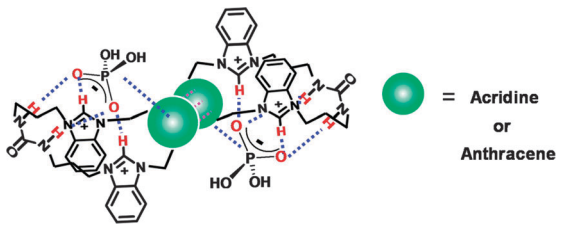


Fig. 4 ^{1}H NMR titrations of sensor **3** (15 mM) upon addition of $H_2PO_4^-$ in DMSO-d_6. Inset: fluorescent color of sensor **3** in the absence or presence of 3 equiv. of $H_2PO_4^-$ in DMSO-d_6 under a UV lamp excited at 365 nm.

change after addition of 3 equiv. of $H_2PO_4^-$ (from blue to green). In terms of the spectra, as expected, the peaks of the benzimidazolium C(2)–H and urea–NH of sensor **3** showed large downfield shifts with progressive addition of $H_2PO_4^-$, which is a typical phenomenon of hydrogen bonds with $H_2PO_4^-$.[5] In addition, noticeable upfield shifts of the aromatic protons of the anthracene ring were observed, demonstrating the formation of the face-to-face π–π interaction between two anthracenes.[6m,n] Unfortunately, the ^{1}H NMR titration of sensor **1** with $H_2PO_4^-$ cannot be performed even in DMSO-d_6 because of the precipitation after addition of $H_2PO_4^-$. Absorption experiments were also performed to investigate the binding mechanism (Fig. S12, ESI†). The phenomenon that only $H_2PO_4^-$ induced the significant bathochromic-shift of the absorption bands of sensor **1**/**3** was consistent with the formation of π–π interaction between two fluorophores.[3j,6m]

Based on the above discussions, the possible binding mode between sensor **1**/**3** and $H_2PO_4^-$ was proposed and is illustrated in Scheme 2. It is worth mentioning that both benzimidazolium and urea moieties of sensor **1**/**3** participated in the anion complexation and exhibited a synergistic effect for binding $H_2PO_4^-$.



Scheme 2 Possible binding mode of sensor **1**/**3** with $H_2PO_4^-$.

In summary, we have designed and synthesized the first two novel macrocyclic compounds **1** and **3** bearing benzimidazolium and urea groups based on acridine and anthracene fluorophores respectively. This new class of cyclic compounds could be used as highly selective ratiometric fluorescent sensors for $H_2PO_4^-$ *via* the anion-induced fluorophore dimer formation. Compared with sensors **2** and **4**, sensors **1** and **3** exhibited better anion binding performance towards $H_2PO_4^-$ due to the synergistic binding effect of benzimidazolium and urea moieties.

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