Conjugated Molecules for Colourimetric and Fluorimetric Sensing of Sodium and Potassium

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Abstract

We present a series of conjugated molecules for colourimetric and fluorimetric sensing of alkali metal cations Na^+ and K^+. The dye molecules are based on an electron-rich bithiophene core bridged by an oligoethylene glycol bridge capable of selectively binding either sodium or potassium. The molecules are further functionalised with electron-rich or electron-deficient moieties to modulate the band gap and thus shift the absorbance across the visible range. We observe distinct colour changes and high selectivity for alkali metal cations at millimolar concentrations. We moreover see highly selective fluorimetric responses with the molecules exhibiting either turn-on, turn-off or ratiometric sensing behaviour. We finally demonstrate a dual optical sensor capable of distinguishing between sodium and potassium in solution.

Introduction

Colourimetric measurement of physical properties is commonplace, with every practicing chemist having at some point employed universal indicator paper as a simple method to measure pH. Commonly, pH paper contains a series of dyes, which exhibit colour change dependant on pH allowing for visual determination of acidity of a solution. In order to examine biological samples, dyes have been employed in microscopy for many years and recent advancements in fluorescent materials have been employed in confocal, fluorescence as well as two-photon microscopy with a number of selective fluorescent probes having been developed[1,2].

Two of the most common intra- and extracellular biologically active cations are the sodium and potassium ions, associated with a range of biological processes including propagation of nerve impulses, muscle contraction, and regulation of blood pressure.[3] A deviation from a narrow typical concentration range of 100-200 mM for Na^+ in serum and 4-5 mM for K^+ in the blood and 140 mM in the intracellular fluid for a healthy individual leads to serious health conditions,[4] thus defining a concentration range on the order of 1-100 mM where accurate and selective measurement of sodium and potassium ions is desirable. Alkali metal ion sensing has previously been carried out electrochemically, with either ion-selective membranes on organic electrochemical transistors[5] or with crown ether functionalised polymers[6] and commercially with ion-selective electrodes. Optical sensors are generally characterised by a slightly simpler operation over ion-selective electrochemical sensors which require careful calibration, temperature and pH control.[7]

Typically, solution phase optical sensors for Na^+ and K^+ and other metal ions have been based on size-selective heteroatom-containing macrocycles such as the crown ether[8,9], azacrown[10,11], cryptand[12] or calixarene[13,14] as the binding unit. The binding unit is covalently bonded to a chromophore or fluorophore which

exhibits a change in absorbance or fluorescence properties as a result of the binding event. The attractiveness of optical sensors is their relative ease of application, high selectivity and high concentration range for quantification. Further, ratiometric sensing, whereby a change in analyte concentration results in a decrease of one optical transition and an increase of a second transition, provide a more robust measurement of concentration. The alternative being an on/off sensor where only depletion or enhancement of an optical event is observed upon change in analyte concentration. Ratiometric sensors eliminate some device-to-device variation and background noise due to the self-referencing measurement of the probe[1]. Vanishingly few Na^+ and K^+ sensors show ratiometric colourimetric detection in the visible range of the spectrum and even fewer fluorescent materials show ratiometric detection.[15–17] Furthermore, if absorbance and emission can be pushed into the 650-950 nm range or the near infrared over 1100 nm then biological sensing becomes more relevant due to the transparency window of tissue[18] as well as being beyond autofluorescence emission wavelength for almost all common endogenous fluorophores[19]. It is moreover advantageous for excitation wavelengths to be red-shifted to mitigate the effect of high energy photon damage to cells.

Conjugated small molecules have been explored extensively as active materials in organic electronic applications from field-effect transistors to photovoltaics, light-emitting diodes and electrochromic devices and more recently biological sensing.[20–24]. Common to these materials is the synthetic flexibility that allows for inclusion of various structural moieties to control solubility, solid state morphology, colour, selectivity to biological analytes, and electronic properties, and is one of the standout advantages of organic electronic materials. Recently, it was demonstrated that a conjugated polymer which included either a 17-crown-5 or a 20-crown-6 ether moiety was capable of ratiometric detection of Na^+ and K^+ in the visible range in both solution and solid state.[25-26] Upon binding of an alkali metal ion, a backbone twist occurred breaking conjugation and thereby resulting in ratiometric colour change in the visible spectrum. This concept has more recently been extended to small conjugated molecules showing ratiometric colourimetric response to Na^+ ions.[27] Here, we present a series of related small conjugated molecules and show how rational molecular design allows for both colourimetric and fluorimetric sensing of sodium and potassium. While all colourimetric responses are ratiometric in nature, we show how different structural motifs can be used to alter fluorimetric responses from ratiometric to turn-off and turn-on. As a proof-of-concept, we furthermore show how access to optical sensor molecules with spectral complementarity allows for mixtures with dual Na^+/K^+ sensing capabilities.

Synthesis
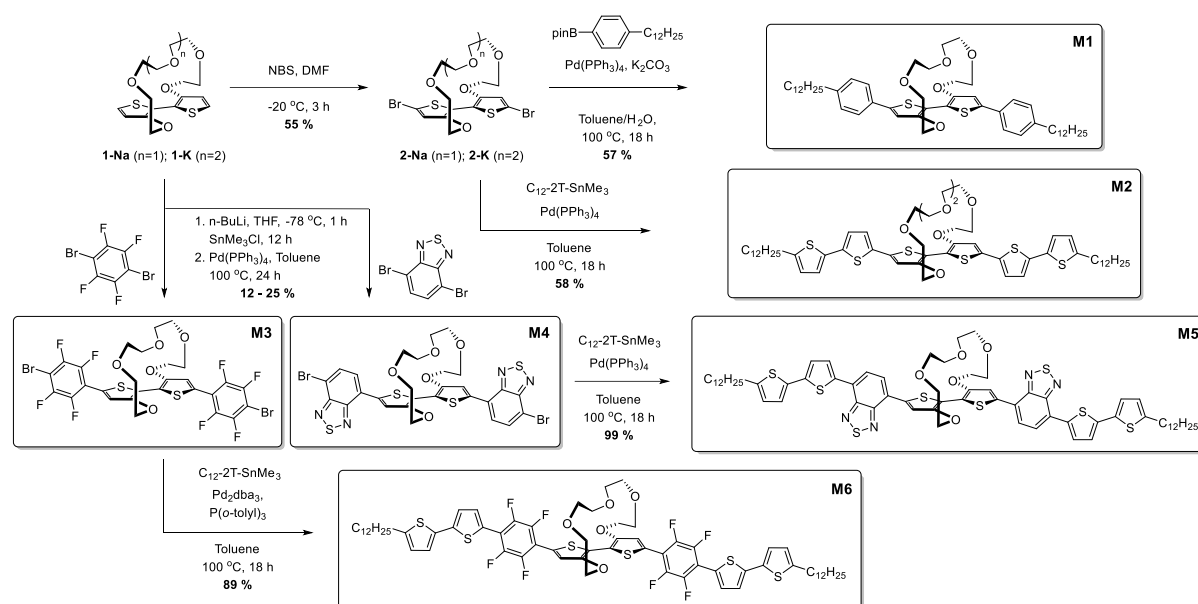
Scheme 1 Synthetic scheme outlining the modular synthesis of molecular ion sensors **M1**-**M6** via stepwise palladium-mediated cross-coupling reactions; C$_{12}$-2T-SnMe$_3$ = 5-dodecyl-5′-trimethylstannyl-2,2′-bithiophene.

In an effort to create soluble donor-acceptor small molecule ion sensors, we initially synthesised 2,2′-bithiophene tethered at the 3 and 3′ positions by a polyether bridge,[28] followed by a series of cross coupling reactions to afford the optical ion sensing materials; full experimental details are available in the supporting information and described in brief here and in **Scheme 1**. The sodium-binding unit **1-Na** was brominated to afford **2-Na**, after which Suzuki coupling with 4-(n-dodecyl)phenylboronic acid pinacol ester afforded **M1** in 57 % yield as a yellow solid. To afford a second all-donor potassium sensor, **2-K** was reacted under Stille conditions with 5-dodecyl-5′-trimethylstannyl-2,2′-bithiophene to afford **M2** as an orange solid in 58% yield. We then developed a series of donor-acceptor materials by introducing either 2,1,3-benzothiadiazole (BT) or 2,3,5,6-tetrafluorophenylene moieties flanking the bithiophene core through stannylation of **1-Na** *in situ* followed by reaction with excess acceptor unit under Stille conditions. Reaction with 4,7-dibromo-2,1,3-benzothiadiazole afforded **M3** in a yield of 12 % as a purple solid, while reaction with 1,4-dibromo-2,3,5,6-tetrafluorphenylene gave **M4** in a yield of 25% as a yellow solid. **M3** and **M4** were further reacted under Stille conditions with 5-dodecyl-5′-trimethylstannyl-2,2′-bithiophene to afford molecules **M5** and **M6** as blue and orange powders respectively in good yields of 99 % and 89 % respectively. Thus, a total of six uniquely coloured materials were synthesised as sodium and potassium ion-selective chromo- and fluoroionophores.

Results and Discussion

Initial characterisation was carried out using UV-Vis spectroscopy. The molecules were dissolved in chloroform or tetrahydrofuran (THF) and titrated with a solution of NaBPh$_4$ or KBPh$_4$. Chloroform and THF were chosen to emphasise the behaviour of these novel sensor molecules in solvents miscible and immiscible with water. In the ion-free (unbound) form, the molecules absorb across most of the visible spectrum appearing from yellow to orange through to blue and purple in solution (Figure 1a). Upon binding with Na⁺ (**M1**, **M3**, **M4**, **M5**,

and **M6**) or K^{+} (**M2**) in solution, there is a quenching of the dominant optical absorption band and a simultaneous growth of a new blue-shifted (29-88 nm) absorption feature from the alkali metal ion complex, consistent with previous reports for this binding unit (Figure 1c).[25–27] This blue-shift in absorbance is rationalised from a twist in the central S-C-C-S dihedral angle of the ion selective bithiophene core upon Na^{+} or K^{+} binding. The conjugation along the backbone is disrupted as the dihedral twists as much 70 ° as has been demonstrated by previous crystal structures and theoretical calculations (Figure 1b).[26] Representative titration plots can be seen in Figure 2 for **M2** and **M5** with the remaining plots depicted in Figure S1-12 in the supporting information and all data summarised in Table 1.
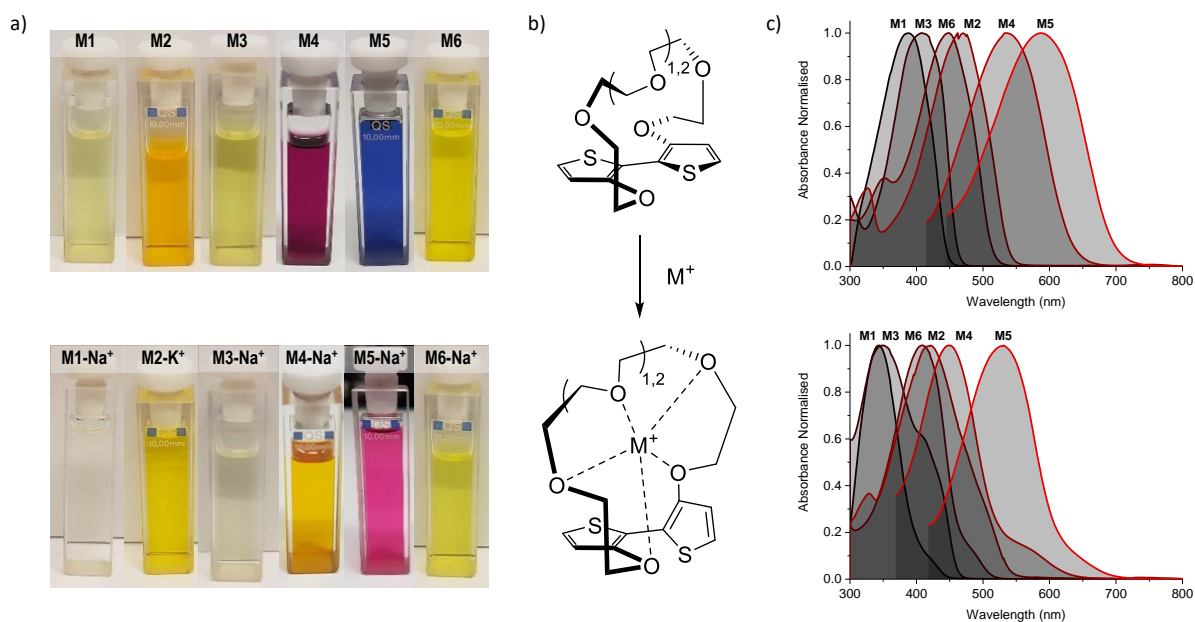

Figure 1 (a) Photographs of the molecules (top) and their alkali metal ion complexes (bottom) in chloroform solution; (b) Illustration of backbone twist of crown ether tethered bithiophene sensing unit adapted from ref. [26]; (c) Collated UV-Vis absorption spectra for the molecules (top) and their alkali metal ion complexes (bottom) in chloroform solution at approximately 10^{-5} M concentration at room temperature.

Table 1 Summarised spectrophotometric data and sensing parameters for sensor molecules **M1**-**M6**. Dissociation constants (K_d), limit-of-detection (LOD) and limit-of-quantification (LOQ) reported for Na^{+} for **M1**, **M3**-**M6** and for K^{+} for **M2**. [a]Data obtained from tetrahydrofuran solution at room temperature; [b]Extinction coefficients (ε) determined in chloroform solution at room temperature.

	λ_{max} M (nm)[a]	λ_{max} M-Na^{+} (nm)[a]	λ_{max} M-K^{+} (nm)[a]	$\Delta\lambda_{max}$ (nm)[a]	ε M (10^3 cm^{-1} M^{-1})[b]	K_d (mM)[a]	LOD (nM)[a]	LOQ (nM)[a]
M1	397	338	-	59	32.6	1.45	70	220
M2	468	-	400	68	72.8	0.13	90	300
M3	412	347	-	65	31.6	34.4	1100	3700
M4	540	452	-	88	43.0	6.81	240	790
M5	595	531	-	64	83.5	0.33	180	590
M6	453	424	-	29	123.0	18.2	590	1960

The molecules can be divided into three categories. **M1** and **M2** are all-donor molecules comprising only phenylene and/or thiophene building blocks. In solution, **M1** is pale yellow, turning colourless upon titration with Na$^+$ caused by a 44 nm blue-shift (Figure 1a). The increased conjugation length of the sexithiophene backbone in **M2** causes a red-shift of the absorption maximum (λ_{max}) from 397 nm for **M1** to 468 nm for **M2**. When titrated with KBPh$_4$, the λ_{max} blue-shifts 49 nm as depicted in Figure 2a. The K$^+$ sensing unit (**1-K**) was employed for **M2** in order to have complementary Na$^+$ and K$^+$ molecular sensors available. The second set of molecules (**M3** and **M6**) are weak donor-acceptor systems containing electron-deficient tetrafluorophenylene units with additional extension of conjugation in **M6** with flanking bithiophene moieties. **M3** displays a λ_{max} at 412 nm with a significant 65 nm blue-shift upon ion-sensing to form the colourless **M3-Na$^+$** complex. The π-extended **M6** also appears yellow with a λ_{max} of 453 nm in solution (Figure 1a); however, it displays the smallest blue-shift of 29 nm when undergoing complexation to form **M6-Na$^+$**. The third set of molecules are stronger donor-acceptor systems where the central **1-Na** core is flanked by highly electron-deficient 2,1,3-benzothiadiazole groups, thus affording **M4** and its bithiophene-extended derivative **M5**. These red-shifted materials achieved the highest visual contrast of the series upon sensing of sodium ions. In solution, **M4** is purple with a λ_{max} of 540 nm; the colour changes from purple to yellow when the **M4-Na$^+$** complex forms (Figure 1a). This molecule displayed the largest blue-shift of 88 nm upon complexation and displayed two isosbestic points at 481 nm and 392 nm indicating a direct conversion from **M4** to **M4-Na$^+$** without interfering side-reactions. **M5** is blue when ion-free and when complexed with Na$^+$ has a magenta hue (Figure 1a). The shift in λ_{max} was 64 nm from 595 nm to 531 nm upon Na$^+$ sensing as depicted in Figure 2a. It should be noted that the presence of sodium ions can be detected visually at concentrations below 1 mM using a 10^{-5} M solution of **M5** as illustrated in Figure 2b.
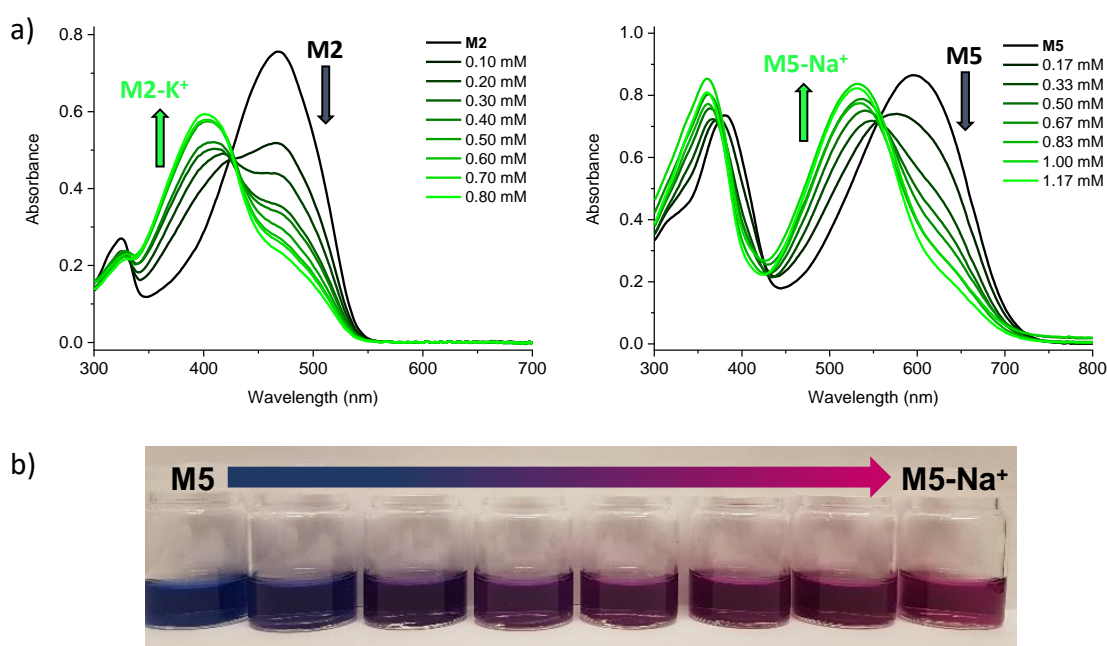

Figure 2 (a) Representative UV-Vis absorption spectra in tetrahydrofuran solution for **M2** upon titration with aliquots of 0.002 M KBPh$_4$ in tetrahydrofuran (left) and for **M5** upon titration with aliquots of 0.005 M NaBPh$_4$ in tetrahydrofuran (right); (b) photographs of **M5** titration series with NaBPh$_4$ in tetrahydrofuran. All data recorded at room temperature.

The affinities of the sensor molecules for Na^+ and K^+ were investigated at room temperature and quantified using the Benesi-Hildebrand method to afford the dissociation constants, K_d, listed in Table 1 with further details available in the SI (Figure S12-23).[29,30] The limit of detection (LOD) and limit of quantification (LOQ) were quantified from the absorbance of the complex (M-Na^+ or M-K^+) relative to the absorbance of the ion-free sensor molecule (M) at their respective absorption maxima during titration experiments (Table 1 and Figure S24-34). We observe slightly lower K_d values in chloroform than in THF, indicating stronger affinities, , likely due to the ability of THF to coordinate ions in solution thus competing with the binding of the molecule[31]. Deviations from linearity in the Benesi-Hildebrand and LOD/LOQ plots obtained in chloroform lead us to focus mainly on the alkali metal ion affinities in THF in the following. We observe that the dissociation constant drops markedly as the conjugation length of the sensor molecule increases with K_d of **M6** (18.2 mM) lower than that of **M3** (34.4 mM) and similarly K_d of **M5** (0.33 mM) lower than that of **M4** (6.81 mM). We hypothesise that this is caused by the fact that breaking of the π-conjugation upon complexation is more unfavourable in a shorter π-conjugated molecule than in a longer molecule as the highest occupied molecular orbital would be significantly more localised in the first instance. Interestingly, the fluorinated molecules, **M6** and **M3**, exhibit the highest K_d values followed by the brominated sensor molecule **M4**, which are all significantly higher than that of the non-halogenated molecules. It is likely that the halogen lone pairs and the partial negative charge on the polarised C—X bonds compete as binding sites for the alkali metal ions and therefore reduce the binding efficiency of the crown ether moiety.[32] For all the sensor molecules, the alkali metal ion binding is at least an order of magnitude weaker than for the parent crown ethers 15-crown-5 (K_d < 0.1 mM) and 18-crown-6 (K_d < 0.01 mM).[33] This allows for a reversible process as the unbound state can be regenerated upon addition of either 15-crown-5 or 18-crown-6. Characteristic of π-conjugated materials, the sensor molecules show very high extinction coefficients of 32,600 – 123,000 $M^{-1} cm^{-1}$ with the longer molecules **M2**, **M5** and **M6** showing the highest values as expected. Sensor molecules **M2**, **M4**, **M5** and **M6** are highly bench stable having been stored as solids for six months under ambient conditions without any change in UV-Vis spectra, while small changes are seen for **M1** and **M3** possible due to oxidation and/or aggregation (Figure S35-S40).

Table 2 Summarised fluorescence data for sensor molecules **M1-M6**. [a]Data obtained from tetrahydrofuran solution at room temperature at approximately 10^{-5} M concentration (see Figures S41-S50) with excitation wavelengths 362 nm (**M1**), 426 nm (**M2**), 481 nm (**M4**), 556 nm (**M5**) and 427 nm (**M6**); [b]Quantum yields (ϕ) determined in either dichloromethane (**M2**) or chloroform (**M1**, **M4-M6**) solution at room temperature (see Figures S51-S63).

	λ_{em} M (nm)[a]	λ_{em} M-Na^+ (nm)[a]	λ_{em} M-K^+ (nm)[a]	Stokes Shift M (cm^{-1})[a]	Stokes Shift M-Na^+/M-K^+ (cm^{-1})[a]	ϕ(M)[b]	ϕ(M-Na^+/M-K^+)[b]
M1	476	459	-	4,180	7,800	0.06	0.01
M2	546	-	542	3,050	6,550	0.12	0.12
M4	712	650	-	4,470	6,740	0.005	0.02
M5	733	661	-	3,160	3,700	0.006	0.02
M6	524	528	-	2,990	4,650	0.36	0.07

We subsequently explored the emissive properties of the sensor molecules by exciting at the isosbestic point identified from the UV-Vis titration experiments (Figure 3 and Figure S41-50). In line with the colourimetric

studies, the sensor molecules were examined in both tetrahydrofuran and chloroform with our main focus devoted to the behaviour in tetrahydrofuran due to more reliable extraction of sensing parameters and tetrahydrofuran generally solvating alkali metal salts better than chloroform. Upon titration with $NaBPh_4$ in tetrahydrofuran, **M1** exhibited a decrease in fluorescence intensity (turn-off), with a slight shift in emission wavelength (λ_{em}) from 476 nm to 459 nm. With $KBPh_4$, **M2** showed a similar decrease in fluorescence intensity with a slight broadening and blue-shift of the emission band. The second set of sensor molecules, **M4** and **M5**, showed a significant fluorescence enhancement (turn-on) upon complexation with Na^+. This turn-on fluorimetric response also had the advantage of being significantly shifted towards the red compared to the other materials, with the λ_{em} being 712 nm and 733 nm for the ion-free sensor molecules in solution and 650 nm and 661 nm upon Na^+ complexation for **M4** and **M5**, respectively. The molecules behave similarly in chloroform exhibiting strong fluorescence turn-on (Figures S46 and S48). It is likely that there is significant charge transfer character from donor to acceptor moiety in these molecules, which in the ion-free form quenches the emission. Complexation with sodium, on the other hand, is expected to disrupt effective charge transfer and thus enhance emission. While **M3** did not fluoresce, **M6** showed a ratiometric fluorimetric response to titration with sodium ions. Upon titration with $NaBPh_4$ in THF, a decrease in the emission peak at λ_{em} 530 nm occurred with a concurrent increase in intensity of a second fluorescence feature at 480 nm; the ratiometric response is even clearer in chloroform as illustrated in Figure 3. The selectivity of all the molecules to Na^+ and K^+ examined by colourimetry and fluorimetry is summarized in Figure 4 (details in Figures S64-73). As expected from the crown ether ring size, **M1**, **M3**, **M4**, **M5** and **M6** were all highly selective to Na^+ with **M2** being moderately selective to K^+. The Stokes shifts (Table 2) for the unbound molecules were on the order of $3,000 - 4,000$ cm^{-1} with the shorter molecules **M1** and **M4** showing the larger Stokes shifts and the longer and more conformationally locked molecules showing lower values.[34] The metal ion complexes have significantly larger Stokes shifts with values approaching 8,000 cm^{-1}, again with the shorter sensor molecules with more conformational freedom having the larger values[35,36]. Quantum yields (Table 2) for the unbound molecules were lowest for the bromine-containing molecules **M3** (no fluorescence detected) and **M4**, while strong donor-acceptor character (**M4** and **M5**) was also seen to promote non-radiative emission. The longer molecules **M2** and **M6** showed relatively high quantum yields suggesting that the bulky tethered crown ether effectively prevents intermolecular interactions and the associated non-radiative processes.
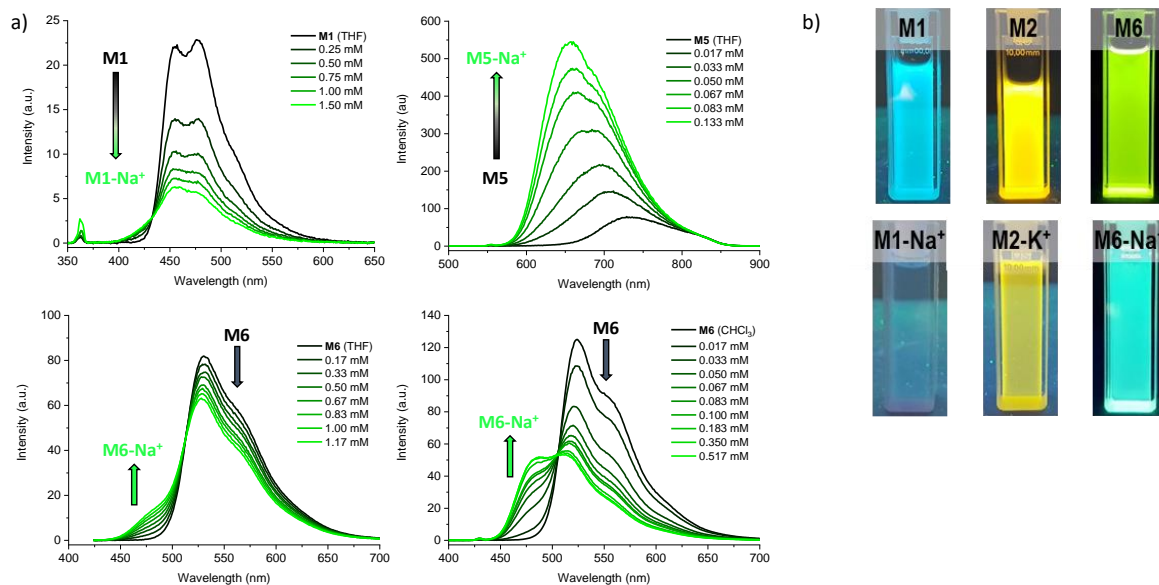
Figure 3 (a) Representative fluorescence spectra of **M1** (1.7×10^{-5} M) and **M5** (1.1×10^{-5} M) in tetrahydrofuran and **M6** in tetrahydrofuran (1.0×10^{-5} M) and chloroform (2.3×10^{-5} M) upon titration with aliquots of NaBPh$_4$; (b) photographs of representative unbound sensor molecules and their alkali metal ion complexes in chloroform solution upon excitation at 365 nm. All data recorded at room temperature.
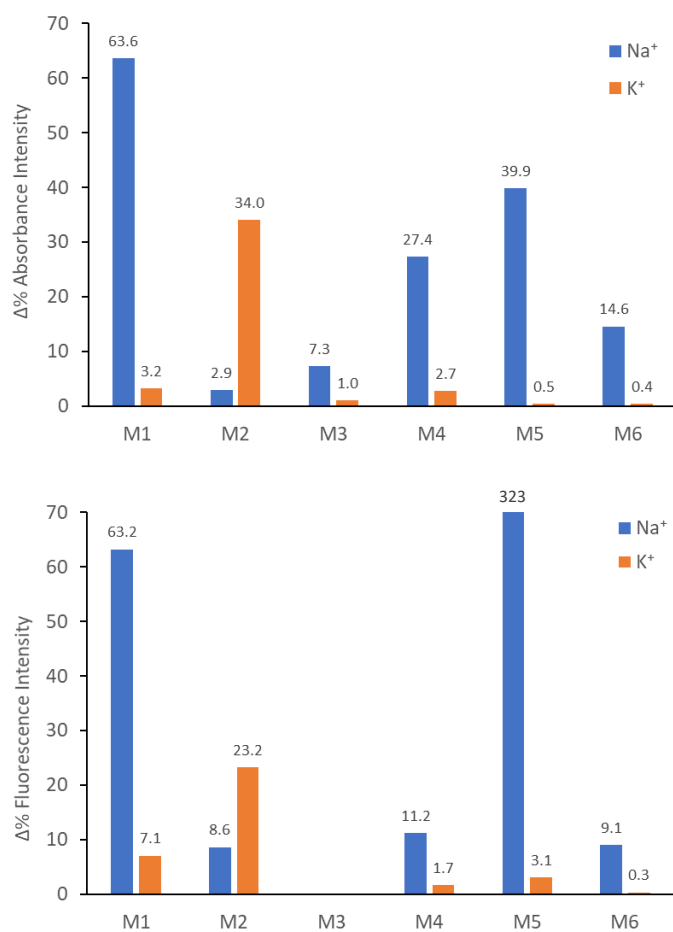

Figure 4 Colorimetric (top) and fluorimetric (bottom) selectivity of the sensor molecules for Na$^+$ and K$^+$ (added as BPh$_4$ salts at 0.33 μM concentration) measured at 10^{-5} M sensor molecule concentration in tetrahydrofuran at room temperature. The change in emission is 323 % for **M5** upon addition of Na$^+$, the axis was cropped for clarity.

Having confirmed alkali metal ion selectivity and the ability of the sensor molecules to give visual responses to Na$^+$ and K$^+$, the two most complementary sodium and potassium sensor molecules in terms of spectral response were investigated as a blend. Employing **M2** as the K$^+$ selective chromophore and **M5** as the Na$^+$ selective chromophore, a 1:1 blend of the two materials was used to create a colorimetric sensor for sodium and potassium ions (Figure 5). The two molecules have similar molar extinction coefficients and exhibit a large separation in λ_{max} for both unbound and bound species in solution and thus make for an optimal dual sensor system. The blended **M2**:**M5** solution was greenish when ion-free and turned blue upon addition of KBPh$_4$ and orange/red upon addition of NaBPh$_4$.
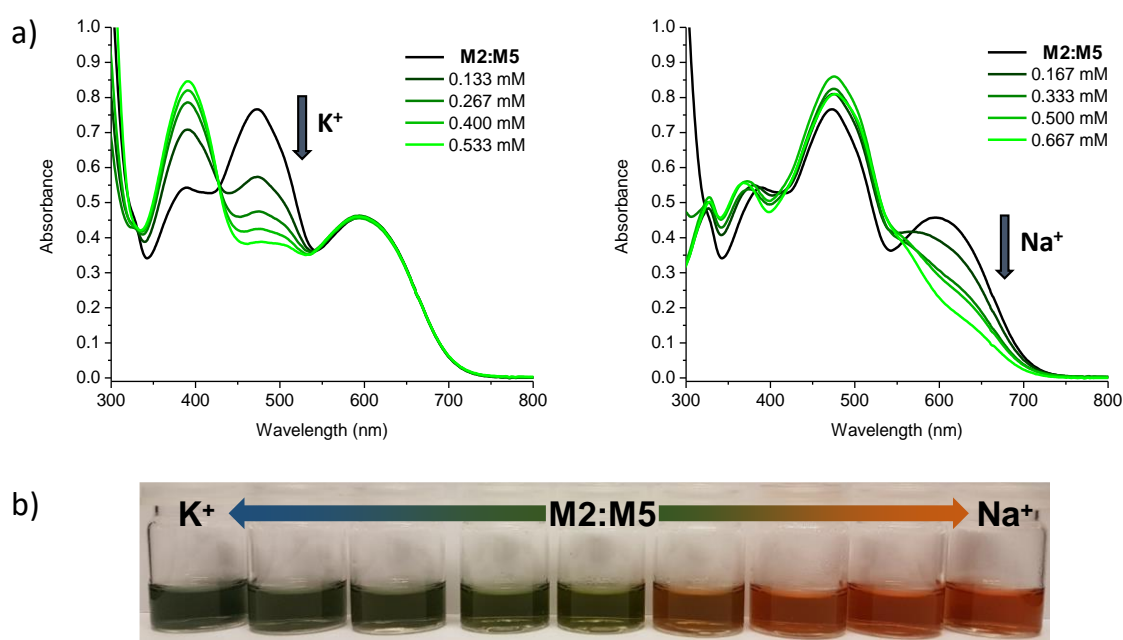

Figure 5 (a) UV-Vis absorption spectra of the **M2**:**M5** blend at approximately 3×10^{-5} M in tetrahydrofuran titrated with aliquots of KBPh$_4$ (left) and NaBPh$_4$ (right) in tetrahydrofuran; (b) photographs of **M2**:**M5** titration series with KBPh$_4$ and NaBPh$_4$ in tetrahydrofuran. All data recorded at room temperature.

Conclusions

In conclusion, we have shown the design and modular synthesis of six novel ratiometric sensor molecules, capable of selective colourimetric and fluorimetric sensing of sodium and potassium cations. By rational design and choice of peripheral π-conjugated donor or acceptor moieties, we have created ion-selective sensor molecules with colours covering the entire visible spectrum in solution. This ability to navigate the colour palette was demonstrated with relatively short π-conjugated sensor molecules (**M1** and **M3**) that go from coloured to colourless upon sensing and longer π-conjugated sensors such as **M5** that exhibit a very clear colour change from blue to magenta. Spectral complementarity was furthermore utilised to create a dual sodium and potassium sensor that turned blue in the presence of potassium and orange/red in the presence of sodium cations. Effective alkali metal ion binding – realised by a tethered crown ether that can be varied in size to host either sodium or potassium ions – resulted in low dissociation constants, in particular for the non-halogenated sensor molecules with extended π-conjugation, **M2** and **M5**. The ratiometric colourimetric response, due to the

breaking of π-conjugation upon ion complexation, has furthermore enabled low detection and quantification limits in the 100 nM range well within a typical physiological concentration range. We further examined the potential of these molecules as fluorimetric sensors. Depending on the peripheral π-conjugated segments, the molecular sensors exhibited either turn-on, turn-off or ratiometric fluorimetric sensing of Na^+ and K^+ in both tetrahydrofuran and chloroform. The all-donor materials **M1** and **M2** displayed turn-off fluorimetric responses, while the strong donor-acceptor systems with 2,1,3-benzothiadiazole (**M4** and **M5**) exhibited turn-on fluorimetric responses. **M6**, on the other hand, with weak donor-acceptor character owing to the weakly electron-withdrawing tetrafluorophenylene moiety, showed clear ratiometric fluorimetric response. We believe that these efforts to understand structure-property relations in π-conjugated sensor molecules will help pave the way for the development of efficient molecular sensors. In this context, we have laid out several molecular design strategies including all-donor and weak and strong donor-acceptor type π-conjugated systems for selective colorimetric and fluorimetric sensing of alkali metal cations at biological relevant concentrations. While this proof-of-principle study was carried out with peripheral alkyl chains impairing good solubility and thus sensing behaviour in tetrahydrofuran and chloroform, recent work has demonstrated aqueous activity with π-conjugated molecules bearing ethylene glycol-based chains.[37] Further biological relevance can thus be sought through further synthetic design in particular through substituting the peripheral alkyl chains with more polar counterparts.

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