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8-(1,4,7,10-Tetraoxa-13-azacyclopentadec-13-ylmethyl)quinolin-7-ol: synthesis and application as a highly sensitive metal cation probe†

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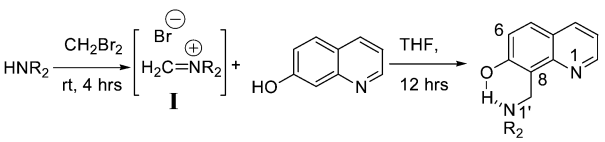
A new metal ion probe 8-(1,4,7,10-tetraoxa-13-azacyclopentadec-13-ylmethyl)quinolin-7-ol (1a) was synthesized via a modified Mannich reaction, in which the mechanism of recognition incorporates excited-state proton transfer reactions. The remarkable differentiation in spectral properties upon metal complexation makes 1a a highly sensitive fluorescence probe.

The application of fluorescence detection for the sensing and monitoring of cation, anion and neutral molecules has received considerable attention.[1] We report herein a very intriguing molecule 8-(1,4,7,10-tetraoxa-13-azacyclopentadec-13-ylmethyl)quinolin-7-ol (**1a**), which exhibits drastic spectral alternation upon metal ion complexation and can thus be used as a highly sensitive fluorescence probe. **1a** was synthesized through the condensation between parent 7-hydroxyquinoline (7HQ) and 1-aza-15-crown-5-ether via a modified Mannich reaction depicted in Scheme 1.

In this study, CH_2Br_2 was found to be an excellent reagent/solvent in forming a Mannich base with respect to dialkylamines,[2] giving rise to a dominant **1a** (or **1b**) species. Condensation at C(6) was negligible due to the destruction of aromaticity in the intermediate. The subsequent work-up procedure is straightforward, and merely involves the evaporation of the neat solvent, *i.e.* CH_2Br_2, giving rise to yields of **1a** and **1b** as high as 85 and 90%, respectively.

As shown in Fig. 1, ion-free **1a** in CH_3CN exhibits an $S_0 \rightarrow S_1$ ($\pi\pi^*$) absorption maximized at 337 nm, of which the spectral feature resembles that of the parent molecule 7-HQ. In contrast to a normal Stokes shifted fluorescence ($\lambda_{max} \sim 370$ nm) for 7HQ, **1a** exhibits multiple emission maxima at 375 (very weak) and 460 nm, accompanied by a shoulder at 540 nm. Similar luminescent properties were observed in **1b** except for the appearance of a peak maximum at 540 nm (see supporting information†). The origin of multiple fluorescence can be rationalized by an excited-state proton transfer (ESPT) mechanism based on an analogue of **1b**.[3] Upon electronically exciting the neutral form (**N**, Scheme 2), **1b** (or **1a**) undergoes intramolecular proton transfer from the phenolic proton to the dialkylamino nitrogen, forming species **A** in the excited state. The protonated dialkylamino group in **A*** serves as a proton crane, which subsequently undergoes a long-range, diffusive rotation within the excited-state life span to anchor the proton at



Scheme 1 R_2 = $-(CH_2)_2O(CH_2)_2O(CH_2)_2O(CH_2)_2O(CH_2)_2-$ (**1a**); or $(CH_2CH_3)_2$ (**1b**).

† Electronic supplementary information (ESI) available: detailed experimental procedures, absorption, fluorescence and ^1H NMR spectra. See http://www.rsc.org/suppdata/cc/b3/b300941f/

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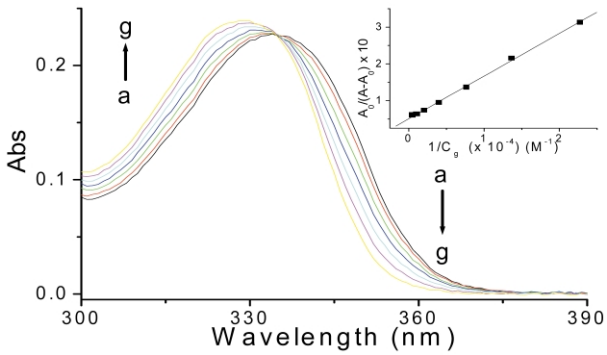
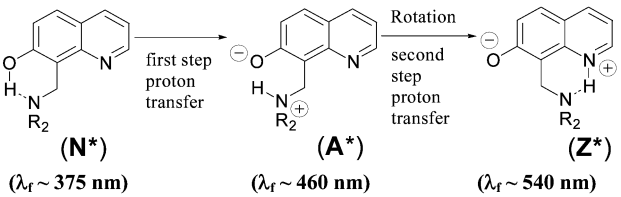


Fig. 1 Absorption spectra of **1a** (2.2×10^{-5} M) in CH_3CN by adding anhydrous $NaClO_4$ concentrations (C_g) of (a) 0, (b) 15, (c) 25, (d) 45, (e) 85, (f) 165, (g) 645 equiv (1 equiv = 2.9×10^{-6} M). Insert: the plot of $A_0/A - A_0$ against $1/C_g$.

the quinolinic nitrogen, giving rise to an excited zwitterionic form **Z***.

The Na^+ absorption and fluorescence titration spectra of **1a** (2.2×10^{-5} M) in CH_3CN are shown in Fig. 1. Increasing [Na^+] leads to a hypsochromic shift of the absorption profile, in which the appearance of an isosbestic point at 335 nm verifies a two-species equilibrium. The 1 : 1 **1a**/Na^+ complexation was further supported by a straight-line plot for the ratio of absorbance, $A_0/(A - A_0)$,[4] versus 1/[Na^+] throughout the titration, and an association constant of $\sim 4.5 \times 10^3$ M^{-1} was thus deduced in CH_3CN. As shown in Fig. 2, drastic changes on the Na^+ fluorescence titration spectra were observed, in which both 460



Scheme 2

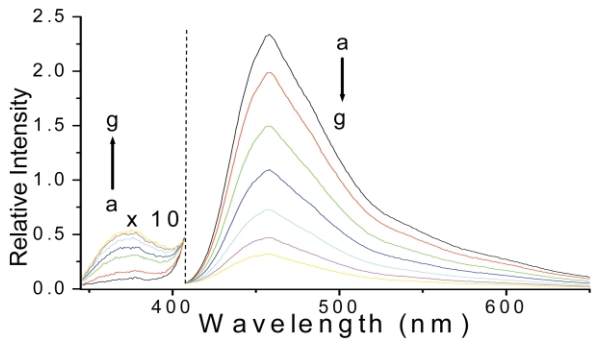


Fig. 2 Corresponding fluorescence titration spectra of Fig. 1 λ_{ex}: 340 nm.

nm anion and 540 nm zwitterion emissions decreased, accompanied by the increase of a 375 nm normal emission. The results can be rationalized by the weakening of O(7)H···N(1′) hydrogen bond upon the Na^+/azacrown complex formation, resulting in an absorption blue shift. Accordingly, the O(7)–H → N(1′) ESPT process is prohibited due to the usage of dialkylamino lone pair electrons upon Na^+ complexation, giving rise to a normal Stokes shifted emission.

In a comparative study, the absorption spectra of **1a** as a function of the divalent metal ions, *e.g.* [Ca^{2+}], in CH_3CN are shown in Fig. 3. At very low [Ca^{2+}] of e.g. $< 5.0 \times 10^{-5}$ M, a decrease of the 335 nm absorption band was observed, accompanied by a gradual increase of a shoulder at 365 nm and an appearance of isosbestic points at 310 nm and 347 nm. The 365 nm excitation gives rise to a ~450 nm emission, of which the spectral features are the same as those of the free **1a** anionic species (**A***, 460 nm). Further addition of [Ca^{2+}] revealed the appearance of a new 425 nm absorption band, accompanied by a decrease of the 365 nm anion-like band. Within these concentrations nonlinear behavior for the A_{425} versus [Ca^{2+}] was obtained.† The excitation of the 425 nm band gives rise to a strong fluorescence maximized at 510 nm ($\Phi_f \sim 0.36$, $\tau_f \sim 5.5$ ns Fig. 4), which are quite different from the absorption (355 nm) and emission (440 nm) maxima of 7HQ cationic form. Accordingly, the possibility that spectra originate from a 1:1 **1a**/Ca^{2+} complex in which Ca^{2+} binds the N(1) site of **1a** is eliminated. Instead the spectral and dynamic features are similar to those of the zwitterionic tautomer emission resulting from ESPT of free **1a** (540 nm, $\tau_f \sim 2.8$ ns). Similar absorption titration experiments were performed for **1b**, and the result is shown in the insert of Fig. 3. Comparing **1a** and **1b** in the Ca^{2+} absorption titration, two remarkable differences are promptly

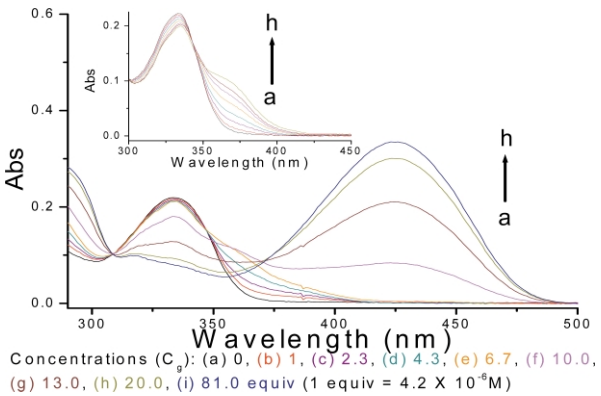


Fig. 3 Absorption spectra of **1a** (2.2×10^{-5} M) in CH_3CN by adding anhydrous $Ca(ClO_4)_2$ concentrations (C_g). Insert: the plot of absorption spectrum of compound (**1b**) (3.2×10^{-5} M) in CH_3CN by adding $Ca(ClO_4)_2$ concentrations (C_g): (a) 0, (b) 1, (c) 3, (d) 5, (e) 7, (f) 10, (g) 13, (h) 30 equiv (1 equiv = 1.4×10^{-5} M).

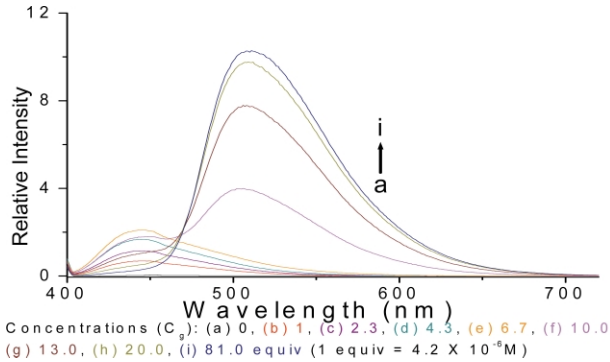


Fig. 4 Emission spectra of **1a** (2.2×10^{-5} M) in CH_3CN by adding Ca^{2+} concentrations (C_g). λ_{ex}: 400 nm.

pointed out: 1. Although a Ca^{2+} concentration-dependent spectral change was observed at ~365 nm for **1b**, the association constant of 1.4×10^3 M^{-1} is smaller than that in **1a** by ~40 fold. 2. Throughout the titration, the appearance of the 425 nm zwitterionic absorption band is negligible in the case of **1b**.

According to the above results, a **1a**/Ca^{2+} complexation mechanism based on a sequential, two-step coordination is tentatively proposed. The first Ca^{2+}/**1a** complexation incorporates oxy-anion ($O(7)^-$) site and azacrown, forming a six-member coordinated complex. The oxy-anion in **1a** acts as an axial ligand and is supported by its anion-like absorption (365 nm) and emission (450 nm) spectra upon complexing Ca^{2+}. Evidence of azacrown playing a role in the first-step complexation is given by the much smaller association constant in **1b** that lacks the stabilization of the crown ether.

To rationalize the zwitterion-like chromophore in **1a** upon further increasing [Ca^{2+}], the second coordination step should entail the attachment of one more stoichiometry Ca^{2+}, most plausibly, to the quinolinic nitrogen (N(1)) site of **1a**. Because a similar 425 nm zwitterion-like absorption spectrum was obscure in **1b** throughout the titration (Fig. 3), it is reasonable to propose a flip of the azacrown toward the N(1) nitrogen during the second-step complexation in **1a**. On one hand, the first Ca^{2+} binding strength decreases via altering a six-member coordinated complex to a possible bidentate coordination in that the structure is similar to that proposed for **1b**/Ca^{2+}. On the other hand, more stabilization energy is gained by introducing an additional complexation among second added Ca^{2+}, N(1) and crown-ether. The Ca^{2+}/N(1) dative bond, in combination with the oxy-anion formation, makes the parent 7HQ chromophore in **1a** a zwitterion-like configuration that exhibits absorption and emission at 425 and 510 nm, respectively. In this proposed scheme azacrown acts as a crane to regulate dual Ca^{2+} coordination. Based on the existence of equilibrium among **1a**, **1a**/Ca^+ and **1a**/$(Ca^{2+})_2$ the association constants of **1a**/Ca^{2+} and **1a**/Ca^{2+} → **1a**/$(Ca^{2+})_2$ formation were deduced to be 5.5×10^4 (K_1) and 4.6×10^3 (K_2), respectively.† Because K_1 is much greater than K_2, a switch between 1:1 **1a**/Ca^{2+} and 1:2 **1a**/Ca^{2+} states is possible, as indicated by the observation of a pseudo-isosbestic point at ~370 nm.

In conclusion, we have reported the design and synthesis of a new metal-cation probe in which the recognition is based on either an ESPT manipulating (e.g. Na^+) or a sequential, double complexation (e.g. Ca^{2+}) mechanism. In the former case the intensity ratio for 460 nm versus 375 nm emission renders a sensitive fluorescence method for probing the **1a**/Na^+ complexation. In the latter case, the fluorescence yield for the zwitterionic form was measured to be as high as 0.36. By selecting the excitation at >425 nm where the absorbance is solely attributed to the zwitterionic form, low detection limit can be achieved on the basis of the background-free 510 nm emission. The ratiometric fluorescence proved to be a very reliable and sensitive method for the real time detection of **1a**/metal ions complexation.

Notes and references

1 For recent examples, see: (*a*) B. Witulski, M. Weber, U. Bergsträsser, J. P. Desvergne, D. M. Bassani and H. Bouas-Laurent, *Org. Lett.*, 2001, **3**, 1467; (*b*) T. Gunnlaugsson, M. Nieuwenhuyzen, L. Richard and Thoss, *J. Chem. Soc., Perkin Trans. 2*, 2002, 141; (*c*) T. Gunnlaugsson, A. J. Harte, J. P. Leonard and M. Nieuwenhuyzen, *Chem. Commun.*, 2002, **18**, 2134; (*d*) J. H. Liao, C. T. Chen, H. C. Chou, C. C. Cheng, P. T. Chou, J. M. Fang, Z. Slanina and T. Chow, *Org. Lett.*, 2002, **4**, 3107.

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4 A_0 and A denote the absorbance of free **1a**, and solution after adding Ca^{2+}, respectively at a selective wavelength.†.