ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 12092–12094

www.rsc.org/chemcomm

COMMUNICATION

A selective colorimetric and fluorometric ammonium ion sensor based on the H-aggregation of an aza-BODIPY with fused pyrazine rings†

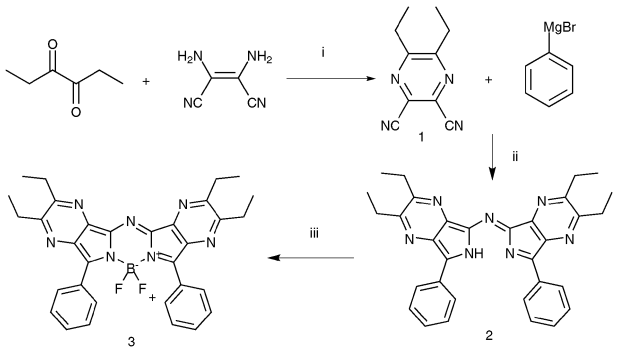
Hanzhuang Liu,[ab] John Mack,[b] Qiuli Guo,[a] Hua Lu,[c] Nagao Kobayashi*[b] and Zhen Shen*[a]

Received 17th September 2011, Accepted 7th October 2011
DOI: 10.1039/c1cc15746a

The synthesis of a novel aza-BODIPY dye functionalized with fused pyrazine rings, suitable for use as a selective colorimetric and fluorometric sensor for NH_4^+, is outlined. In addition to significant fluorescence quenching, an obvious colorimetric change from green to red-pink is observed enabling facile "naked-eye" detection of NH_4^+.

Boradiazaindacenes (BODIPY dyes, BDPs, difluoroboradipyrromethenes, *etc.*) have been studied extensively,[1] since their spectroscopic properties are suitable for many applications,[2] including use in ion sensing and signalling,[3] and as fluorescent labels in biomolecules.[4] The absorption and emission bands associated with the S1 state of the unmodified BODIPY parent complex lie at *ca.* 500 nm. While this is satisfactory for many applications, a red shift of the absorption and fluorescence maxima into the red end of the visible region, or still further into the near-infrared, would be advantageous in others, given the recent advances in optical techniques for imaging, microarrays, and electrophoresis, and the Rayleigh scattering and pigmentation problems that are often encountered with biological samples.[5]

Many different approaches have been explored to obtain this red shift of the main BODIPY absorption band, including the introduction of aromatic or heteroaromatic rings as substituents at the 3-, 5- and/or 1-,7-positions on the pyrrole moieties[6] and aromatic ring fusion.[7] Replacing the *meso*-carbon atom with an aza-nitrogen atom to form an aza-BODIPY[8] typically results in a *ca.* 90 nm red shift of the main absorption band with respect to the analogous non-substituted BODIPY derivatives.[9] Until recently a key drawback in the context of sensor applications was that suitable ion binding groups can no longer be introduced at the *meso*-carbon. Recent advances in aza-BODIPY synthesis based on the use of phthalonitrile precursors[2] have enabled the facile synthesis of fused ring expanded aza-BODIPYs, which considerably enhances the scope for introducing structural modifications that enhance the ion binding properties.



Scheme 1 Synthetic procedures for aza-BODIPY **3**. (i) H_2O/ethanol (2 : 3), acetic acid, reflux; (ii) dry diethyl ether, RT, 1 h; (iii) $BF_3{\cdot}OEt_2$, triethylamine, dry CH_2Cl_2, reflux.

In this communication, we report the rational design and synthesis of a novel aza-BODIPY, **3**, containing two fused pyrazine rings (Scheme 1). The rationale for introducing fused pyrazine rings is that it results in the presence of close-lying nitrogen atoms, which can potentially bind large cations in the *meso*-pocket or between neighboring aza-BODIPY complexes. A survey of the interaction between **3** and a wide range of metal ions subsequently demonstrated that marked changes in the optical properties are only observed for the NH_4^+ ion in a manner which facilitates its colorimetric and fluorometric detection. The aza-diisoindolmethine precursor, **2**, was prepared by adding a phenyl Grignard reagent to a suspension of 5,6-diethylpyrazine-2,3-dicarbonitrile, **1**, in diethyl ether (Scheme 1 and ESI†) according to the published procedures for benzo-fused aza-BODIPYs.[2] The corresponding boron difluoride complex was obtained from a reaction with borondifluoride diethyl ether complexes and a base under reflux in CH_2Cl_2. The structure of **3** was confirmed by ^1H NMR spectroscopy, MS and single-crystal X-ray diffraction analysis.

A single crystal of **3** suitable for X-ray structural analysis was obtained by diffusion of hexane into a solution of **3** in CH_2Cl_2 (Fig. 1 and ESI†). The structure is comparable to

[a] *State Key Laboratory of Coordination Chemistry, Nanjing National Laboratory of Microstructures, Nanjing 210093, P. R. China. E-mail: zshen@nju.edu.cn; Fax: +86 (0)25-83314502; Tel: +86 (0)25-83686679*
[b] *Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan. E-mail: nagaok@m.tohoku.ac.jp; Fax: +81 (0)22-795-7719*
[c] *Key Laboratory of Organosilicon Chemistry and Material Technology, Ministry of Education, Hangzhou Normal University, Hangzhou, 310012, P. R. China*

† Electronic supplementary information (ESI) available: ^1H NMR spectra, X-ray analysis of aza-BODIPY **3**, synthesis details, *etc.* CCDC 843443. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc15746a

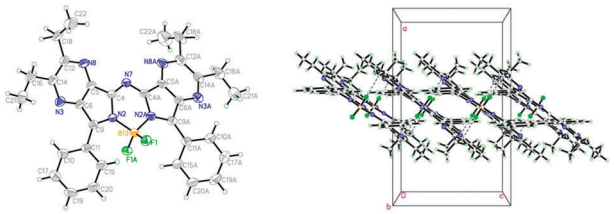


Fig. 1 Front ORTEP view of the molecular structure of **3** with the thermal ellipsoids set at 30% probability (left). A one-dimensional chain of **3** viewed along the *c* axis (right).

those reported previously for other aza-BODIPY compounds.[9b] The boron atom is coordinated in a tetrahedral geometry by two nitrogen and two fluorine atoms. The indacene plane of **3** is nearly planar. The average deviation from the mean plane is only 0.1181 Å. The neighboring aza-BODIPY molecules are linked by intermolecular C–H···F hydrogen bonds to form a one dimensional chain along the *c* axis (Fig. 1). The distance between neighboring indacene planes is 3.59 Å. This indicates that there is a strong π–π interaction within the chain.

The absorption and fluorescence spectra of **3** in THF (Fig. S3, ESI†) exhibit the characteristic properties normally anticipated for the aza-BODIPY chromophore. An intense absorption peak is observed at 685 nm with a relatively narrow band width, which lies 24 nm to the blue of the corresponding band in the spectrum of the benzo-fused compound, **4**.[9b] The band in the fluorescence spectrum at 721 nm exhibits mirror symmetry with the absorption band. The Stokes shift observed for **3** (36 nm) is significantly larger than that reported for **4** (17 nm).

Molecular orbital (MO) calculations were performed for **3** and **4** using the B3LYP functional with 6-31G (d) basis sets (Fig. 2). Larger MO coefficients are observed on the pyrazine moieties of **3** relative to the fused benzene rings of **4** due to the higher electronegativity of the nitrogen atoms. Since the HOMO of **3** has significant MO coefficients on all four pyrazine nitrogen atoms, while the LUMO does not, the relative stabilization of the HOMO of **3** can be readily accounted for. The greater HOMO–LUMO band gap value,

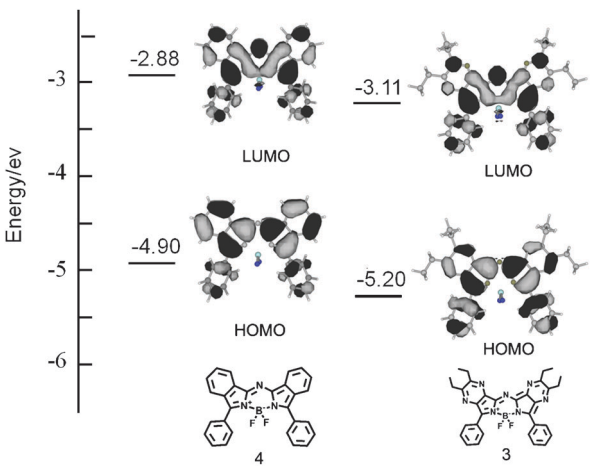


Fig. 2 Energy-level diagram for the frontier π-MOs of **3** and **4**. The nodal patterns of each MO are shown at an isosurface value of 0.02 a.u.

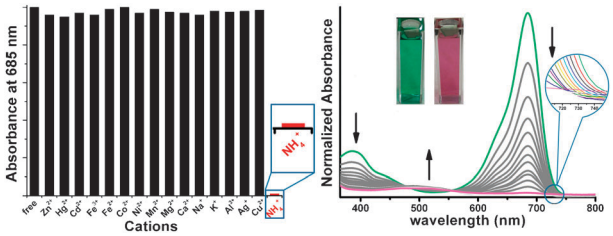


Fig. 3 Absorption intensity observed at 685 nm upon addition of various metal ions (black) and the NH_4^+ ion (red) to 10 μM solutions of **3** in THF solution (left). Changes in the absorption spectrum of aza-BODIPY **3** (10 μM in THF) as the ammonium acetate concentration is increased. The inset shows the solution colour before (green) and after (pink) addition of NH_4^+ (right).

which results from this, causes the blue-shift of the lowest-energy absorption band relative to that of **4**.

Almost no change is observed in the absorption intensity of **3** upon addition of excess of Zn^{2+}, Cd^{2+}, Hg^{2+}, Co^{2+}, Fe^{3+}, Fe^{2+}, Ni^{2+}, Mn^{2+}, Cu^{2+}, Mg^{2+}, Na^+, Al^{3+} and Ca^{2+}, but when NH_4^+ is added to the THF solution, the typical transition bands for aza-BDP decrease significantly and a weak broader band appears at 505 nm instead (Fig. 3). This results in a visible colorimetric change from green to red-pink. Although an isosbestic point is observed at 555 nm, the lack of similar isosbestic points at *ca.* 480 and 740 nm is consistent with the presence of at least three different species, since isosbestic points would be observed across the entire spectrum in the context of interconversion between two species (Fig. 3).[10] Turn-off fluorescent detection of the NH_4^+ ion can also be carried out (Fig. 4).

The most obvious explanation for the NH_4^+ mediated color change and fluorescent quenching is that there is H-aggregation[11] of the aza-BODIPY. In the absence of the NH_4^+ ion, an intense $S_0 \rightarrow S_1$ transition associated primarily with the core aza-BODIPY π-system results in the intense absorption band with a narrow band width typically observed for BODIPY dyes. Upon addition of the NH_4^+ ion, there is a marked decrease in the molar absorption coefficient and a broader band is observed at shorter wavelength and a quenching of the fluorescence intensity. This is the pattern typically observed for H-aggregates. Although their solution structures are often still poorly understood, it is generally accepted that this is due to face-to-face stacking of the monomer and a parallel alignment of electric dipole transition moments perpendicular to the axis of stacking.[12] The key difference between the NH_4^+ ion and the metal ions that were studied is the tetrahedral structure due

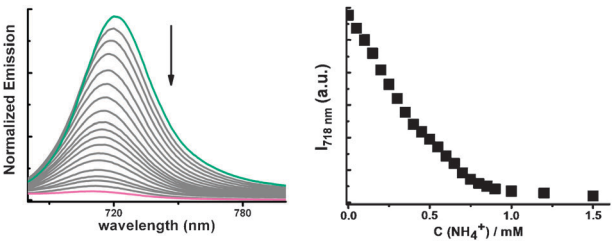


Fig. 4 Emission spectrum of aza-BODIPY **3** in the presence of increasing NH_4^+ concentration in THF (left, λ_{ex} = 630 nm). The emission intensity at 718 nm changes as a function of NH_4^+ concentration (right).

to the four N–H bonds. This provides scope for hydrogen bonding similar to that reported previously by Ahn *et al.* in the context of an alaninol-derived tripodal oxazoline,[13] and hence for aggregation. If aza-BODIPY complexes are aligned face-to-face in an opposite direction as is required to avoid steric crowding due to the phenyl rings and BF_2, an NH_4^+ ion can potentially interact with the four nitrogen atoms of two pyrazine rings in a tetrahedral geometry (Fig. S4, ESI†). There is also scope for hydrogen bonding with the central *meso*- and pyrrole nitrogens. H-aggregation is not observed with **4**, since hydrogen bonding is not possible with the peripheral fused benzene rings.

A blue-shifted absorption band is typically observed for H-aggregates, since only the transition to a higher energy exciton state is optically allowed (Fig. S4, ESI†) when the electric dipole transition moments are aligned parallel to the axis of stacking.[12] H-aggregate spectra usually do not contain the unusually narrow and intense bands that are observed in the spectra of J-aggregates, but tend instead to contain bands of comparable width to the monomer with associated vibrational bands.[14] The intensity mechanism for the blue-shifted H-aggregate band is currently less well understood and more difficult to predict than that of the red-shifted bands of J-aggregates.[14] Calculations on a model trimer structure predict that even with a relatively limited degree of aggregation the lowest energy state is greatly stabilized (Fig. S5, ESI†). H-aggregates are usually weakly or non-fluorescent, since either non-radiative decay is the dominant pathway back to the ground state for this reason or there is an enhancement of intersystem crossing to the triplet manifold.[12]

In conclusion, the rational design of an aza-BODIPY dye with fused pyrazine rings provides the first example of the use of a fused-ring-expanded aza-BODIPY complex as a chemosensor. Highly selective colorimetric and fluorometric detection of the NH_4^+ ion is observed and the pronounced spectral changes enable naked-eye detection. The successful rational design and synthesis of this dye and its apparent H-aggregation further demonstrate how the flexibility which is introduced by the use of phthalonitriles as precursors[2] can provide scope for the development of efficient aza-BODIPY chemosensors suitable for use in the NIR region, despite the absence of the *meso*-carbon typically used to incorporate recognition units in the context of BODIPYs.

Financial support was provided by the National Natural Science Foundation of China (nos. 20971066 and 21021062), the Chinese Ministry of Education's Program for New Century Excellent Talents in Universities (no. NCET-08-0272), the Major State Basic Research Development Program of China (grant nos. 2011CB808704 and 2007CB925103), and a Grant-in-Aid for Scientific Research on Innovative Areas (no. 20108007, "pi-Space") from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT), Japan.

Notes and references

1 (*a*) R. Gresser, M. Hummert, H. Hartmann, K. Leo and M. Riede, *Chem.–Eur. J.*, 2011, **17**, 2939; (*b*) Z. Dost, S. Atilgan and E. U. Akkaya, *Tetrahedron*, 2006, **62**, 8484; (*c*) R. P. Haugland, Handbook of Fluorescent Probes and Research Products, 9th edn, 2002, 830–932.
2 H. Lu, S. Shimizu, J. Mack, Z. Shen and N. Kobayashi, *Chem.–Asian J.*, 2011, **6**, 1026.
3 (*a*) B. Turfan and E. U. Akkaya, *Org. Lett.*, 2002, **4**, 2857; (*b*) G. Ulrich and R. Ziessel, *J. Org. Chem.*, 2004, **69**, 2070; (*c*) K. Rurack, M. Kollmannsberger, U. Resch-Genger and J. Daub, *J. Am. Chem. Soc.*, 2000, **122**, 968.
4 F. Bergstrom, I. Mikhalyo and P. Hagglof, *J. Am. Chem. Soc.*, 2002, **124**, 196.
5 (*a*) Z. Shen, H. Rohr, K. Rurack, H. Uno, M. Spieles, B. Schulz, G. Reck and N. Ono, *Chem.–Eur. J.*, 2004, **10**, 4853; (*b*) K. Rurack, M. Kollmannsberger and J. Daub, *Angew. Chem., Int. Ed.*, 2001, **40**, 385; (*c*) A. Coskun, E. Deniz and E. U. Akkaya, *Org. Lett.*, 2005, **7**, 5187.
6 (*a*) R. Guliyev, A. Coskun and E. U. Akkaya, *J. Am. Chem. Soc.*, 2009, **131**, 9007; (*b*) Y. H. Yu, A. B. Descalzo, Z. Shen, Q. Liu, Y. W. Wang, M. Spieles, Y. Z. Li, K. Rurack and X. Z. You, *Chem.–Asian J.*, 2006, **1**, 176; (*c*) D. Kumaresan, R. P. Thummel, T. Bura, G. Ulrich and R. Ziessel, *Chem.–Eur. J.*, 2009, **15**, 6335; (*d*) K. Rurack, M. Kollmannsberger and J. Daub, *New J. Chem.*, 2001, **25**, 289; (*e*) Q. Zheng, G. Xu and P. N. Prasad, *Chem.–Eur. J.*, 2008, **14**, 5812; (*f*) O. Buyukcakir, O. A. Bozdemir, S. Kolemen, S. Erbas and E. U. Akkaya, *Org. Lett.*, 2009, **11**, 4644; (*g*) O. A. Bozdemir, O. Buyukcakir and E. U. Akkaya, *Chem.–Eur. J.*, 2009, **15**, 3830; (*h*) T. Rousseau, A. Cravino, T. Bura, G. Ulrich, R. Ziessel and J. Roncali, *Chem. Commun.*, 2009, 1673; (*i*) T. Rousseau, A. Cravino, T. Bura, G. Ulrich, R. Ziessel and J. Roncali, *J. Mater. Chem.*, 2009, **19**, 2298; (*j*) J. Y. Liu, E. A. Ermilov and B. Roder, *Chem. Commun.*, 2009, 1517; (*k*) S. Diring, F. Puntoriero, F. Nastasi, S. Campagna and R. Ziessel, *J. Am. Chem. Soc.*, 2009, **131**, 6108.
7 (*a*) A. B. Descalzo, H. J. Xu, Z. L. Xue, K. Hoffmann, Z. Shen, M. G. Weller, X. Z. You and K. Rurack, *Org. Lett.*, 2008, **10**, 1581; (*b*) K. Umezawa, Y. Nakamura, H. Makino, D. Citterio and K. Suzuki, *J. Am. Chem. Soc.*, 2008, **130**, 1550; (*c*) Z. Shen, H. Röhr, K. Rurack, H. Uno, M. Spieles, B. Schulz, G. Reck and N. Ono, *Chem.–Eur. J.*, 2004, **10**, 4853; (*d*) S. Atilgan, Z. Ekmekci, A. L. Dogan, D. Guc and E. U. Akkaya, *Chem. Commun.*, 2006, 4398.
8 (*a*) J. Killoran, L. Allen, J. Gallagher, W. Gallagher and D. F. O'Shea, *Chem. Commun.*, 2002, 1862; (*b*) A. Coskun, M. D. Yilmaz and E. U. Akkaya, *Org. Lett.*, 2007, **9**, 607; (*c*) W. Zhao and E. M. Carreira, *Chem.–Eur. J.*, 2006, **12**, 7254; (*d*) A. Loudet, R. Bandichhor, K. Burgess, A. Palma, S. O. McDonnell, M. J. Hall and D. F. O'Shea, *Org. Lett.*, 2008, **10**, 4771; (*e*) Y. H. Yu, Z. Shen, H. Y. Xu, Y. W. Wang, T. Okujima, N. Ono, Y. Z. Li and X. Z. You, *J. Mol. Struct.*, 2007, **827**, 130; (*f*) H. Lu, L. Q. Xiong, H. Z. Liu, M. X. Yu, Z. Shen, F. Y. Li and X. Z. You, *Org. Biomol. Chem.*, 2009, **7**, 2554.
9 (*a*) H. C. Kang and R. P. Haugland, *U.S. Patent* 5433896, July 18, 1955; (*b*) V. F. Donyagina, S. Shimizu, N. Kobayashi and E. A. Lukyanets, *Tetrahedron Lett.*, 2008, **49**, 6152.
10 (*a*) N. Kobayashi, M. Fujihira, T. Osa and T. Kuwana, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 2195; (*b*) N. Kobayashi and A. B. P. Lever, *J. Am. Chem. Soc.*, 1980, **109**, 7433.
11 (*a*) V. Novakova, P. Zimcik, M. Miletin, L. Vachova, K. Kopecky, K. Lang, P. Chábera and T. Polívka, *Phys. Chem. Chem. Phys.*, 2010, **12**, 2555; (*b*) S. Kim, T. K. An, J. Chen, L. Kang, S. H. Kang, D. S. Chung, C. E. Park, Y. H. Kim and S. K. Kwon, *Adv. Funct. Mater.*, 2011, **21**, 1616; (*c*) Y. Tokoro, A. Nagai and Y. Chujo, *Tetrahedron Lett.*, 2010, **51**, 3451; (*d*) S. Gadde, E. K. Betchelor, J. P. Weiss, Y. H. Ling and A. E. Kaifer, *J. Am. Chem. Soc.*, 2008, **130**, 17119; (*e*) A. Chowdhury, S. Wachsmannhogiu, P. R. Bangal, I. Raheem and L. A. Peteanu, *J. Phys. Chem. B*, 2001, **105**, 12196; (*f*) Y. H. Zhang and Y. Wu, *Chin. Chem. Lett.*, 2005, **16**, 279; (*g*) J. Kang, O. Kaczmarek, J. Liebscher and L. Dähne, *Int. J. Polym. Sci.*, 2010, 264781.
12 (*a*) M. Kasha, H. R. Rawis and M. A. El-Bayoumi, *Pure Appl. Chem.*, 1965, **11**, 371; (*b*) T. Katoh, Y. Inagaki and R. Okazaki, *Bull. Chem. Soc. Jpn.*, 1997, **70**, 2279.
13 K. H. Ahn, H.-Y. Ku, Y. Kim, S.-G. Kim, Y. K. Kim, H. S. Son and J. K. Ku, *Org. Lett.*, 2003, **5**, 1419.
14 A. Eisfeld and J. S. Briggs, *Chem. Phys.*, 2006, **324**, 376.

