RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 3591

Dual off–on and on–off fluorescent detection of Zn^{2+}/Cd^{2+} ions based on carbazolone substituted 2-aminobenzamides†

Qin-Chao Xu,[a] Xue-Hui Zhu,[a] Can Jin,[a] Guo-Wen Xing*[a] and Yuan Zhang*[ab]

Received 10th October 2013
Accepted 2nd December 2013

DOI: 10.1039/c3ra45717f

www.rsc.org/advances

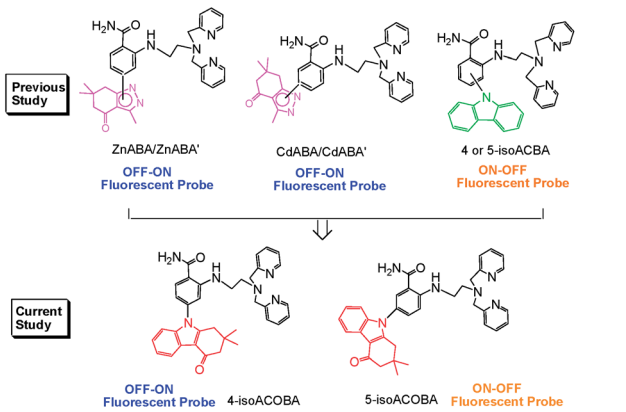
Two new 2-aminobenzamide structural isomers, 4-isoACOBA and 5-isoACOBA, as fluorescent probes for Cd^{2+} and Zn^{2+} were fabricated with carbazolone as fluorophore and *N*,*N*-bis(2-pyridylmethyl) ethylenediamine (BPEA) as chelator. With Cd^{2+}/Zn^{2+} as input, the two probes are characteristic of the transformation from "off–on" to "on–off" molecular switch by interchanging the substitution position of the fluorophore from C-4 to C-5 at the benzene ring. 4-IsoACOBA is a Cd^{2+}-specific *turn-on* fluorescent probe exhibiting good discrimination between Cd^{2+} and Zn^{2+} with $F_{Cd2+}/F_{Zn2+} = 2.48$, while 5-isoACOBA is a Zn^{2+}-specific *turn-off* probe with $F_{Cd2+}/F_{Zn2+} = 4.50$. The binding behaviours of 4-isoACOBA–Cd(II) and 5-isoACOBA–Zn(II) were deeply investigated by UV and fluorescence titration, ESI-MS analysis, and DFT study. The results indicate that both the electron donating/withdrawing ability and the substituted position of the fluorophore have remarkable influences on the probe sensing properties and selectivity.

Introduction

Zinc and cadmium are both in the IIB group of the periodic table. However, they exert distinct influence on animals and human beings. For one thing, cadmium plays an essential role in many processes including electroplating, metallurgy, agriculture and war industry, *etc.*;[1] for another, it is a toxic heavy metal element and considered as one of 126 priority pollutants as pronounced by the U.S. Environmental Protection Agency. The long-term cadmium intake will affect human hematopoietic, neural, kidney, and other organ function, bringing great harm to human health, especially to children.[2] By contrast, zinc, an essential element for human, is widely distributed in almost all tissues and organs. It is the component of a variety of enzymes, directly involved in the synthesis of the nucleic acid and protein and stimulating lymphocytes into the division.[3]

Fluorescence is a highlighted method to recognize and sense ions and small molecules due to its operational simplicity effectiveness, high sensitivity and low detection limit. The design and application of various fluorogenic probes have made great progress in recent years.[4] Even though the fluorescent recognition and sensing systems for zinc and cadmium ions have been extensively investigated,[5–7] it is still challenging to develop efficient fluorescent sensors which can distinguish Zn^{2+} and Cd^{2+} with high selectivity and sensitivity, since zinc and cadmium are usually coordinated with fluorescent sensors with similar fluorescent signal output.

In recent years, 2-aminobenzamide analogues have been concerned as heat shock protein 90 inhibitors.[8] Soon afterwards we developed a novel 2-aminobenzamide analogue BJ-B11 (ref. 9) and elucidated its inspiring antitumor and anti-HSV activities. Meanwhile, some attractive fluorescent properties of these compounds were observed in the study. Inspired by the observations, we successfully designed a series of Zn(II) and Cd(II)-specific off–on fluorescent probes ZnABA/ZnABA′ and CdABA/



Scheme 1 Design route of carbazolone substituted 2-aminobenzamide fluorescent probes for Zn(II)/Cd(II) ions.

[a]*Department of Chemistry, Beijing Normal University, Beijing 100875, China. E-mail: gwxing@bnu.edu.cn; yuanzhang@bnu.edu.cn*

[b]*Key Laboratory of Theoretical and Computational Photochemistry, Ministry of Education, College of Chemistry, Beijing Normal University, Beijing 100875, China*

† Electronic supplementary information (ESI) available: Detailed synthetic procedures and characterization of 4- and 5-isoACOBA. Fig. S1–S5 and copies of NMR spectra for all the new compounds. See DOI: 10.1039/c3ra45717f

CdABA′ (Scheme 1),[10] with tetrahydroindazolone as fluorophore and *N*,*N*-bis(2-pyridylmethyl)ethylenediamine (BPEA) as chelator. More recently, carbazole was introduced into the sensing system to generate 4 and 5-isoACBA (Scheme 1),[11] which exhibit an excellent fluorescence on–off–on response for Zn(II) and pyrophosphate (PPi) ions. Based on these results, herein we focus on carbazolone, an alternative fluorophore, to fabricate new fluorescent probes 4 and 5-isoACOBA for Zn(II)/Cd(II) ions (Scheme 1).

Results and discussion

Indeed, fluorescent sensor, usually consist of a signal label and a receptor. The exquisite combination of them usually leads to excellent recognition for the target analytes. We have synthesized a series of 2-aminobenzamide analogues with indazolone and carbazole as fluorophore respectively which exhibit high selectivity and sensitivity for Zn(II), Cd(II) or PPi ions.[10,11] It is inspiring to explore the relationship between the nature of the fluorophore and the photophysical properties of the sensor. We found two important facts from the studies.[10,11]

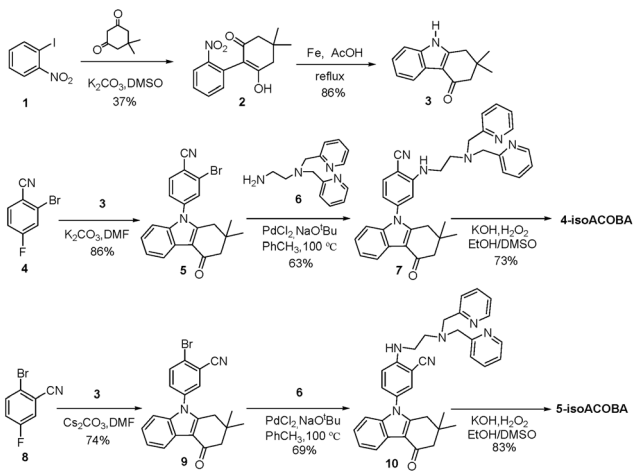
First, when the electron donating/withdrawing ability of the fluorophore changed, the fluorescence response is switched from on–off to off–on sensing action. With indazolone, a relative electron-deficient aromatic substituent, as the fluorophore, all the four metal probes (ZnABA/ZnABA′, CdABA/CdABA′) possess off–on fluorescent functionality.[10] In sharp contrast, when carbazole, a relative electron-rich aromatic substituent, was employed as the fluorophore, the two probes (4 and 5-isoACBA) exhibit on–off type fluorescent response to Zn(II)/Cd(II).[11]

Second, the substituted position of fluorophore on the benzamide ring is crucial to the probe for preference of Cd^{2+} or Zn^{2+}. Upon changing the indazolone group at the aromatic ring from 4- to 5-position, the structures of ZnABA/ZnABA′ are converted into CdABA/CdABA′. Correspondingly, the metal ions selectivity of CdABA/CdABA′ was switched to discriminate Cd^{2+} from Zn^{2+} with $F_{Cd2+}/F_{Zn2+} = 2.27–2.36$.[10b]

In general, both the electron donating/withdrawing ability and the substituted position of the fluorophore have remarkable influence on the probe sensing behaviour and selectivity. In this study, we selected carbazolone as the fluorophore, which possesses the moderate electron-withdrawing ability between indazolone and carbazole, and expect the designed probe 4- and 5-isoACOBA could have different fluorescence sensing activities to Cd^{2+} or Zn^{2+} compared with the former probes[10,11] reported by us.

Carbazolone **3** was prepared from 2-nitroiodobenzene (**1**) and dimedone in two steps according to the literature method (Scheme 2).[12] Then, **3** was attached to the benzene ring by aromatic nucleophilic substitution in the presence of K_2CO_3/Cs_2CO_3 to afford **5**/**9** in 74–86% yield. Subsequently, the BPEA moiety was incorporated into the aromatic ring under Buchwald–Hartwig coupling conditions[13] to provide **7**/**10** in 63–69% yield. After hydration of **7**/**10** with KOH and H_2O_2, the desired probe 4-/5-isoACOBA was accomplished in good yield.

The metal ion selectivity of 4-/5-isoACOBA was investigated by adding various metal salts in 25 mM HEPES buffer containing 15% ethanol at pH 7.4. 4-IsoACOBA exhibited weak fluorescence emission (Fig. 1). Interestingly, most heavy and transition metal ions, such as Cr^{3+}, Mn^{2+}, Fe^{3+}, Sm^{2+}, Co^{2+} and Cu^{2+} had no *turn-on* response to the sensor, except that Cd^{2+} and Zn^{2+} induced 8.3-fold and 3.4-fold fluorescence enhancement respectively. Moreover, the fluorescence of 4-isoACOBA showed no changes upon adding 100-fold excess of Na^+, K^+, Mg^{2+}, Ca^{2+} into the solution. The results indicate that 4-isoACOBA is a Cd^{2+}-sepecific off–on fluorescent probe with $F_{Cd2+}/F_{Zn2+} = 2.48$.



Scheme 2 Synthetic routes for 4- and 5-isoACOBA.

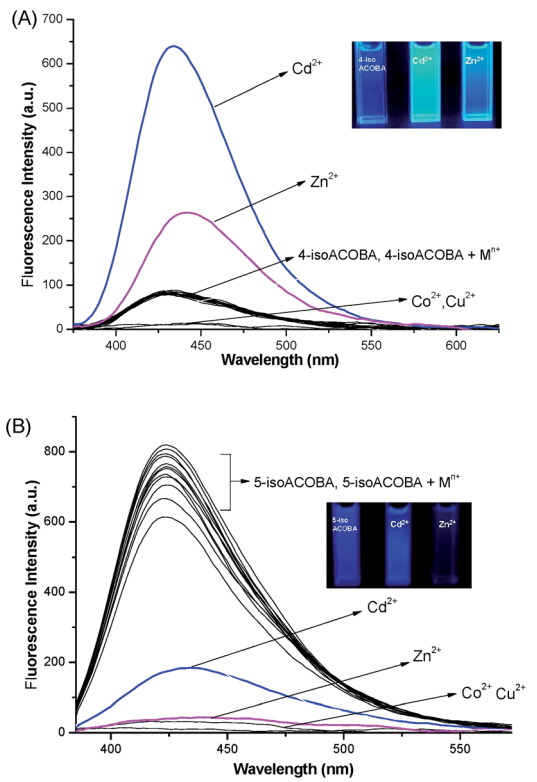


Fig. 1 Fluorescence spectra of (a) 4-isoACOBA and (b) 5-isoACOBA on the addition of various metal ions. *Experimental conditions*: 4- or 5-isoACOBA (10 μM, 25 mM HEPES buffer containing 15% ethanol, 0.1 M $NaClO_4$, pH 7.4), 10 μM Li^+, K^+, Rb^+, Cs^+, Ca^{2+}, Mg^{2+}, Ba^{2+}, Sr^{2+}, Cr^{3+}, Mn^{2+}, Fe^{3+}, Sm^{2+}, Co^{2+}, Cu^{2+}, Cd^{2+} and Zn^{2+}, $\lambda_{ex} = 318$ nm.

Table 1 Spectroscopic data for the probes used in this study

Compound	$\lambda_{abs,max}$ (nm)	ε^a (M^{-1} cm^{-1})	$\lambda_{em}{}^b$ (nm)	Φ^c	$K_a{}^d$ (M^{-1})
4-IsoACOBA	245, 312, 360	12 744	430	0.032	—
4-IsoACOBA + Cd^{2+}	245, 312	12 744	434	0.103	1.89×10^{12}
4-IsoACOBA + Zn^{2+}	243, 312	12 294	448	0.037	9.70×10^{8}
5-IsoACOBA	263, 312, 365	23 237	422	0.074	—
5-IsoACOBA + Zn^{2+}	263, 312	18 740	464	0.039	1.62×10^{9}
5-IsoACOBA + Cd^{2+}	262, 312	17 392	443	0.083	1.02×10^{12}

[a] Data were examined at λ_{abs} 312 nm. [b] The excitation wavelength was 318 nm. [c] Quantum yields were determined by using quinine sulfate (in 0.05 M H_2SO_4, $\Phi = 0.55$) as the reference. [d] The association constant (K_a) was determined according to the methods reported in ref. 6*a*, 7*g*, *j* and 14.

To our surprise, 5-isoACOBA itself displays much stronger fluorescent emission at 422 nm than 4-isoACOBA (Fig. 1). When adding 1.0 equiv. of Zn^{2+}, the emission intensity presented an almost complete quenching (≥94%), while Cd^{2+} only led to a moderate quenching (~73%). Additionally, other metal ions including Li^+, K^+, Rb^+, Cs^+, Ca^{2+}, Mg^{2+}, Ba^{2+}, Sr^{2+}, Cr^{3+}, Mn^{2+}, and Fe^{3+} gave no obvious fluorescent changes, indicating that 5-isoACOBA is an on–off fluorescent probe for Zn^{2+} and Cd^{2+}, especially for Zn^{2+} with $F_{Cd2+}/F_{Zn2+} = 4.50$.

The detailed binding behaviours of 4-isoACOBA and 5-isoACOBA with Cd^{2+}/Zn^{2+} were examined by absorption and emission titrations in HEPES buffer containing 15% ethanol under physiological conditions. Table 1 shows the photophysical properties of 4-/5-isoACOBA. As indicated in Fig. 2a, UV spectra of 4-isoACOBA have three obvious absorption peaks at 245, 312 and 360 nm. With increasing the amounts of Cd^{2+} from 0 to 1.0 equiv., the absorbance gradually decreased at 245 and 360 nm, and simultaneously a slight increase emerged in the absorbance at 312 nm with two typical isobestic points arising at 296 and 318 nm, suggesting that the 4-isoACOBA–Cd(II) complex could be formed. Meanwhile, UV spectra of 5-isoACOBA also exhibited three absorption peaks at 263, 312 and 365 nm (Fig. 2b). But interestingly all the absorption peaks decreased gradually with the addition of Zn^{2+} (0–1.0 equiv.) and no obvious isobestic point was observed. In addition, similar absorption titration results

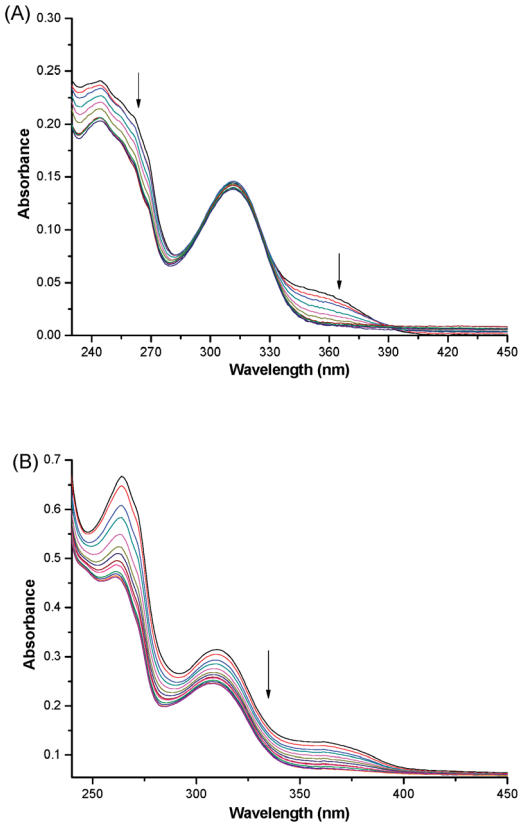


Fig. 2 UV absorption spectra of (a) 4-isoACOBA (10 μM) upon addition of Cd^{2+} (0–1.0 equiv.) and (b) 5-isoACOBA (10 μM) upon addition of Zn^{2+} (0–1.0 equiv.) in 25 mM HEPES buffer containing 15% ethanol (0.1 M $NaClO_4$, pH = 7.4).

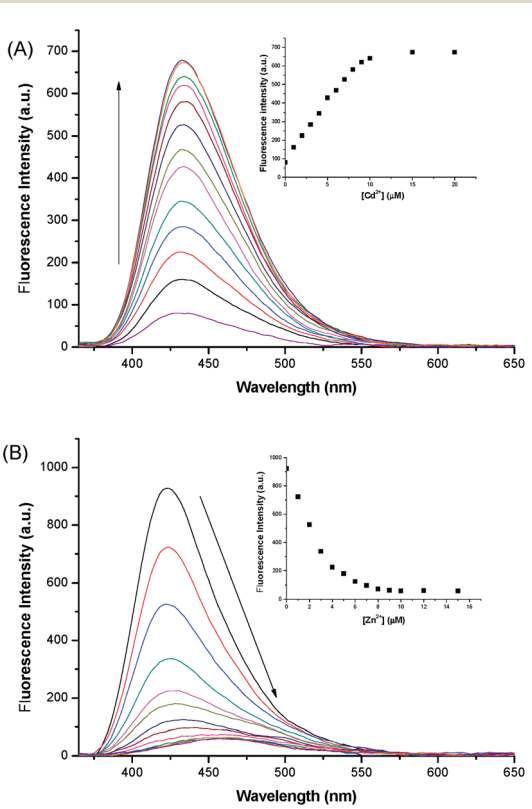


Fig. 3 Fluorescence spectra of (a) 4-isoACOBA upon addition of Cd^{2+} (0–2.0 equiv.) and (b) 5-isoACOBA upon addition of Zn^{2+} (0–1.5 equiv.). *Experimental conditions*: 4- or 5-isoACOBA (10 μM, 25 mM HEPES buffer containing 15% ethanol, 0.1 M $NaClO_4$, pH = 7.4), λ_{ex} = 318 nm.

were obtained for 4-isoACOBA–Zn(II) and 5-isoACOBA–Cd(II) complexes respectively (Fig. S3†).

As the fluorescence titration indicated (Fig. 3 and S4†), in the absence of Cd^{2+}, 4-isoACOBA showed a weak fluorescence emission peak at 430 nm with low quantum yield of 0.032 (Table 1). Upon addition of Cd^{2+} from 0 to 2 equiv., the intensity of the emission band gradually increased to reach a plateau at Cd^{2+} ≥1.0 equiv. Meanwhile, the maximum fluorescence emission peak was redshifted to 434 nm with improved quantum yield of 0.103. The Job's plot further confirmed that 1 : 1 complex between 4-isoACOBA and Cd^{2+} was formed (Fig. S1a†). The binding affinity of 4-isoACOBA towards Cd^{2+} was determined using cadmium–EGTA (ethylene glycol bis(2-aminoethyl ether)-*N*,*N*,*N*′,*N*′-tetraacetic acid) buffer as described by Jiang[7j] and Guo,[7g] and the association constant (K_a) of 4-isoACOBA–Cd(II) was evaluated to be 1.89×10^{12} M^{-1}.

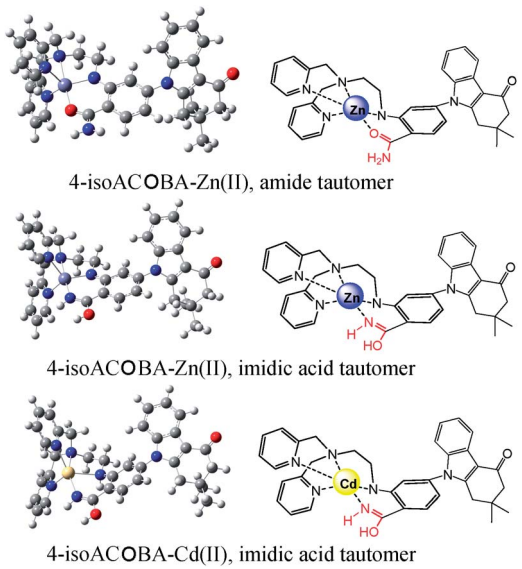


Fig. 4 The optimized geometry structures of 4-isoACOBA–Zn(II) and 4-isoACOBA–Cd(II).

For 5-isoACOBA, the addition of Zn^{2+} caused a large bathochromic shift from 422 nm to 464 nm (Table 1). It is reported that the coordination of probes with Zn^{2+} usually accompanies deprotonation.[7d,10] As shown in ESI-MS spectrum (Fig. S2†), the major peak at 635.5 corresponding to $[5\text{-isoACOBA} + Zn–H]^+$ was observed, suggesting that 5-isoACOBA binds Zn^{2+} in a 1 : 1 stoichiometry. In addition, the 1 : 1 binding ratio of 5-isoACOBA with Zn^{2+} was further confirmed by Job's plot (Fig. S1b†). The association constant of 5-isoACOBA for Zn^{2+} was calculated to be 1.62×10^9 M^{-1} by fluorescence spectroscopy in metal–ligand-buffered solutions with different Zn^{2+} concentrations.[6a,14]

Density functional theory (DFT) calculations were utilized to rationalize the dual fluorescence off–on and on–off sensing process for Cd^{2+}/Zn^{2+} with 4- and 5-isoACOBA as probes.

We carried out DFT calculations with B3LYP method using 6-31G(d) as basis sets to obtain two optimized structures of 4-isoACOBA–Zn(II), which are amide tautomer and imidic acid tautomer respectively (Fig. 4). Interestingly, the total electronic energies of the two tautomers were very close to each other, suggesting that the amide tautomer and imidic acid tautomer of 4-isoACOBA–Zn(II) should have the same stabilities. When we performed the geometry optimization of 4-isoACOBA–Cd(II), its amide tautomer structure calculation can not be converged. However, the calculation finally provided the optimized structure of the imidic acid tautomer of 4-isoACOBA–Cd(II) (Fig. 4). Similar results were also obtained for the geometry optimizations of 5-isoACOBA–Zn(II) and 5-isoACOBA–Cd(II) (Fig. S5†). Based on above findings, the structures of imidic acid tautomer of 4- or 5-isoACOBA with Cd^{2+}/Zn^{2+} ions are further investigated in the following study to rationalize the fluorescence off–on and on–off switch effects.

Tables 2 and 3 show the calculated molecular orbital (MO) surfaces of 4-/5-isoACOBA and its complex with Cd^{2+}/Zn^{2+} respectively. For free 4-isoACOBA, the HOMO electron density resides on benzamide and the lone pairs of ethylenediamine group. By contrast, the LUMO electron density is located on benzamide and the hetero atoms (N and O) of carbazolone.

Table 2 Surfaces of the MOs of 4-isoACOBA, 4-isoACOBA–Zn(II) and 4-isoACOBA–Cd(II)

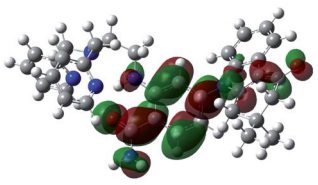
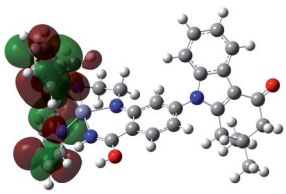
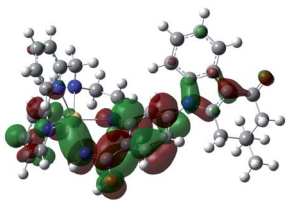
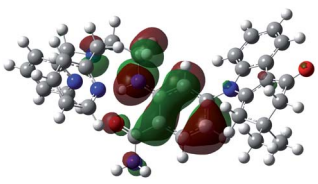
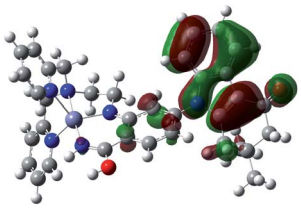
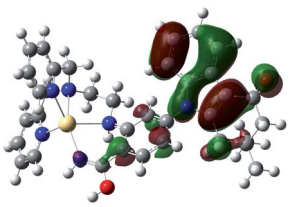
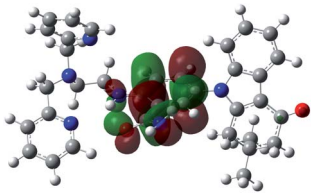
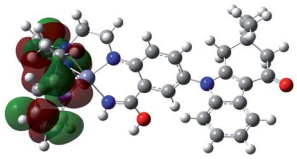
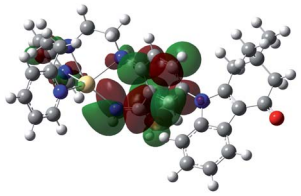
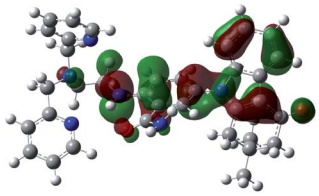
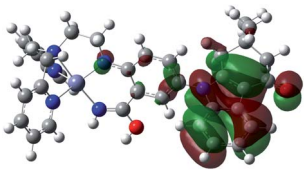
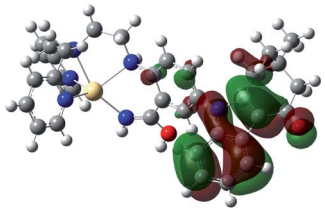
	4-IsoACOBA	4-IsoACOBA–Zn(II)	4-IsoACOBA–Cd(II)
LUMO			
HOMO			

Table 3 Surfaces of the MOs of 5-isoACOBA, 5-isoACOBA–Zn(II) and 5-isoACOBA–Cd(II)

	5-IsoACOBA	5-IsoACOBA–Zn(II)	5-IsoACOBA–Cd(II)
LUMO			
HOMO			

Since the $\pi^* \rightarrow n$ radiative pathway is inhibited during the excited state, only benzamide moiety of 4-isoACOBA generates very weak fluorescence emission (off state). In the case of 5-isoACOBA, the HOMO electron density is equally distributed on benzamide and carbazolone moieties, but the LUMO is mainly located on the benzamide. During the emissive state of 5-isoACOBA, the electron density between HOMO and LUMO is significantly redistributed. Therefore, an ICT (intramolecular charge transfer) process takes place to cause the strong fluorescence emission of 5-isoACOBA (on state).

Upon complexation with Zn^{2+}, interestingly, 4- and 5-isoACOBA–Zn(II) have almost the same localizations of HOMO and LUMO, in which HOMO resides on carbazolone and LUMO is mainly located on the BPEA chelating fragment. Under the conditions, either PET or ICT process cannot be carried out. As a result, 4-isoACOBA–Zn(II) still shows low fluorescence emission, however, 5-isoACOBA–Zn(II) exhibits a significant fluorescence quenching (off state). The results are well consistent with the spectral studies in which 5-isoACOBA is a Zn^{2+}-specific *turn-off* fluorescent probe.

As for Cd^{2+} sensing process, 4- and 5-isoACOBA–Cd(II) also have the similar surfaces of HOMO and LUMO. The HOMO is on carbazolone moiety, and LUMO mainly resides on benzamide unit. Both 4-isoACOBA–Cd(II) and 5-isoACOBA–Cd(II) display fluorescence enhancement (on state), which is characterized with typical ICT emission. The calculations rationalize that 4-isoACOBA is an efficient Cd^{2+}-specific *turn-on* probe.

Conclusion

In summary, we have successfully constructed two new fluorescent chemosensors 4- and 5-isoACOBA based on 2-aminobenzamide scaffold with carbazolone as fluorophore and *N*,*N*-bis(2-pyridylmethyl)ethylenediamine as chelator. 4- and 5-isoACOBA are structural isomers with each other, and exhibit unique properties to detect Zn^{2+}/Cd^{2+} by dual off–on and on–off fluorescent sensing process. When interchanging the substitution position of carbazolone moiety from C-4 to C-5 at the benzene ring, the structure of 4-isoACOBA is converted into 5-isoACOBA. It is worth noting that the 4- and 5-isoACOBA show remarkably different fluorescent characteristics for preference of Cd^{2+} or Zn^{2+}. 4-IsoACOBA is a Cd^{2+}-specific *turn-on* fluorescent probe exhibiting good discrimination between Cd^{2+} and Zn^{2+} with $F_{Cd2+}/F_{Zn2+} = 2.48$; while 5-isoACOBA is a Zn^{2+}-specific *turn-off* probe with $F_{Cd2+}/F_{Zn2+} = 4.50$.

In the previous study, indazolone-substituted 2-aminobenzamides probes show off–on fluorescent response for both Zn^{2+} and Cd^{2+}; however, carbazole-substituted 2-aminobenzamides sensors are on–off molecular switchs with Zn^{2+} or Cd^{2+} as input. All of the observations enlighten us that both the electron donating/withdrawing ability and the relative position of the fluorophore moiety have significant impacts on the probe sensing property and selectivity. The results illustrated in the study not only open up a new route for the design of sensors for metal ions based on the electron effect of the fluorophore, but also provide a simple and useful 2-aminobenzamide platform to further design other fluorescent probes for important analytes.

Acknowledgements

The project was financially supported by Beijing National Natural Science Foundation (2122031), the National Natural Science Foundation of China (20772013, 21272027), and Beijing Municipal Commission of Education. Y. Zhang thanks the grant support from the Fundamental Research Funds for the Central Universities.

Notes and references

1 R. L. Chaney, J. A. Ryan, Y. M. Li and S. L. Brown, in *Cadmium in Soils and Plants*, ed. M. J. McLaughlin and B. R. Singh, Kluwer, Boston, 1999, pp. 219–256.

2 (*a*) M. Waisberg, P. Joseph, B. Hale and D. Beyersmann, *Toxicology*, 2003, **192**, 95; (*b*) R. K. Zalups and S. Ahmad,

Toxicol. Appl. Pharmacol., 2003, **186**, 163; (*c*) C. C. Bridges and R. K. Zalups, *Toxicol. Appl. Pharmacol.*, 2005, **204**, 274.

3 (*a*) B. L. Vallee and K. H. Falchuk, *Physiol. Rev.*, 1993, **73**, 79; (*b*) T. V. O'Halloran, *Science*, 1993, **261**, 715.

4 For recent reviews of fluorogenic probes, see: (*a*) X. Li, X. Gao, W. Shi and H. Ma, *Chem. Rev.*, 2013, DOI: 10.1021/cr300508p; (*b*) Y. Yang, Q. Zhao, W. Feng and F. Li, *Chem. Rev.*, 2013, **113**, 192.

5 (*a*) Z. C. Xu, J. Yoon and D. R. Spring, *Chem. Soc. Rev.*, 2010, **39**, 1996; (*b*) J. Jia, X. Tang, Y. F. He, M. Y. Zhang and G. W. Xing, *Chin. J. Org. Chem.*, 2012, **32**, 1803.

6 For examples of fluorescent sensors for Zn^{2+} ions, see: (*a*) H. M. Kim, M. S. Seo, M. J. An, J. H. Hong, Y. S. Tian, J. H. Choi, O. Kwon, K. J. Lee and B. R. Cho, *Angew. Chem., Int. Ed.*, 2008, **47**, 5167; (*b*) E. Tomat and S. J. Lippard, *Curr. Opin. Chem. Biol.*, 2010, **14**, 225; (*c*) J.-F. Zhu, H. Yuan, W.-H. Chan and A. W. M. Lee, *Tetrahedron Lett.*, 2010, **51**, 3550; (*d*) Z. Xu, K.-H. Baek, H. N. Kim, J. Cui, X. Qian, D. R. Spring, I. Shin and J. Yoon, *J. Am. Chem. Soc.*, 2010, **132**, 601; (*e*) F. Sun, G. Zhang, D. Zhang, L. Xue and H. Jiang, *Org. Lett.*, 2011, **13**, 6378; (*f*) X.-Y. Chen, J. Shi, Y.-M. Li, F.-L. Wang, X. Wu, Q.-X. Guo and L. Liu, *Org. Lett.*, 2009, **11**, 4426; (*g*) S. A. Ingale and F. Seela, *J. Org. Chem.*, 2012, **77**, 9352; (*h*) L. Xue, G. Li, D. Zhu, Q. Liu and H. Jiang, *Inorg. Chem.*, 2012, **51**, 10842; (*i*) Y. Mikata, K. Kawata, S. Iwatsuki and H. Konno, *Inorg. Chem.*, 2012, **51**, 1859; (*j*) Y.-P. Li, H.-R. Yang, Q. Zhao, W.-C. Song, J. Han and X.-H. Bu, *Inorg. Chem.*, 2012, **51**, 9642; (*k*) X. Zhou, P. Li, Z. Shi, X. Tang, C. Chen and W. Liu, *Inorg. Chem.*, 2012, **51**, 9226; (*l*) S. Mizukami, S. Okada, S. Kimura and K. Kikuchi, *Inorg. Chem.*, 2009, **48**, 7630; (*m*) Z. Guo, G.-H. Kim, I. Shin and J. Yoon, *Biomaterials*, 2012, **33**, 7818; (*n*) M. Chen, X. Lv, Y. Liu, Y. Zhao, J. Liu, P. Wang and W. Guo, *Org. Biomol. Chem.*, 2011, **9**, 2345.

7 For examples of fluorescent sensors for Cd^{2+} ions, see: (*a*) X. Peng, J. Du, J. Fan, J. Wang, Y. Wu, J. Zhao, S. Sun and T. Xu, *J. Am. Chem. Soc.*, 2007, **129**, 1500; (*b*) T. Cheng, Y. Xu, S. Zhang, W. Zhu, X. Qian and L. Duan, *J. Am. Chem. Soc.*, 2008, **130**, 16160; (*c*) M. Taki, M. Desaki, A. Ojida, S. Iyoshi, T. Hirayama, I. Hamachi and Y. Yamamoto, *J. Am. Chem. Soc.*, 2008, **130**, 12564; (*d*) C. Lu, Z. Xu, J. Cui, R. Zhang and X. Qian, *J. Org. Chem.*, 2007, **72**, 3554; (*e*) L. Xue, G. Li, Q. Liu, H. Wang, C. Liu, X. Ding, S. He and H. Jiang, *Inorg. Chem.*, 2011, **50**, 3680; (*f*) Q. Zhao, R.-F. Li, S.-K. Xing, X.-M. Liu, T.-L. Hu and X.-H. Bu, *Inorg. Chem.*, 2011, **50**, 10041; (*g*) Z. Liu, C. Zhang, W. He, Z. Yang, X. Gao and Z. Guo, *Chem. Commun.*, 2010, **46**, 6138; (*h*) M. Mameli, M. C. Aragoni, M. Arca, C. Caltagirone, F. Demartin, G. Farruggia, G. De Filippo, F. A. Devillanova, A. Garau, F. Isaia, V. Lippolis, S. Murgia, L. Prodi, A. Pintus and N. Zaccheroni, *Chem. – Eur. J.*, 2010, **16**, 919; (*i*) X. Tang, X. Peng, W. Dou, J. Mao, J. Zheng, W. Qin, W. Liu, J. Chang and X. Yao, *Org. Lett.*, 2008, **10**, 3653; (*j*) L. Xue, C. Liu and H. Jiang, *Org. Lett.*, 2009, **11**, 1655; (*k*) Y. Yang, T. Cheng, W. Zhu, Y. Xu and X. Qian, *Org. Lett.*, 2011, **13**, 264; (*l*) T. Cheng, T. Wang, W. Zhu, X. Chen, Y. Yang, Y. Xu and X. Qian, *Org. Lett.*, 2011, **13**, 3656; (*m*) Y. Liu, X. Dong, J. Sun, C. Zhong, B. Li, X. You, B. Liu and Z. Liu, *Analyst*, 2012, **137**, 1837.

8 (*a*) K. H. Huang, J. M. Veal, R. P. Fadden, J. W. Rice, J. Eaves, J. P. Strachan, A. F. Barabasz, B. E. Foley, T. E. Barta, W. Ma, M. A. Silinski, M. Hu, J. M. Partridge, A. Scott, L. G. DuBois, T. Freed, P. M. Steed, A. J. Ommen, E. D. Smith, P. F. Hughes, A. R. Woodward, G. J. Hanson, W. S. McCall, C. J. Markworth, L. Hinkley, M. Jenks, L. Geng, M. Lewis, J. Otto, B. Pronk, K. Verleysen and S. E. Hall, *J. Med. Chem.*, 2009, **52**, 4288; (*b*) Y. Okawa, T. Hideshima, P. Steed, S. Vallet, S. Hall, K. Huang, J. Rice, A. Barabasz, B. Foley, H. Ikeda, N. Raje, T. Kiziltepe, H. Yasui, S. Enatsuand and K. C. Anderson, *Blood*, 2009, **113**, 846.

9 (*a*) H. Q. Ju, Y. F. Xiang, B. J. Xin, Y. Pei, J. X. Lu, Q. L. Wang, M. Xia, C. W. Qian, Z. Ren, S. Y. Wang, Y. F. Wang and G. W. Xing, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 1675; (*b*) H. Q. Ju, S. X. Wang, Y. F. Xiang, Z. Liu, J. Y. Liu, Z. P. Chen, F. L. Zeng, M. Xia, Z. H. Liu, G. W. Xing, S. Y. Wang and Y. F. Wang, *Eur. J. Pharmacol.*, 2011, **666**, 26.

10 (*a*) J. Jia, Z. Y. Gu, R. C. Li, M. H. Huang, C. S. Xu, Y. F. Wang, G. W. Xing and Y. S. Huang, *Eur. J. Org. Chem.*, 2011, 4609; (*b*) J. Jia, Q.-C. Xu, R.-C. Li, X. Tang, Y.-F. He, M.-Y. Zhang, Y. Zhang and G. W. Xing, *Org. Biomol. Chem.*, 2012, **10**, 6279.

11 Q. C. Xu, X. F. Wang, G. W. Xing and Y. Zhang, *RSC Adv.*, 2013, **3**, 15834.

12 D. Janreddy, V. Kavala, J. W. J. Bosco, C. W. Kuo and C. F. Yao, *Eur. J. Org. Chem.*, 2011, 2360.

13 (*a*) J. P. Wolf, S. Wagaw and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 7215; (*b*) B. C. Hamann and J. F. Hartwig, *J. Am. Chem. Soc.*, 1998, **120**, 7369.

14 S. Huang, R. J. Clark and L. Zhu, *Org. Lett.*, 2007, **9**, 4999.

