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# An amine-functionalized metal–organic framework as a sensing platform for DNA detection†

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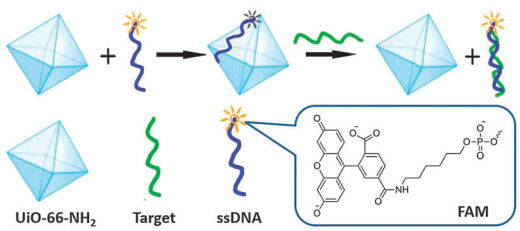
**An amine-functionalized metal–organic framework (MOF) has been employed as an effective fluorescent sensing platform for DNA detection and is capable of distinguishing complementary and mismatched target sequences with high sensitivity and selectivity.**

The detection of DNA sequences is of particular interest and importance in genetics, pathology, criminology, pharmacogenetics, food safety, and so on.[1] The polymerase chain reaction (PCR) method suffers from high cost, risk of contamination, and false-negative results, although it is well-known for DNA amplification and sequencing and has extensive applications in modern biological and medical sciences.[2] Another mature technique involving gene chips is widely employed for high-throughput DNA detection; however, it requires high-cost instrumentation for fluorescence signal readout and sophisticated numerical algorithms for data explanation.[3] Therefore, it is necessary to develop simple, rapid, sensitive and cost-effective approaches for this purpose. In recent years, many endeavors have been devoted to developing homogeneous fluorescence assays, most of which are based on fluorescence resonance energy transfer (FRET) *via* fluorophore–quencher pairs for the detection of DNA sequences, including carbon nanostructures with different forms, Au nanoparticles (NPs) and other nanomaterials.[4] Although they have been proven to be effective fluorescent platforms, the respective drawbacks limit their practical use; the preparation of the detection agent in many systems is time-consuming, tedious or labor-intensive, and some of them cannot be prepared on a large scale or suffer from stability issues.[4a–c,5]

On the other hand, metal–organic frameworks (MOFs), constructed by metal ions/clusters and organic linkers, are a class of crystalline porous materials.[6] In recent two decades, MOFs have captured widespread research interest due to their intriguing structural topologies and potential applications as functional materials in a wide range of fields.[7–10] Particularly, MOFs have been demonstrated to be fluorescent sensors for the detection and recognition of various cations, anions, vapors and small molecules based on their fluorescence response.[10] However, to the best of our knowledge, very rare MOFs have been studied for the detection of DNA or biomolecules.[11]

The organic linkers involved in MOFs usually have a conjugated π-electron system and offer a source for possible hydrogen bonds that allow suitable interaction between MOFs and single-stranded DNA (ssDNA). Therefore, MOFs could be reasonably able to recognize DNA molecules *via* fluorescence changes, similar to previously reported detection agents. In this work, we have developed an amine-functionalized MOF, UiO-66-$NH_2$ (UiO = University of Oslo), as an efficient biosensor for the detection of DNA with high selectivity. The principle of this assay is proposed in Scheme 1. The free ssDNA with a fluorophore (FAM) at its 5′ end has strong fluorescence emission at 518 nm ($\lambda_{ex}$ = 480 nm). Electrostatic attractions such as π···π stacking or hydrogen bond interactions between aromatic nucleotide bases in the ssDNA and UiO-66-$NH_2$ allow them to attach or come in close proximity to each other, which results in the substantial fluorescence quenching of FAM (off-state), possibly due to the photoinduced electron transfer.[12] The absorption spectrum of MOF dispersed in Tris-HCl buffer (pH: 7.42) exhibits two absorption peaks at 217 nm




Scheme 1 Proposed principle for the fluorophore-labeled DNA detection by a MOF, UiO-66-$NH_2$, as a sensing platform.

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and 328 nm (Fig. S3, ESI†), suggesting that there is no spectral overlap and thus no FRET occurs between the MOF and ssDNA. Upon the introduction of target ssDNA (tDNA) into the system, double-stranded DNA (dsDNA) detaches from UiO-66-$NH_2$. As a result, the energy transfer process is inhibited and the fluorescence of ssDNA is recovered (turn-on state). It is proposed that hydrogen bond interaction between ssDNA and the amino group in UiO-66-$NH_2$ could play a critical role in the DNA detection.

UiO-66-$NH_2$ was constructed from $Zr^{IV}$ and 2-amino-1,4-benzenedicarboxylic acid ($NH_2$-BDC) exhibiting great chemical and thermal stability. The framework built up from $Zr_6O_4(OH)_4$ oxoclusters linked together by 12 $NH_2$-BDC ligands, formulated as $Zr_6O_4(OH)_4$(BDC-$NH_2$)$_6$, features a 3D network involving tetrahedral and octahedral cages of 6 and 11 Å, respectively, accessible through microporous windows (4–6 Å) (Fig. 1A–C). Powder X-ray diffraction (XRD) profiles demonstrate its phase purity and great water stability. The scanning electron microscopy (SEM) image indicates that the sizes of UiO-66-$NH_2$ particles are in the range of 50–100 nm (Fig. 1D), suitable for dispersion in the aqueous solution. $N_2$ sorption isotherms confirm their permanent porosity and the BET surface area is 615 $m^2\ g^{-1}$ (Fig. S2, ESI†).

To demonstrate the feasibility of employing UiO-66-$NH_2$ as a fluorescent sensing platform for DNA detection, an oligonucleotide sequence associated with human immunodeficiency virus (HIV) was employed as a model system. As displayed in Fig. 2, the FAM-ssDNA probe ($P_{HIV}$) exhibits fairly strong fluorescence emission due to the presence of a fluorescein-based dye, FAM. The introduction of UiO-66-$NH_2$ leads to around 56% drop in the fluorescence intensity, suggesting that the MOF has interaction with ssDNA and quenches the fluorescence effectively. Significantly, the MOF–$P_{HIV}$ composite exhibits remarkable fluorescence enhancement with a recovery of up to 70% upon its incubation with complementary target $T_1$ (tDNA), revealing the release of ssDNA due to its binding to tDNA. Actually, the fluorescence of $P_{HIV}$ is nearly not affected by the tDNA without MOF and the MOF itself has no fluorescence contribution in the investigated wavelength range.

The influence of the amount of MOF introduced in the system shows that the fluorescence quenching efficiency increases while the recovery efficiency decreases along with more MOFs used ranging from 0–50 μL. More MOFs nearly do not affect both efficiencies (Fig. 3A). It is understandable because more MOFs would result in more efficient adsorption of ssDNA and thus maximize the fluorescence quenching to some extent. In this case, some tDNA may also be adsorbed on MOFs and the

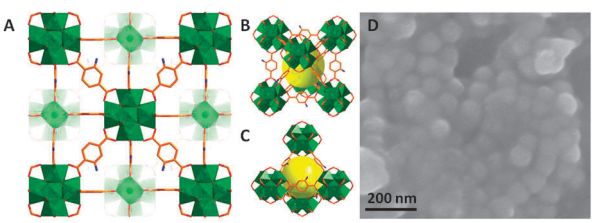


Fig. 1 (A) The 3D structure of UiO-66-$NH_2$ and it contains (B) large octahedral and (C) small tetrahedral cages. The Zr, C, O and N atoms are represented by olive, orange, red and blue, respectively, and $Zr_6O_4(OH)_4$ clusters are shaded in olive polyhedra. (D) A SEM image of UiO-66-$NH_2$.

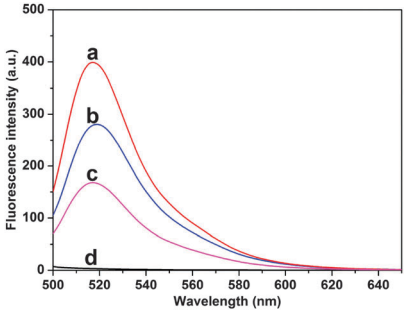


Fig. 2 Fluorescence spectra of $P_{HIV}$ (50 nM) in different systems ($\lambda_{ex}$ = 480 nm): (a) $P_{HIV}$; (b) $P_{HIV}$ + UiO-66-$NH_2$ + $T_1$ (150 nM); (c) $P_{HIV}$ + UiO-66-$NH_2$; (d) UiO-66-$NH_2$ in the absence of $P_{HIV}$.

binding between ssDNA and tDNA is suppressed, thus reducing the release of ssDNA and the fluorescence recovery. Therefore, 20 μL of the MOF as an optimized volume was used in this study, otherwise specified. In addition, the amount of tDNA has a positive influence on the fluorescence recovery of MOF–ssDNA. The fluorescence recovery efficiency increases when more tDNA, ranging from 10–150 nM, is introduced into the system, while more tDNA would not cause the change any more (Fig. 3B).

To further understand the kinetics of the fluorescence quenching and recovery, the time-dependent fluorescence intensity of $P_{HIV}$ by UiO-66-$NH_2$ and the MOF–$P_{HIV}$ composite with tDNA as a function of incubation time was examined (Fig. 3C). In the absence of tDNA, the curve shows a rapid decrease in the first 5 min and reaches an equilibrium in around 20 min, suggesting that UiO-66-$NH_2$ can adsorb ssDNA effectively and quickly. Moreover, it seems to be a trend that more MOFs make the system reach equilibrium more quickly (Fig. S4, ESI†). The introduction of tDNA allows the

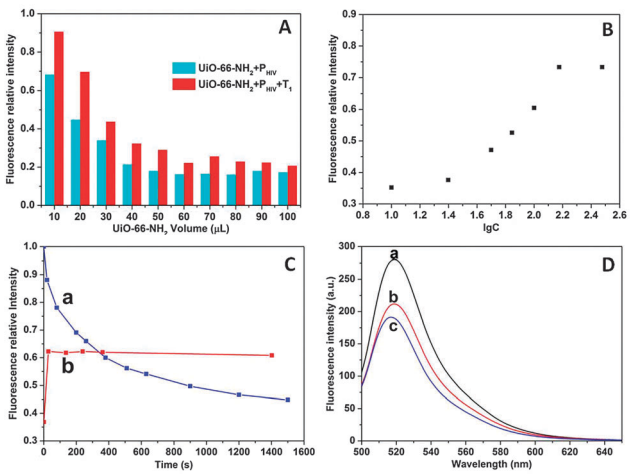


Fig. 3 Influence of the amount of (A) UiO-66-$NH_2$ or (B) $T_1$ on the fluorescence quenching efficiency ($P_{HIV}$: 50 nM). (C) Kinetic behavior study: (a) fluorescence quenching of $P_{HIV}$ (50 nM) by UiO-66-$NH_2$ and (b) fluorescence recovery of $P_{HIV}$–UiO-66-$NH_2$ by $T_1$ (150 nM) as a function of incubation time. (D) Fluorescence intensity of $P_{HIV}$ + UiO-66-$NH_2$ under $\lambda_{ex}$ = 480 nm upon introducing different targets: (a) $T_1$; (b) single-base mismatched target $T_2$ to ssDNA; (c) mismatched target $T_3$ to ssDNA. All measurements were done in Tris-HCl buffer with 5 mM $Mg^{2+}$ (pH: 7.42).

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fluorescence recovery in a faster kinetics. Upon the addition of tDNA, the fluorescence intensity increases rapidly and reaches equilibrium in around 3 min, suggesting that $T_1$ can detach ssDNA from UiO-66-$NH_2$ effectively in a very short time. Rapid adsorption and detachment of ssDNA make UiO-66-$NH_2$ promising for fluorescent sensing of DNA molecules.

In addition to the complementary target $T_1$, mismatched sequences (single-base mismatched $T_2$ and mismatched $T_3$ to ssDNA) were introduced into the system to investigate the discrimination ability of the sensing platform (Fig. 3D). It was observed that the fluorescence intensity of the system in the presence of $T_1$, $T_2$ and $T_3$ exhibits 67%, 26%, and 14% enhancement, respectively, compared to that in the absence of the target. The fluorescence intensity is clearly associated with the matching level of base pairs between ssDNA and the target. These results indicate that the sensing platform is able to distinguish between the complementary and unmatched target sequences, no matter whether only single-base or total mismatching exists.

To understand the role of the amino group in UiO-66-$NH_2$ for the sensing property, another MOF bearing the same structure but without an amino group, UiO-66, was examined. Unexpectedly, although the introduction of UiO-66 leads to around 42% drop in the fluorescence intensity, a bit less than that observed with UiO-66-$NH_2$ (56%), the fluorescence intensity of the system in the presence of $T_1$ and $T_2$, respectively, exhibits 58% and 56% enhancement compared to that observed in the absence of the target, indicating that UiO-66 cannot distinguish the complementary and the single-base mismatching targets (Fig. S5, ESI†). Given the negatively charged backbone of ssDNA,[13] the zeta potentials of UiO-66 and UiO-66-$NH_2$ of +1.28 and −5.54 mV, respectively, indicate that UiO-66 has weak electrostatic interactions with ssDNA while a bit of electrostatic repulsion between UiO-66-$NH_2$ and ssDNA could exist. Meanwhile, UiO-66 has a similar structure and a conjugated π-electron system to UiO-66-$NH_2$. In this context, what interaction is able to offset the electrostatic repulsion and enables the successful adsorption of ssDNA on the surface of UiO-66-$NH_2$? It is well known that a DNA double helix is formed depending on the hydrogen bonds between amino groups of bases on two single-stranded DNAs. Accordingly, we may infer that there are hydrogen bonds between the amino groups in UiO-66-$NH_2$ and bases in ssDNA, resulting in the adsorption of ssDNA on UiO-66-$NH_2$. In contrast, UiO-66 without an amino group does not form hydrogen bonds with ssDNA, which could be responsible for its indistinguishableness for different target DNAs. The infrared (IR) absorption spectrum of the MOF–$P_{HIV}$ composite shows the N–H stretching vibration at 3460 and 3376 $cm^{-1}$ (Fig. S6, ESI†), which exhibits a blue shift compared to the characteristic peaks of the unbounded $NH_2$ group at 3500 and 3386 $cm^{-1}$ in pristine UiO-66-$NH_2$.[14] The peak shift further supports the existence of hydrogen bond interaction between the amino group in UiO-66-$NH_2$ and ssDNA bases.[15]

In conclusion, our results indicate that an amine-functionalized MOF, UiO-66-$NH_2$, can afford an effective fluorescent sensing platform for DNA detection. The sensing system can distinguish complementary and mismatched DNA sequences down to single-base mismatch with high selectivity and good reproducibility. In contrast, UiO-66 with a similar structure in the absence of an amino group cannot realize such a function. For the first time, the hydrogen bond interaction between MOFs and ssDNA has been proposed to account for DNA detection. Given the high stability and the facile and scalable synthesis using cheap reactants, the UiO-66-$NH_2$-based assay holds great promise for practical applications in clinical sample analysis.

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## Notes and references

1 D. Gresham, D. M. Ruderfer, S. C. Pratt, J. Schacherer, M. J. Dunham, D. Botstein and L. Kruglyak, *Science*, 2006, **311**, 1932.
2 (*a*) K. B. Mullis and F. A. Faloona, *Methods Enzymol.*, 1987, **155**, 335; (*b*) A. Gopi, S. M. Madhavan, S. K. Sharma and S. A. Sahn, *Chest*, 2007, **131**, 880.
3 (*a*) M. Ramsey, *Nat. Biotechnol.*, 1998, **16**, 40; (*b*) R. Moeller and W. Fritzsche, *IEE Proc.: Nanobiotechnol.*, 2005, **152**, 47.
4 (*a*) B. Dubertret, M. Calame and A. J. Libchaber, *Nat. Biotechnol.*, 2001, **19**, 365; (*b*) D. J. Maxwell, J. R. Taylor and S. Nie, *J. Am. Chem. Soc.*, 2002, **124**, 9606; (*c*) R. H. Yang, J. Y. Jin, Y. Chen, N. Shao, H. Z. Kang, Z. Xiao, Z. W. Tang, Y. R. Wu, Z. Zhu and W. H. Tan, *J. Am. Chem. Soc.*, 2008, **130**, 8351; (*d*) L. B. Zhang, T. Li, B. L. Li, J. Li and E. K. Wang, *Chem. Commun.*, 2010, **46**, 1476; (*e*) C. H. Lu, H. H. Yang, C. L. Zhu, X. Chen and G. N. Chen, *Angew. Chem., Int. Ed.*, 2009, **48**, 4785; (*f*) S. J. He, B. Song, D. Li, C. F. Zhu, W. P. Qi, Y. Q. wen, L. H. Wang, S. P. Song, H. P. Fang and C. H. Fan, *Adv. Funct. Mater.*, 2010, **20**, 453; (*g*) H. L. Li, Y. W. Zhang, L. Wang, J. Q. Tian and X. P. Sun, *Chem. Commun.*, 2011, **47**, 961; (*h*) H. L. Li, Y. W. Zhang, Y. L. Luo and X. P. Sun, *Small*, 2011, **7**, 1562.
5 (*a*) H. L. Li and X. P. Sun, *Chem. Commun.*, 2011, **47**, 2625; (*b*) L. Wang, Y. W. Zhang, J. Q. Tian, H. L. Li and X. P. Sun, *Nucleic Acids Res.*, 2011, **39**, 37.
6 (*a*) G. Férey, C. Mellot-Draznieks, C. Serre and F. Millange, *Acc. Chem. Res.*, 2005, **38**, 217; (*b*) S. Horike, S. Shimomura and S. Kitagawa, *Nat. Chem.*, 2009, **1**, 695; (*c*) J. R. Long and O. M. Yaghi, *Chem. Soc. Rev.*, 2009, **38**, 1213; (*d*) H.-C. Zhou, J. R. Long and O. M. Yaghi, *Chem. Rev.*, 2012, **112**, 673.
7 (*a*) H. Wu, W. Zhou and T. Yildirim, *J. Am. Chem. Soc.*, 2009, **131**, 4995; (*b*) K. Sumida, D. L. Rogow, J. A. Mason, T. M. McDonald, E. D. Bloch, Z. R. Herm, T.-H. Bae and J. R. Long, *Chem. Rev.*, 2012, **112**, 724; (*c*) M. P. Suh, H. J. Park, T. K. Prasad and D.-W. Lim, *Chem. Rev.*, 2012, **112**, 782; (*d*) J.-R. Li, J. Sculley and H.-C. Zhou, *Chem. Rev.*, 2012, **112**, 869; (*e*) Y.-X. Tan, Y.-P. He and J. Zhang, *ChemSusChem*, 2012, **5**, 1597; (*f*) Y. Hu, W. M. Verdegaal, S. H. Yu and H. L. Jiang, *ChemSusChem*, 2014, **7**, 734.
8 (*a*) J. S. Seo, D. Whang, H. Lee, S. I. Jun, J. Oh, Y. J. Jeon and K. Kim, *Nature*, 2000, **404**, 982; (*b*) L. Q. Ma, C. Abney and W. B. Lin, *Chem. Soc. Rev.*, 2009, **38**, 1248; (*c*) D. Farrusseng, S. Aguado and C. Pinel, *Angew. Chem., Int. Ed.*, 2009, **48**, 7502; (*d*) H.-L. Jiang and Q. Xu, *Chem. Commun.*, 2011, **47**, 3351; (*e*) Y. Fu, D. Sun, Y. Chen, R. Huang, Z. Ding, X. Fu and Z. Li, *Angew. Chem., Int. Ed.*, 2012, **51**, 3364; (*f*) J. Gascon, A. Corma, F. Kapteijn, F. X. Llabrés and I. Xamena, *ACS Catal.*, 2014, **4**, 361; (*g*) Y.-Z. Chen, Q. Xu, S.-H. Yu and H.-L. Jiang, *Small*, 2014, DOI: 10.1002/smll.201401875.
9 (*a*) Z. Q. Wang and S. M. Cohen, *Chem. Soc. Rev.*, 2009, **38**, 1315; (*b*) S. C. Sahoo, T. Kundu and R. Banerjee, *J. Am. Chem. Soc.*, 2011, **133**, 17950; (*c*) J. D. Rocca, D. M. Liu and W. B. Lin, *Acc. Chem. Res.*, 2011, **44**, 957; (*d*) P. Horcajada, R. Gref, T. Baati, P. K. Allan, G. Maurin, P. Couvreur, G. Férey, R. E. Morris and C. Serre, *Chem. Rev.*, 2012, **112**, 1232; (*e*) X. Zhao, F. Liu, L. Zhang, D. Sun, R. Wang, Z. Ju, D. Yuan and D. Sun, *Chem. – Eur. J.*, 2014, **20**, 649.
10 (*a*) B. L. Chen, S. C. Xiang and G. D. Qian, *Acc. Chem. Res.*, 2010, **43**, 1115; (*b*) H.-L. Jiang, Y. Tatsu, Z.-H. Lu and Q. Xu, *J. Am. Chem. Soc.*, 2010, **132**, 5586; (*c*) Y. Takashima, V. M. Martinez, S. Furukawa, M. Kondo, S. Shimomura, H. Uehara, M. Nakahama, K. Sugimoto and S. Kitagawa,

Published on 14 August 2014. Downloaded by University of Science and Technology of China on 17/09/2014 07:07:38.

*Nat. Commun.*, 2011, **2**, 168; (*d*) L. E. Kreno, K. Leong, O. K. Farha, M. Allendorf, R. P. Van Duyne and J. T. Hupp, *Chem. Rev.*, 2012, **112**, 1105; (*e*) S.-R. Zhang, D.-Y. Du, J.-S. Qin, S.-J. Bao, S.-L. Li, W.-W. He, Y.-Q. Lan, P. Shen and Z.-M. Su, *Chem. – Eur. J.*, 2014, **20**, 3589; (*f*) Z. C. Hu, B. J. Deibert and J. Li, *Chem. Soc. Rev.*, 2014, **43**, 5815.

11 (*a*) X. Zhu, H. Y. Zheng, X. F. Wei, Z. Y. Lin, L. H. Guo, B. Qiu and G. N. Chen, *Chem. Commun.*, 2013, **49**, 1276; (*b*) S. Liu, L. Wang, J. Q. Tian, Y. L. Luo, G. H. Chang, A. M. Abdullah, A. O. Al-Youbi and X. P. Sun, *ChemPlusChem*, 2012, **77**, 23.

12 (*a*) Y. J. Cui, Y. F. Yue, G. D. Qian and B. L. Chen, *Chem. Rev.*, 2012, **112**, 1126; (*b*) in *Photoinduced electron transfer*, ed. M. A. Fox, M. Chanon, Elsevier, Amsterdam, 1988; (*c*) A. P. de Silva, H. Q. N. Gunaratne, T. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher and T. E. Rice, *Chem. Rev.*, 1997, **97**, 1515; (*d*) B. Valeur, *Molecular Fluorescence: Principles and Applications*, Wiley-VCH, Weinheim, 2001.

13 J. F. Zhai, H. L. Li and X. P. Sun, *RSC Adv.*, 2011, **1**, 36.

14 M. Kandiah, M. H. Nilsen, S. Usseglio, S. Jakobsen, U. Olsbye, M. Tilset, C. Larabi, E. A. Quadrelli, F. Bonino and K. P. Lillerud, *Chem. Mater.*, 2010, **22**, 6632.

15 (*a*) L.-S. Teo, C.-Y. Chen and J.-F. Kuo, *Macromolecules*, 1997, **30**, 1793; (*b*) T. Kondo and C. Sawatari, *Polymer*, 1996, **37**, 393.

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