Electronic Supplementary Information (ESI) for New Journal of Chemistry

A three-dimensional Nd(III)-based metal-organic framework as a smart drug carrier

Pei-Yao Du,[a] Wen Gu [*a] and Xin Liu [*a]

† College of Chemistry, Key Laboratory of Advanced Energy Materials Chemistry (MOE), Collaborative Innovation Center of Chemical Science and Engineering, Nankai University, Tianjin 300071, P. R. China
E-mail: guwen68@nankai.edu.cn; liuxin64@nankai.edu.cn

Experimental Section

Reagents and Physical Measurements

All reagents and solvents for synthesis and analysis were obtained from commercially and used without further purification. Elemental analyses (C, H, and N) were performed on a Perkin-Elmer Model 2400 II elemental analyzer. Powder X-ray diffraction (PXRD) was carried out on a Rigaku D/max-IIIA diffractometer (Cu Kα, λ =1.54056 Å). Fourier Transform-Infrared Spectroscopy were obtained within the 400−4000 cm^{-1} region using KBr pellets on a Perkin-Elmer spectrometer. Thermogravimetric analyses were performed on a NETZSCH TG 209 instrument from room temperature to 800 ℃ at a heating rate of 10 ℃ min^{-1} under nitrogen gas. The UV-vis spectra were recorded on a JASCO V-570 spectrophotometer. HPLC analysis was performed on an Agilent 1100 series HPLC system.

X-ray Crystallography

Single crystal X-ray diffraction analyses were carried out on a Bruker SMART APEX CCD diffractometer equipped with a graphite-monochromated Mo-Ka radiation (λ = 0.71073 Å). The structure was solved by direct methods and refined by full-matrix least-squares fitting on F^2 using OLEX2.[1] Absorption corrections were applied by using multi-scan program SADABS. Crystallographic and refinement details are summarized in Table S1. Selected bond lengths and bond angles are listed in Table S2 in the ESI†. Crystallographic information file (CIF) corresponding to **1** has been deposited to Cambridge Crystallographic Data Centre (CCDC number 1046359).

Encapsulation of 5-Fu

20 mg of activated **1** (**1a**) was suspended in 4 ml of 5-Fu solutions, then the mixture suspensions were stirred for 72 h at 37 °C. Finally, 5-Fu loaded **1a** was obtained through centrifugation for 5 min, water wash and dried at room temperature. **1a** before and after the 5-Fu entrapping were characteristic by IR and PXRD. The concentration of 5-Fu in the supernatant was determined by the absorbance of 5-Fu at 265 nm with the help of a calibration curve. Then the drug loading efficiency were calculated. Drug encapsulation efficiency= (total amount-without loading amount)/ total amount ×100%

5-Fu release

Drug release was carried out by soaking the drug-loaded **1a** in phosphate buffer solution at 37 ℃ under bidimensional continuous shaking at two different pH values, 5.7 and 7.4. After certain periods, an aliquot of supernatant was recovered by centrifugation and replaced with the same volume of fresh medium. The contents of 5-Fu released in PBS solution were determined by high-performance liquid chromatography. Sunfire-C18 reverse-phase colume (4.6*250mm) was employed. The mobile phase consist of 15% of water: 85% of acetonitrile with a 1ml/min flow. The colume temperature was fixed at 35 ℃. Retention time of 5-Fu was 2.30 min. Semiquantitative analysis was performed using standard calibration of 5-Fu in the range of 0.0035-0.085 mg/ml. 5-Fu was identified by direct comparison with 5-Fu standard on the basis of the retention time.

In Vitro Toxicity Tests

The cytotoxicity of 5-Fu@**1a** and **1** toward HeLa cells was determined using MTT assays. HeLa cells were seeded in a 96-wells microplate. After 24h of cell attachment, the cells were treated and incubated with increasing concentrations of 5-Fu@**1a** and **1** for 24h and 48h. Then, 25 μl of MTT solution was added into each well. After the cells were incubated for another 4 hours, 150 μl of DMSO was added to each well to dissolve the MTT formazan crystals. At last, the absorbance of each well was monitored through a microplate reader.

Drug release experiments in vivo

The controlled-released effects of the 5-Fu@**1a** was also demonstrated by *in vivo* drug-release assay in Wistar rats. In the test, male Wistar rats (with a weight approx. 200 g) were intragastric administration by using 5-Fu loaded **1a** (40 mg) which were suspended in 1.50 ml normal saline. Blood samples (100 μl) were withdrawn at different time intervals and centrifuged to get plasma samples. The plasma samples were added with 300 μl acetonitrile to precipitate protein, followed by centrifuged to produce the analytes. The solution was dried by nitrogen at room temperature. Residues were reconstituted by mobile phase, and then subjected to HPLC. The content of 5-Fu contained in rat plasma was measured by HPLC.

Table S1 Crystal data and structure refinement for **1**

complex	**1**
Formula	$C_{32}H_{35}N_5Nd_2O_{18}$
Fw	1066.13
Crystal system	triclinic
Space group	$P\overline{1}$
a (Å)	11.090(2)
b (Å)	11.320(2)
c (Å)	16.243(3)
α (˚)	74.94(3)
β (˚)	82.76(3)
γ (˚)	75.06(3)
V (Å^3)	1898.7(8)
Z	2
R(int)	0.0962
GOF	1.082
R_1,wR_2 [$I > 2\sigma$(I)]	0.0801, 0.2135
R_1, wR_2 (all data)	0.1055, 0.2344

Table S2 Selective bond lengths [Å] and angles [deg] for **1**

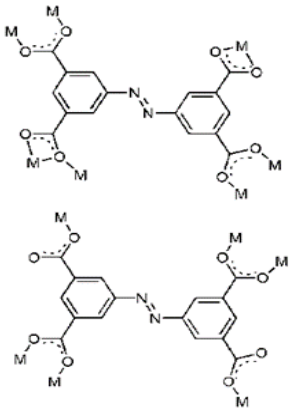
Nd(1)-O(3)#1	2.378(10)	Nd(1)-O(9)	2.329(9)
Nd(1)-O(4)#6	2.397(9)	Nd(1)-O(13)	2.438(10)
Nd(1)-O(12)#9	2.349(9)	Nd(1)-O(1)	2.759(9)
Nd(1)-O(7)#7	2.479(10)	Nd(1)-O(2)	2.549(10)
Nd(2)-O(15)	2.545(10)	Nd(2)-O(14)	2.469(10)
Nd(2)-O(16)	2.493(9)	Nd(2)-O(1)#3	2.431(10)
Nd(2)-O(8)#2	2.301(10)	Nd(2)-O(11)#4	2.386(10)
Nd(2)-O(5)	2.465(9)	Nd(2)-O(6)	2.515(10)
O(1)-Nd(1)-O(4)#6	153.9(3)	O(2)-Nd(1)-O(3)#1	85.0(3)
O(2)-Nd(1)-O(4)#6	145.0(4)	O(2)-Nd(1)-O(1)	48.5(3)
O(12)#8-Nd(1)-O(3)#1	76.2(3)	O(12)#8-Nd(1)-O(4)#6	125.8(3)
O(12)#8-Nd(1)-O(1)	72.9(3)	O(12)#8-Nd(1)-O(2)	76.9(4)
O(7)#7-Nd(1)-O(1)	95.7(3)	O(9)-Nd(1)-O(1)	70.2(3)
O(9)-Nd(1)-O(2)	101.7(3)	O(13)-Nd(1)-O(1)	98.9(3)
O(13)-Nd(1)-O(2)	69.4(3)	O(13)-Nd(1)-O(9)	79.4(4)
O(6)-Nd(2)-O(5)	51.0(3)	O(15)-Nd(2)-O(5)	73.0(3)
O(15)-Nd(2)-O(6)	117.8(3)	O(16)-Nd(2)-O(5)	77.4(3)
O(16)-Nd(2)-O(6)	113.2(3)	O(16)-Nd(2)-O(15)	71.8(3)
O(14)-Nd(2)-O(5)	82.1(3)	O(14)-Nd(2)-O(6)	75.6(3)
O(14)-Nd(2)-O(15)	71.7(3)	O(14)-Nd(2)-O(16)	141.9(3)

Symmetry transformations used to generate equivalent atoms:

#1 -x, 1-y, 2-z; #2 1+x, +y, +z; #3 1-x, 1-y, 1-z;
#4 1-x, -y, 1-z; #5 +x, -1+y, +z; #6 -1+x, +y, +z;
#7 -x, 1-y, 1-z; #8 +x, 1+y, +z; #9 -1-x, -y, 2-z

Table S3 Comparison of the drug loading capacity of different MOFs for 5-Fu

Molecular formula	**Solvent used in drug loading experiments**	**Drug loading (wt %)**	**Reference**
{[$NH_2(CH_3)$][$Cu_6(L)_3(OAc)(H_2O)_4$] xsolvent}	ethanol	24.9	S1
{[Cu_{24}(5-NH_2-mBDC)$_{24}$(bpy)$_6(H_2O)_{12}$]72DMA}	methanol	23.76	S2
[$Zn_{10}(OH)O(BTC)_5(HBTC)(DMA)_2(H_2O)_4$] 11DMA	methanol	14.49	S3
[$Nd_2(abtc)_{1.5}(H_2O)_3$(DMA)] H_2O DMA	water	18	this work
($NH_2(CH_3)_2$[$Zn_3(L)_2$ 3.5DMF])	ethanol	22.5	S4
[$Mg_3(H_2O)_4$(5-aip)$_2$(5-Haip)$_2$] 4DMA	ethanol	21.06	S5



Scheme S1 Coordination modes of $abtc^{4-}$.

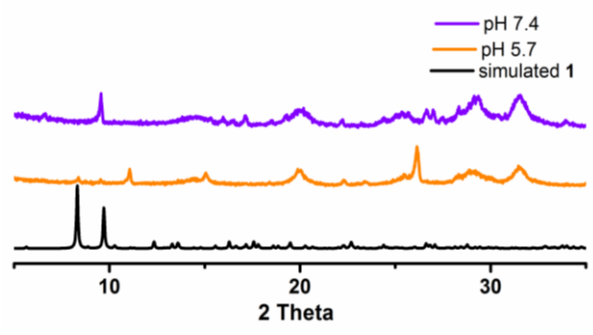


Fig. S1 PXRD patterns of **1** after the drug release experiments in PBS (pH 5.7 and 7.4).

References

1. L. J. Bourhis, O. V. Dolomanov, R. J. Gildea, J. A. K. Howard, H. Puschmann, *Acta Cryst.*, 2015, **A71**, 59-75.

S1. J. Wu, J. W. Xu, W. C. Liu, S. Z. Yang, M. M. Luo, Y. Y. Han, J. Q. Liu and S. R. Batten, *Inorganic Chemistry Communications*, 2016, **71**, 32–34.

S2. H. N. Wang, X. Meng, G. S. Yang, X. L. Wang, K. Z. Shao, Z. M. Su and C. G. Wang, *Chemical Communications*, 2011, **47**, 7128-7130.

S3. H. N. Wang, G. S. Yang, X. L. Wang and Z. M. Su, *Dalton Transactions*, 2013, **42**, 6294-6297.

S4. Q. L. Li, J. P. Wang, W. C. Liu, X. Y. Zhuang, J. Q. Liu, G. L. Fan, B. H. Li, W. N. Lin and J. H. Man, *Inorganic Chemistry Communications*, 2015, **55**, 8-10.

S5. H. N. Wang, X. Meng, X. L. Wang, G. S. Yang and Z. M. Su, *Dalton Transactions*, 2012, **41**, 2231-2233.