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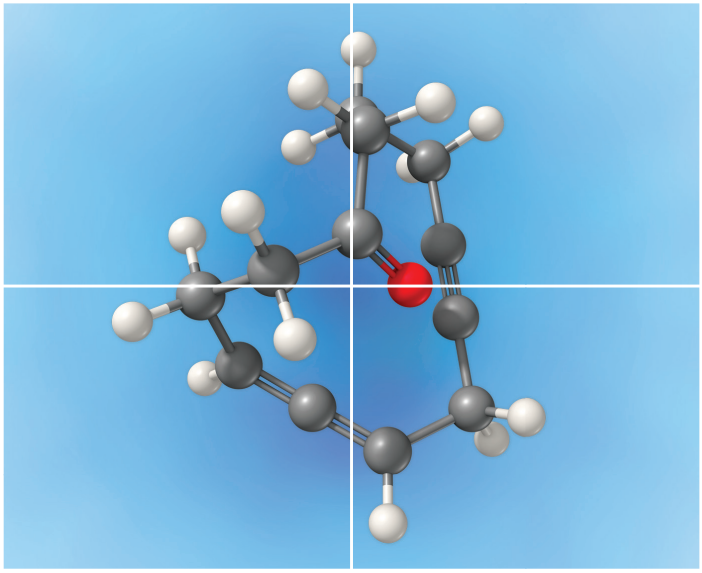

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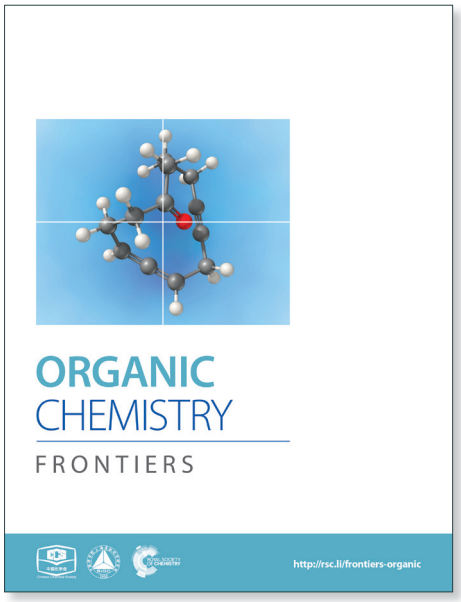

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ARTICLE

Open-cage fullerene with a stopper acts as a molecular vial for a single water molecule

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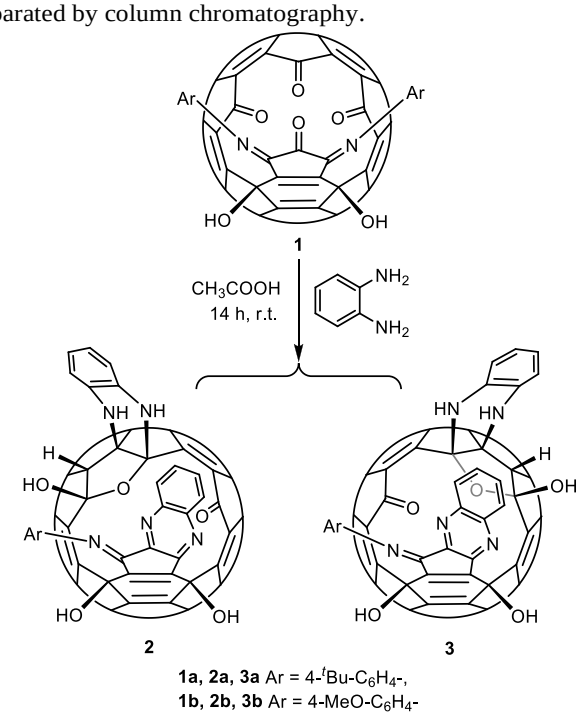
An open-cage fullerene derivative with three carbonyl groups on the rim of the orifice reacts with *o*-diaminobenzene reversibly to form a tetrahydrofuran moiety above the orifice. Water encapsulation and release experiments show that the tetrahydrofuran moiety acts as a stopper effectively blocking the orifice. The addition and removal of *o*-diaminobenzene serve as a chemically controlled switching process for the fullerene-based water container, which is suited for just one water molecule due to its moderate cavity size.

Introduction

Molecular containers for water have attracted much attention. Various molecules have been prepared and studied as host for water molecules.[1] In most cases the cavity of the host molecule is relatively large and water clusters bound by H-bonding can be trapped inside the cavity. Molecular container for a single water molecule is rare. Fullerenes have a unique spherical structure and are suitable for encapsulation of just one water molecule. The water complex $H_2O@C_{60}$ has been successfully prepared through a molecular surgery method.[2] A number of open-cage fullerenes have been prepared with a relatively large orifice,[3,4] through which water can be trapped and released reversibly.[5] These open-cage fullerene compounds act like a vial for a single water molecule but without a stopper since the trapped water molecule can readily exchange with water molecules outside the fullerene cage. To explore practical applications such as molecular containers for radioactive tritiated water, it is desirable to develop open-cage systems with a stopper which can be readily added and removed. We have reported a phosphate modulated open-cage derivative in which the phosphate on the rim of the orifice acts as a removable stopper.[6] Here we report the preparation of a new open-cage fullerene derivative with an orifice large enough for water encapsulation and its reversible reaction with *o*-diaminobenzene. The results show that *o*-diaminobenzene acts as an effective stopper for the open-cage compound.

Results and discussion

In an effort to explore the reactivity of the functional groups on the rim of the orifice, we treated our previously reported compound **1**[7] with *o*-diaminobenzene in the presence of acetic acid as the catalyst (Scheme 1).[8] There is hardly any reaction without the acetic acid. ^{1}H NMR monitoring indicated that three products were formed in the process, one of which appeared to be the precursor for the other two compounds and eventually disappeared. Yields of the two isolated products **2** and **3** depend on the reaction time. Extending the reaction time favours product **3**. Compound **2** slowly converts into compound **3** under the reaction condition. The two products can be easily separated by column chromatography.

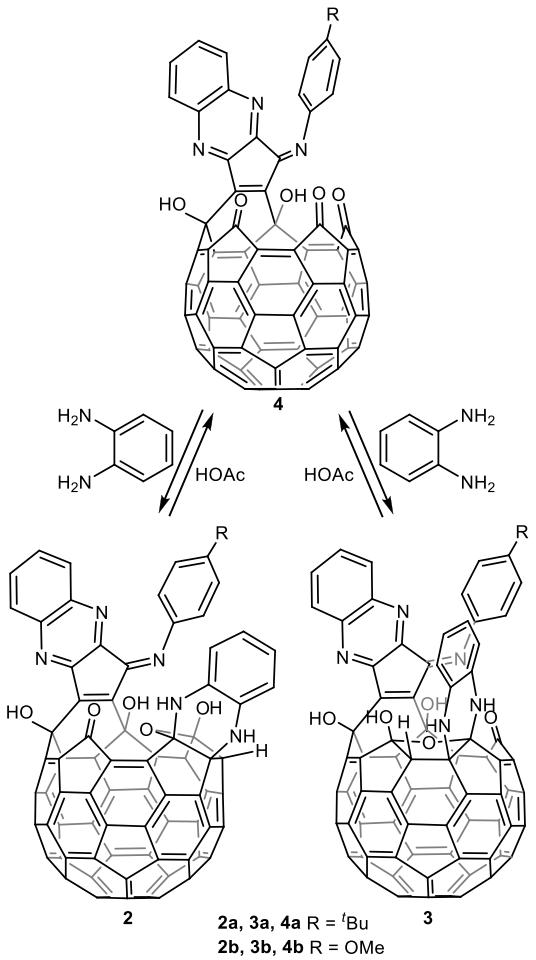


Scheme 1 Preparation of compounds **2** and **3** Yields: **2a** 44%; **2b** 43%; **3a** 33%; **3b** 37%

The intermediate observed in the formation of **2** and **3** is the monoaddition product **4**. It was difficult to isolate **4** directly from the reaction of **1** with excess *o*-diaminobenzene. But treating **2** or **3** with acetic acid removed one *o*-diaminobenzene selectively to form **4** in yields ranging from 79% to 91% (Scheme 2). As expected, compound **4** reacts with *o*-diaminobenzene to form a mixture of compounds **2** and **3** under the same conditions as the reaction of **1** with *o*-diaminobenzene. The combined yields of the isomers **2** and **3** are 84% and 88% for **4a** and **4b** respectively. These yields are much improved

compared to the triethylphosphate stopper system in which the removal of the phosphate is only 27% as we reported before.[6]

The above results indicate that in the conversion from compound **1** to **2** and **3**, the *o*-diaminobenzene first reacted with the carbonyl group adjacent to two imino groups to form **4** with the quinoxaline moiety, followed by the formation of **2** and **3** with a tetrahydrofuran moiety. Similar to the reaction between **1** and triethylphosphite,[6] the carbonyl group on the mirror plane is more reactive than the other two carbonyl groups on the rim of the orifice and probably initiates the formation of the tetrahydrofuran moiety in the formation of both isomers **2** and **3**. The two double bonds connecting the three carbonyl groups on the rim of the orifice are more reactive than other double bonds on the cage towards nucleophiles as we have shown before.[9] In the formation of the quinoxaline moiety, one aryl imino group was replaced. Dehydration efforts failed to remove the adjacent H and OH groups on the tetrahydrofuran moiety.



Scheme 2 Reversible reactions of **4** with *o*-diaminobenzene Conditions: 18 h at 80 °C in PhCl for **2** or **3** to **4**; 16 h at r.t. with CH_3COOH as catalyst in CH_2Cl_2 for **4** to **2** and **3**. Yields: **2a** to **4a** 88%; **2b** to **4b** 91%; **3a** to **4a** 88%; **3b** to **4b** 79%; **4a** to **2a** 24%; **4a** to **3a** 60%; **4b** to **2b** 29%; **4b** to **3b** 59%;

Unlike the isomeric compound **3**, the solubility of **2** is quite low in common organic solvents. Crystals suitable for X-ray diffraction analysis **2a** were obtained from a mixture of hexane/CH_2Cl_2/$CHCl_3$. The X-ray structure shows that **2a** is racemic and 4 molecules (two pairs of enantiomers) of **2a** are present in each unit cell (Figure 1). There are strong intermolecular H-bonds in the crystal between the NH groups and OH groups, thus forming a linear chain structure as shown in Figure 1. Two different enantiomers are adjacent to each other. The polymeric structure probably is responsible for the low solubility of **2a**. Single crystals of **4a** were obtained by a similar method from hexane/CH_2Cl_2. The structure of **4a** also shows a racemic mixture with 4 molecules in each unit cell (Figure 1). But unlike the linear chain structure in **2a**, **4a** forms dimeric structures through H-bonds between the OH groups of two enantiomeric isomers. A similar dimeric structure was reported previously between two open-cage molecules without the hydroxyl groups.[10]

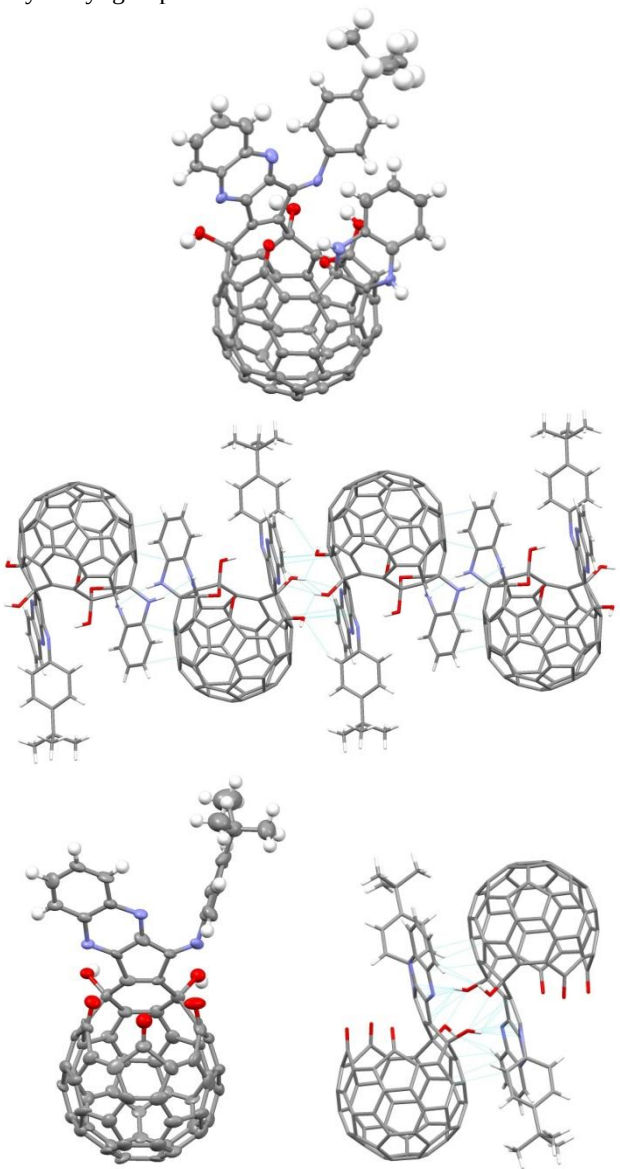


Figure 1 Single-crystal X ray structures of **2a** (top and middle) and **4a** (bottom); Ellipsoids are set at 50% probability. Colour scheme Grey = C, Blue = N, Red = O, White = H; light-blue lines indicate H-bonds and close contacts in the polymeric and dimeric structures.

In light of the X-ray structures of **2a** and **4a**, structures of other compounds were assigned according to their spectroscopic data. The ESI-MS spectra showed the molecular

ion signals. In addition, the ESI-MS spectra of **4a** and **4b** showed minor signals due to the dimer in agreement with the dimeric packing in the X-ray structure of **4a**. The strong dimeric structure of **4** is also observed in solution by NMR spectra. The ^{13}C NMR spectrum of **4a** and **4b** showed a major set of signals and a minor set of signals in about 3:1 intensity ratio corresponding to the monomer and the dimer respectively.

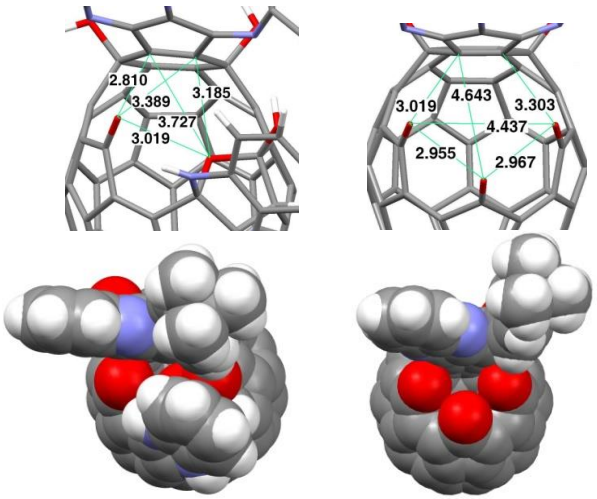
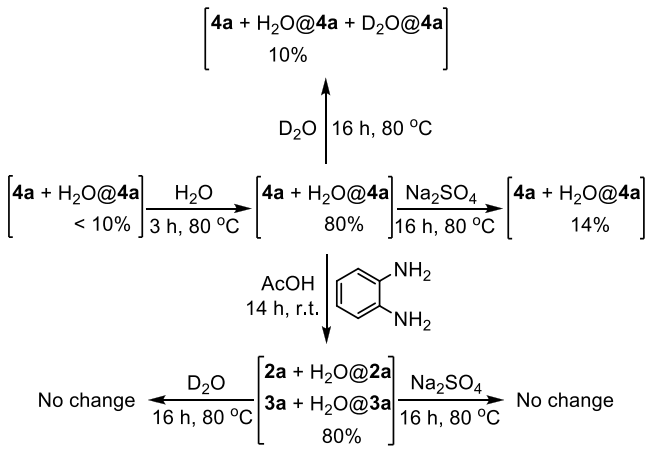


Figure 2 Orifice size parameters (Å) as measured from single-crystal X ray structures of **2a** (top left) and **4a** (top right), and Space-filling model of single-crystal X ray structures of **2a** (top left) and **4a** (top right). Colour scheme Grey = C, Blue = N, Red = O, White = H.

Formation of the tetrahydrofuran moiety on the rim of the orifice in **2a** significantly reduced the size of the orifice as compared to that of **4a**. The size of the orifice can be estimated by measuring the distances among the atoms on the rim of the orifice (Figure 2). Comparison of the longest inter-atomic distances indicates that the orifice of **2a** is reduced by 20% from its precursor **4a**. In addition, the shape of the orifice changed from a roughly round hole in **4a** to the irregular trapezoid in **2a**. Space-filling model of **2a** indicates that the orifice is too small to allow the passage of a water molecule. Compounds **2** to **4** thus correspond to the closed and open states for the open-cage fullerene system. The reversible conversion between **2** and **4** indicates that *o*-diaminobenzene could serve as a removable stopper.

A number of water encapsulation and release experiments were carried out to investigate the efficiency of the *o*-diaminobenzene stopper for compound **4** (Scheme 3). Under normal reaction and routine purification conditions, compounds **4a** and **4b** contain less than 10% water encapsulated complexes as determined by ^{1}H NMR spectrum. Heating a chloroform or toluene solution of **4a** in the presence of added water for a few hours at 80 ^{o}C could increase the water encapsulation ratio up to 80%. The trapped water in **4a** could be removed by heating its solution at 80 ^{o}C in the presence of anhydrous Na_2SO_4. The trapped water in **4a** could also exchange with D_2O by heating its solution at 80 ^{o}C in the presence of D_2O. The water content remained unchanged in the reaction of **4a** with *o*-diaminobenzene at r.t. to form **2a** and **3a**. Under the same Na_2SO_4 dehydration and D_2O exchange conditions at 80 ^{o}C there is hardly any change for the water contents in compounds **2a** and **3a**. The results indicate that the tetrahydrofuran moiety in **2a** and **3a** act as an effective stopper. The results are similar for compounds **2b**, **3b** and **4b**.



Scheme 3 Water encapsulation and release experiments. Solvent of the experiments was $CDCl_3$. Water encapsulation percentages were determined by ^{1}H NMR integrals.

Experimental

Compounds 2a and 3a: Acetic acid (22 drops, 423 mg) and *o*-diaminobenezene (121 mg, 1.12 mmol) were added to a solution of **1a** (74 mg, 0.068 mmol) in CH_2Cl_2 (50 mL) at r. t. After stirring for 14 h, the reaction mixture was washed with water and extracted with dichloromethane three times. The dichloromethane extraction solutions were combined and dried with anhydrous sodium sulfate, and chromatographed on a silica gel column eluting with dichloromethane/ethyl acetate (40:1). The solution was concentrated, and chromatographed again on a silica gel column eluting with dichloromethane. The first band was collected and evaporated to give **2a** (35 mg, 0.030 mmol, 44%). The second band was eluted with dichloromethane/ethyl acetate (100:1) and evaporated to give **3a** (26 mg, 0.030 mmol, 33%).

*Characterization Data for **2a***. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21-8.19 (m, 1H), 7.98-8.05 (m, 1H), 7.90-7.86 (m, 1H), 7.81-7.78 (m, 1H), 7.54-7.52 (d, 2H, J = 8.6 Hz), 7.43 (d, 2H, J = 8.3 Hz), 7.36 (s, 1H), 7.14 (s, 1H), 7.02-7.00 (m, 1H), 6.88 (m, 2H), 6.72-6.67 (m, 1H), 4.36 (d, J = 5.1 Hz, 1H), 1.48 (s, 9H), -10.99 (s). Three H signals were overlapped with toluene impurity. ^{13}C NMR spectrum could not be obtained due to low solubility. ESI-FT-ICR-HRMS: $C_{82}H_{28}N_5O_5$ ($M + H^+$) calcd 1162.2085, found 1162.2073.

Crystals of **2a** suitable for X-ray diffraction were obtained by diffusion of hexane into a solution of **2a** in a mixture of CH_2Cl_2/$CHCl_3$ (10:1). Crystal data: monoclinic, space group $P2_1/c$ (no. 14), a = 17.987 (3) Å, b = 18.451 (4) Å, c = 19.171 (4) Å, β = 117.87 (2)°, V = 5625 (2) Å^3, Z = 4, T = 180.01 (10) K, μ (MoKα) = 0.087 mm^{-1}, *Dcalc* = 1.372 g/cm^3, 22175 reflections measured (6.138° ≤ 2Θ ≤ 50.056°), 9720 unique (R_{int} = 0.1546, R_{sigma} = 0.3486) which were used in all calculations. The final R_1 was 0.0870 (I > 2σ(I)) and wR_2 was 0.2221 (all data). CCDC 1414194.

*Characterization Data for **3a***. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29-8.27 (d, 1H, J = 6.7 Hz), 8.23-8.21 (d, 1H, J = 8.0 Hz), 7.96-7.90 (m, 2H), 7.86-7.82 (m, 3H), 7.64-7.62 (d, 2H, J = 8.3 Hz), 7.43-7.39 (m, 1H), 6.75-6.73 (d, 1H, J = 7.4 Hz), 6.63-6.60 (m, 1H), 6.23-6.17 (m, 1H), 5.03-4.98 (m, 1H), 4.79-4.68 (m, 2H), 4.29 (s, 1H), 4.12 (s, 1H), 1.49 (s, 9H), -11.18 (s). ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD) δ: 8.22-8.20 (d, 1H, J = 8.1 Hz), 7.98-7.91 (m, 2H), 7.87-7.81 (m, 3H), 7.66-7.64 (d, 2H, J

= 8.4 Hz), 6.78-6.77 (d, 1H, *J* =7.4 Hz), 6.67-6.63 (t, 1H, *J* = 7.4 Hz), 6.24-6.20 (t, 1H, *J* = 7.5 Hz), 4.98-4.96 (d, 1H, *J* = 7.5 Hz), 4.13 (s, 1H), 1.50 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3/CD_3OD$): all signals represent 1C except noted, *δ*: 190.64, 161.64, 155.26, 151.38, 151.30, 150.98, 150.93, 150.45, 150.04, 149.67, 149.42, 149.25, 149.12, 148.98, 148.86, 148.80, 148.69, 148.47, 148.42, 148.34, 148.26, 148.18, 148.01, 147.71, 147.66, 147.18, 147.12, 147.00, 146.94, 146.47, 145.55, 145.36, 145.34, 145.30, 144.96, 144.25, 144.19, 143.64, 143.37, 143.11, 143.07, 142.93, 142.47, 142.36, 142.22, 141.41, 141.30, 140.88, 139.25, 139.19, 139.16, 138.97, 138.49, 136.10, 134.73, 134.40, 132.16, 131.30, 130.90, 130.49, 130.35, 128.98, 125.51 (3C), 123.58 (3C), 122.31, 120.21, 117.53, 114.33, 114.18, 108.10, 79.06, 77.65, 76.52, 64.78, 35.00, 31.54 (3C). ESI-FT-ICR-HRMS: $C_{82}H_{28}N_5O_5$ (M + H^+) calcd 1162.2085, found 1162.2082.

Compound 4a Acetic acid (1 ml) was added to a solution of **2a** (25 mg, 0.022 mmol) in PhCl (15 mL) at 80°C. After 18 h, the reaction mixture was washed with water and extracted with dichloromethane three times. The dichloromethane extraction solutions were combined and dried with anhydrous sodium sulfate. The solution was concentrated, and chromatographed on a silica gel column eluting with dichloromethane. The first red band was collected and evaporated to give **4a** (20 mg, 0.019 mmol, 88%). The reaction starting from **3a** was carried out under the same conditions also with 88% yield.

Characterization Data for ***4a*****.** ^{1}H NMR (400 MHz, $C_6D_4Cl_2/CD_3OD$) *δ*: 8.37-8.35 (d, 1H, *J* = 8.1 Hz), 8.23-8.21 (d, *J* = 8.4 Hz, 2H), 8.05-8.03 (d, *J* = 8.2 Hz, 1H), 7.94-7.90 (t, *J* = 7.3 Hz, 1H), 7.84 (s, 1H), 7.82 (s, 1H), 7.81-7.76 (t, *J* = 7.6 Hz, 1H), 1.71 (s, 9H), -12.86 (s). ^{13}C NMR (125 MHz, $C_6D_4Cl_2/CD_3OD$): all signals represent 1C except noted, *δ*: 184.49, 184.16, 184.00, 160.74, 155.91, 151.49, 149.69, 149.44, 149.38, 149.35, 149.29, 149.25, 147.98, 147.90, 147.86, 147.82, 147.78, 147.08, 146.96, 146.50, 146.43, 145.74, 145.72, 145.62, 145.55, 145.21, 145.17, 145.10, 144.92, 144.67, 144.58, 144.36, 144.33, 144.25, 143.61, 143.42, 143.32, 143.27, 142.64, 142.53, 141.42, 141.00, 140.58, 140.44, 140.40, 136.80, 136.63, 135.86, 135.43, 134.88, 134.19, 125.28, 124.64, 78.25, 77.48, 34.86, 31.47. ESI-FT-ICR-HRMS: $C_{76}H_{20}N_3O_5$ (M + H^+) calcd 1054.1398, found 1054.1378. $C_{152}H_{39}N_6O_{10}$ (2M + H^+) calcd 2107.2722, found 2107.2749.

Crystals of **4a** suitable for X-ray diffraction were obtained by diffusion of hexane into a solution of **4a** in dichloromethane. Crystal data: monoclinic, space group $P2_1/n$ (no. 14), a = 13.0600 (8) Å, b = 13.2703 (7) Å, c = 29.7423 (18) Å, β = 95.060 (6)°, V = 5134.5 (5) Å^3, Z = 4, T = 180.00 (10) K, μ(MoKα) = 0.086 mm^{-1}, *Dcalc* = 1.363 g/cm^3, 13765 reflections measured (6.292° ≤ 2Θ ≤ 47.632°), 6501 unique (R_{int} = 0.1193, R_{sigma} = 0.1636) which were used in all calculations. The final R_1 was 0.0965 (I > 2σ(I)) and wR_2 was 0.2328 (all data). Crystallographic data have been deposited in the Cambridge. CCDC 1414193 (**4a**) and 1414194 (**2a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Conclusions

o-diaminobenzene is shown to react with two of the three carbonyl groups on the rim of the orifice of an open-cage fullerene to form a tetrahydrofuran moiety above the orifice, thus blocking the entry and exit of water as confirmed by D_2O exchange and water releasing experiments. The added *o*-diaminobenzene can be readily removed by treatment with acetic acid. The reversible addition and removal of *o*-diaminobenzene corresponds to the controlled closing and opening of the fullerene based molecular container for a single molecule of water.

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Notes and references

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Electronic Supplementary Information (ESI) available: spectroscopic data for compound **1**. See DOI: 10.1039/b000000x/

1 For example: (a) K. Koga, G. T. Gao, H. Tanaka, X. C. Zeng, *Nature* 2001, **412**, 802. (b) J. Garric, J. M. Léger, I. Huc, *Chem. Eur. J.*, 2007, **13**, 8454. (c) Q. Q. Wang, V. W. Day, K. Bowman-James, *Angew. Chem. Int. Ed.*, 2012, **51**, 2119. (d) Q. Q. Wang, V. W. Day, K. Bowman-James, *J. Am. Chem. Soc.*, 2013, **135**, 392.
2 K. Kurotobi, Y. Murata, *Science*, 2011, **333**, 613.
3 For reviews: (a) M. Murata, Y. Murata and K. Komatsu, *Chem. Commun.*, 2008, 6083. (b) G. C. Vougioukalakis, M. M. Roubelakis M. Orfanopoulos, *Chem. Soc. Rev.*, 2010, **39**, 817. (c) L. B. Gan, D. Z. Yang, Q. Y. Zhang, H. Huang, *Adv. Mater.*, 2010, **22**, 1498.
4 For recent examples, (a) S. M. Liu, L. B. Gan, *Chin. J. Chem*., 2014, **32**, 819. (b) R. Zhang, T. Futagoishi, M. Murata, A. Wakamiya, Y. Murata, *J. Am. Chem. Soc.*, 2014, **136**, 8193. (c) Y. Hashikawa, M. Murata, A. Wakamiya, Y. Murata, *Org. Lett.*, 2014, **16**, 2970. (d) C-S. Chen, Y-F. Lin, W-Y. Yeh, *Chem. Eur. J.*, 2014, **20**, 936. (e) Y. M. Yu, T. Zhang, L. B. Gan, Fullerenes, *Nanotubes & Carbon Nanostruct.*, 2014, **22**, 54. (f) A. Krachmalnicoff, M. H. Levitt, R. J. Whitby, *Chem. Commun.*, 2014, **50**, 13037. (g) A. Krachmalnicoff, R. Bounds, S. Mamone, M. H. Levitt, M. Carravetta, R. J. Whitby, *Chem. Commun.*, 2015, **51**, 4993. (h) L. Xu, H. J. Ren, S. S. Liang, J. H. Sun, Y. J. Liu, L. B. Gan, *Chem. Eur. J.*, DOI 10.1002/chem.201502306.
5 For review, L. J. Shi, L. B. Gan, *J. Phys. Org. Chem*., 2013, **26**, 766.
6 Q. Y. Zhang, T. Pankewitz, S. M. Liu, W. Klopper, L. B. Gan, *Angew. Chem., Int. Ed.*, 2010, **49**, 9935.
7 Q. Y. Zhang, Z. S. Jia, S. M. Liu, G. Zhang, Z. Xiao, D. Z. Yang, L. B. Gan, Z. M. Wang and Y. L. Li, *Org. Lett.*, 2009, **11**, 2772.
8 For reactions of open-cage fullerene with *o*-diaminobenezene, (a) S.-i. Iwamatsu, S. Murata, *Tetrahedron Lett.*, 2004, **45**, 6391. (b) Z. Xiao, G. Ye, Y. Liu, S. Chen, Q. Peng, Q. Q. Zuo, L. M. Ding, *Angew.Chem. Int. Ed.*, 2012, **51**, 9038. (c) Y. M. Yu, L. Xu, X. C. Huang, L. B. Gan, *J. Org. Chem*., 2014, **79**, 2156.
9 L. Xu, Q. Y. Zhang, G. Zhang, S. S. Liang, Y. M. Yu, L. B. Gan, *Eur. J. Org. Chem.* 2013, 7272.
10 S. M. Liu, Q. Y. Zhang, Y. M. Yu, L. B. Gan, *Org. Lett.*, 2012, **14**, 4002.

