

Note

**Alkyl-substituted cucurbit[6]uril bridged #-cyclodextrin  
dimer mediated intramolecular FRET behavior**

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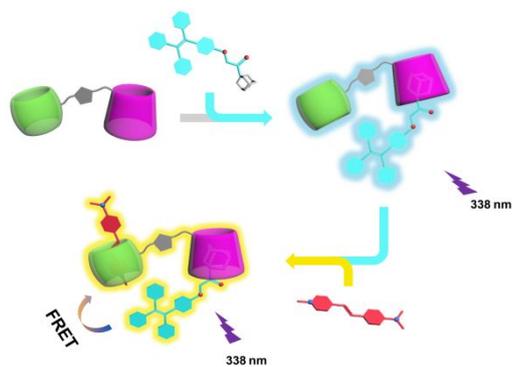
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4 **Alkyl-substituted cucurbit[6]uril bridged  $\beta$ -cyclodextrin dimer**  
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6 **mediated intramolecular FRET behavior**  
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## Graphic Abstract



**Abstract**

A novel triazolyl bridged cucurbituril (CB)-cyclodextrin (CD) dimer was synthesized via click reaction of mono-propargyl modified octamethylcucurbit[6]uril and mono-6-azido- $\beta$ -cyclodextrin. Moreover, it could form stable supramolecular inclusion complexes possessing efficient fluorescence resonance energy transfer, which was benefit from that CD and CB can bind amantadine- and pyridinium-containing fluorophores simultaneously. The supramolecular inclusion complex behaviors were investigated by NMR spectroscopy, UV-vis absorption and fluorescence spectroscopy.

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4 Cucurbit[*n*]urils (CB[*n*]s, *n* = 5–8, 10, 14) are a class of synthetic macrocyclic host  
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6 molecules consisting of *n* glycoluril units with a hydrophobic cavity and two identical  
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8 carbonyl-fringed portals.<sup>1</sup> Although (CB[*n*]s) are potentially used as a type of host  
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10 receptors<sup>2</sup>, their practical applications in chemistry, biology and material areas have  
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12 been limited, probably due to the insufficient solubility and the difficulty of  
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14 introducing functional groups on their surfaces. Since the discovery of the first fully  
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16 alkyl-substituted CB[5], decamethylcucurbit[5]uril, in 1992,<sup>3</sup> a series of fully and  
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18 partially alkyl-substituted cucurbit[*n*]urils (SCB[*n*]s) derivatives have been reported  
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20 successively.<sup>4–6</sup> The physical and chemical properties of alkyl-substituted CB[*n*]s have  
21  
22 been changed, such as cavity size, shape and electron cloud density of carbonyl  
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24 oxygen atoms, which increased the solubility in common solvents and produced other  
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26 special functional properties. The introduction of functional groups on skeletons of  
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28 CB[*n*]s has been a huge challenge in CB[*n*] chemistry due to chemical stability of  
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30 CB[*n*]s. In 2003, Kim and co-workers firstly prepared a series of CB[*n*] derivatives,  
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32 hydroxy-substituted (HO)<sub>2*n*</sub>CB[*n*]s, by simple oxidation of the native CB[*n*]s with  
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34 K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> in water,<sup>7</sup> and this served as a accelerator for the application of functionalized  
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36 CB[*n*]s in vesicles, polymers, nanomaterials, artificial ion channels, and so on.<sup>8–13</sup>  
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38 However, the yields for alkyl-substituted CB[*n*]s in this method was too low for  
39  
40 practical use. Until 2015, Bardelang and Ouari discovered a photochemical method by  
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42 UV and hydrogen peroxide to introduce a limited number of alcohol functional groups  
43  
44 on CB[*n*]s (*n* = 5, 6, 7, and 8).<sup>14</sup> Although they have made a correction of conversions  
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46 from 95–100% to 20–40%,<sup>15</sup> this method can be applied to other selected CB[*n*]s,  
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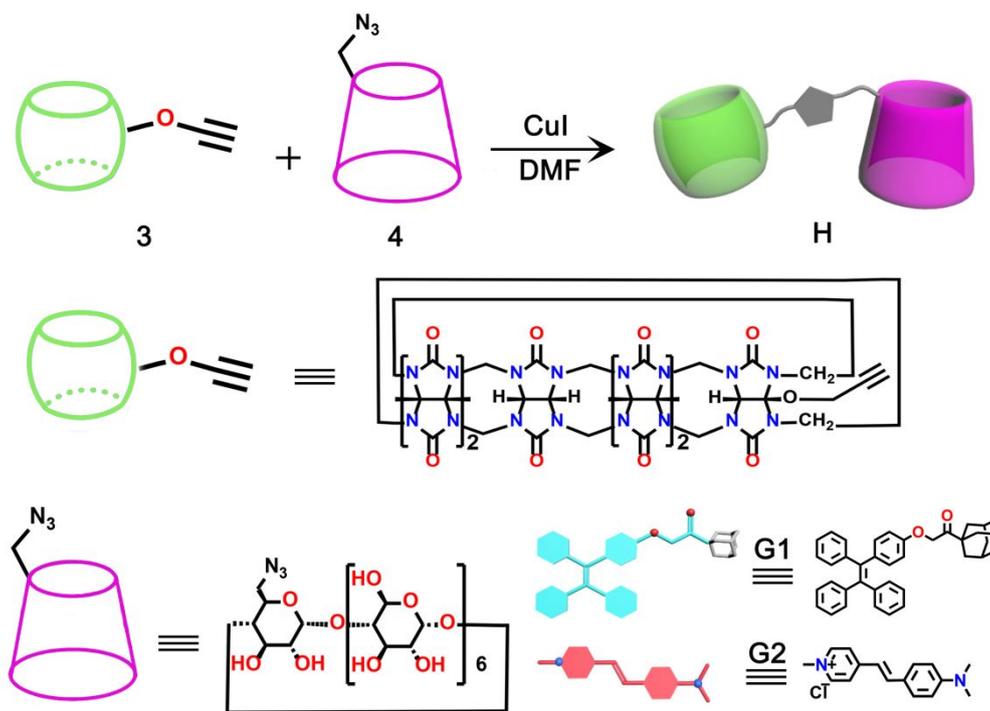
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4 including alkyl-substituted CB[n]s. However, the functionalization of  
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6 alkyl-substituted CB[n]s is still rarely reported.<sup>16,17</sup>  
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9 On the other hand, as one of very important photophysical properties, fluorescence  
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11 resonance energy transfer (FRET) is a research hotspot for scientists in miscellaneous  
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13 fields. The occurrence of a more effective FRET phenomenon requires some criteria.  
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15 That is, a FRET system includes at least two chromophores, the donor and the  
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17 acceptor, which should be located in close proximity and the fluorescence emission  
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19 spectrum of donor should sufficiently fall into the absorption spectrum of acceptor.  
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22 However, there are still several defects in the constructing FRET materials, such as  
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24 the lack of controllability of covalently connected donor and acceptor, the insufficient  
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26 solubility in aqueous solution, and the weak interaction between independent  
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28 fluorophores. Remarkably, through flexible and controllable regulation of the  
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30 interaction between donor and acceptor pairs, the FRET systems constructed in the  
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32 form of supramolecular host–guest chemistry could serve as a promising tool to solve  
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34 these drawbacks. As a result, many interesting supramolecular FRET systems have  
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36 been constructed and applied in various fields.<sup>18</sup> For instance, Zhou and Yang  
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38 exhibited a acid/base-controllable FRET system by a host–guest complex between a  
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40 rhodamine B functionalized pillar[5]arene and cyano-modified boron  
41  
42 dipyrromethene.<sup>19</sup> Park and Kim reported a supramolecular nanosystem based on  
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44 the fusion assay of two different organelles using a novel host–guest pair,  
45  
46 cucurbit[7]uril-Cy3 and adamantane-Cy5 as a FRET pair.<sup>20</sup> Several FRET systems  
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48 were also constructed in our research group, using the strategy of supramolecular  
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4 polymers based on host–guest complexation or in a nano-sized noncovalent  
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6 supramolecular assembly.<sup>21,22</sup> However, in a single supramolecular assembled entity,  
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8 the utilization of two different types of macrocyclic receptors to achieve efficient  
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10 FRET process still remains challenging.  
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14 In order to study the binding and photophysical behaviors of functionalized SCB[*n*]s,  
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16 we utilized SCB[*n*]s possessing OH group at designated position to yield a special  
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18 oxidation product. Inspired by the complementary molecular binding behaviors of  
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20 CB[*n*]s and cyclodextrins (CDs).<sup>23</sup> In this work, we designed and synthesized a novel  
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22 macrocyclic dimer **H** (Figures S4–S6, Supporting Information) consisting of a  
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24 symmetrical octamethylcucurbituril (OMeCB[6]) and β-CD, in which two  
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26 macrocyclic molecules, (propargyl)<sub>1</sub>OMeCB[6] (Figures S1–S3, Supporting  
27  
28 Information) and mono-6-azido-β-CD was covalently conjugated via click reaction.  
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30 In our case, given that β-CD can incorporate neutral guest molecules possessing an  
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32 adamantyl end with high binding affinity, the adamantyl tetraphenylethylene (**G1**)  
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34 (Figures S7–S9, Supporting Information) was accordingly synthesized. Meanwhile,  
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36 OMeCB[6] is capable of encapsulating cationic guests in its hydrophobic cavity and  
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38 the binding constant between OMeCB[6] and  
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40 *trans*-4-[4-(dimethylamino)styryl]-1-methylpyridinium chloride (**G2**) can reach up to  
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42 10<sup>6</sup> M<sup>-1</sup> order of magnitude. Further spectroscopic studies have shown that H has the  
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44 larger binding affinity for these two guest molecules (**G1** and **G2**) than individual  
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46 macrocycle molecules (CB and CD moieties) (Scheme 1). Due to the superior  
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48 solubility of macrocyclic dimers in **H**, an intramolecular FRET system mediated by  
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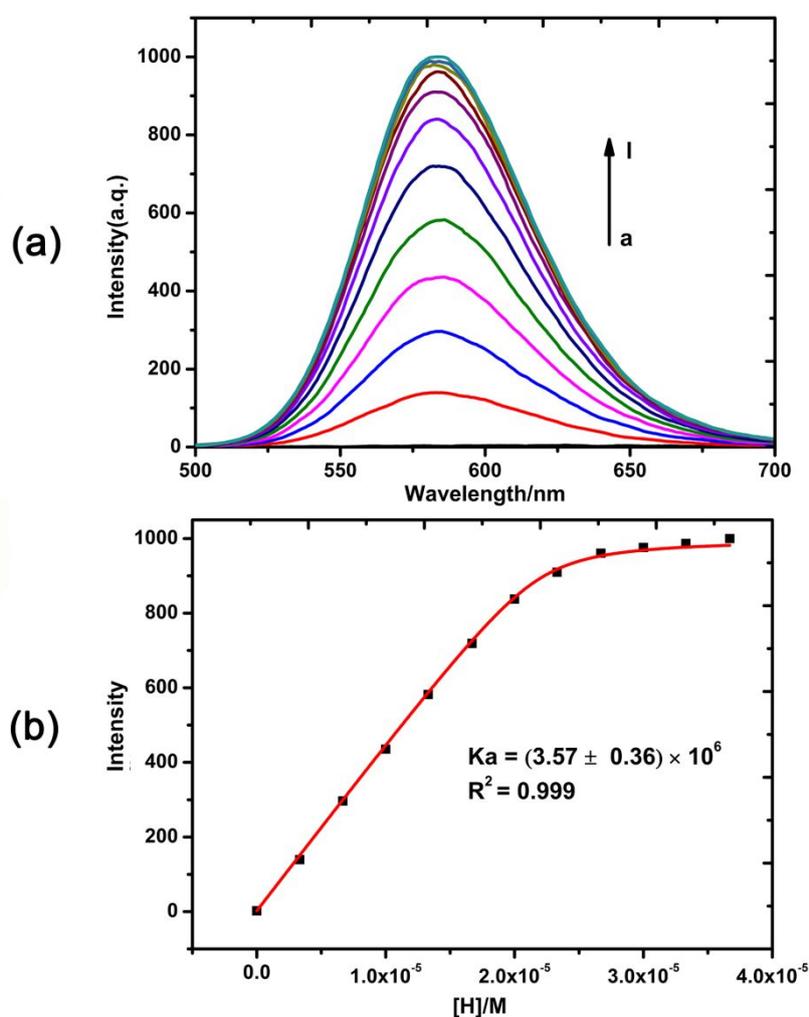
the conjugation of CB with CD moieties was achieved in an aqueous solution, and the FRET efficiency was determined to be 70.3%.



**Scheme 1.** Schematic illustration of the structural formulas of **H**, **G1** and **G2** molecules.

To confirm the formation of the host–guest complexes between the OMeCB[6] moiety of **H** and **G2** as well as free OMeCB[6] and **G2**,  $^1\text{H}$  NMR spectroscopic titrations were first performed by using **G2** as a guest compound and free OMeCB[6] as a model host compound. As shown in Figure S10 (Supporting Information), upon the gradual addition of **G2**, the proton signals of the guest appeared to shift upfield ( $\Delta\delta = -0.22, -0.83, -0.09$ , for  $\text{H}_1, \text{H}_2, \text{H}_3$  respectively), suggesting that these protons of the guest were included in the cavity of the OMeCB[6] and were shielded by the

OMeCB[6]. In contrast, the signal of H<sub>4</sub>, H<sub>5</sub> moved downfield by 0.13 and 0.56 ppm, suggesting that these protons on the guest were excluded at the portals of the OMeCB[6]. Additionally, the NMR assignments were made through <sup>1</sup>H-<sup>1</sup>H COSY experiment (Figure S11, Supporting Information). Moreover, when adding 1.0 equiv. of **H** to **G2**, similar <sup>1</sup>H NMR complexation induced shifts occurs to protons of **G2** compared with OMeCB[6]/**G2** complex (Figure S12 Supporting Information), indicating that **H** and **G2** could form the same host-guest complex as OMeCB[6]/**G2** complex.

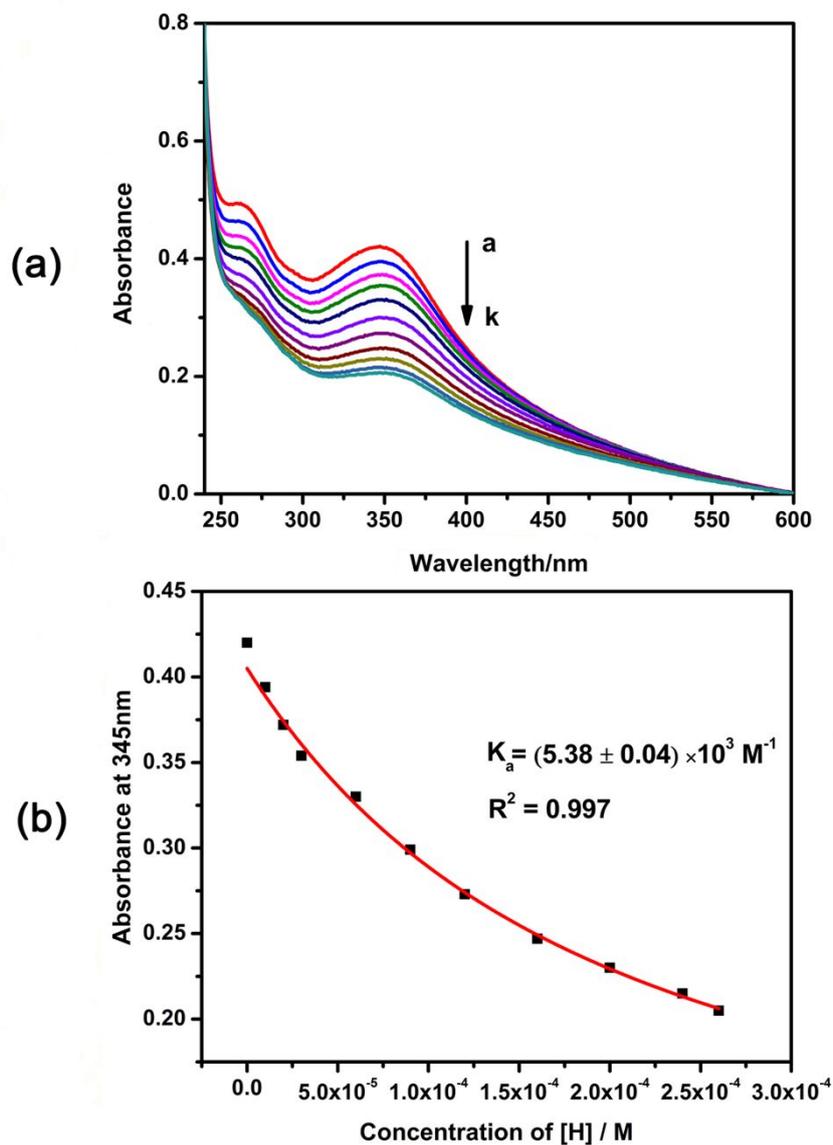


**Figure 1.** Emission spectra (a) and intensity changes of **G2** at 580 nm (b) upon the gradual addition of **H** in an aqueous solution ( $[\mathbf{G2}] = 2 \times 10^{-5} \text{ M}$ ,  $[\mathbf{H}] = 0-3.67 \times 10^{-5} \text{ M}$ ,

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4 25 °C).

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9 It is known that CB[6] and **G2** guest could form an 1:1 inclusion complex with the  
10 absorbance at 450 nm and 270 times fluorescence enhancement at 580 nm.<sup>24</sup> To  
11 investigate the binding behavior between OMeCB[6] moiety of **H** and **G2**, UV-vis  
12 absorption and fluorescence experiments were further conducted. As discerned from  
13 the UV-vis absorption spectra, Job plot of OMeCB[6]/**G2** complex showed a 1:1  
14 stoichiometry by plotting the absorbance at 450 nm against the molar fraction of  
15 OMeCB[6] and **G2** (Figure S13b, Supporting Information).  
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18 For the complexation of **H** and **G2**, the stoichiometry was also determined to be 1:1  
19 based on the fluorescence intensity of **G2** in the presence of **H** (Figure S13a,  
20 Supporting Information). These results also confirmed that the guest molecule **G2**  
21 could be exclusively included into the hydrophobic cavity of OMeCB[6] in aqueous  
22 solution. Meanwhile, according to the fluorescence spectra, **G2** (20 μM) displayed  
23 very poor fluorescence with a maximum emission at 607 nm in aqueous solution,  
24 while upon addition of OMeCB[6] or **H** from 0.1 equiv. to 1.0 equiv., the emission  
25 intensity increased significantly. Additionally, a blue shift from 607 nm to 582 nm  
26 indicated the host-guest interactions between OMeCB[6] moiety and **G2** (Figure 1a,  
27 S14a). The association constant ( $K_a$ ) of **H/G2** was calculated to be  $3.57 \times 10^6 \text{ M}^{-1}$  by  
28 curve fitting method (Figure 1b). As shown in Figure S14b (Supporting Information),  
29 the  $K_a$  value for OMeCB[6]/**G2** was  $3.22 \times 10^6 \text{ M}^{-1}$ , which was in good consistence  
30 with the one in **H/G2** complexation.  
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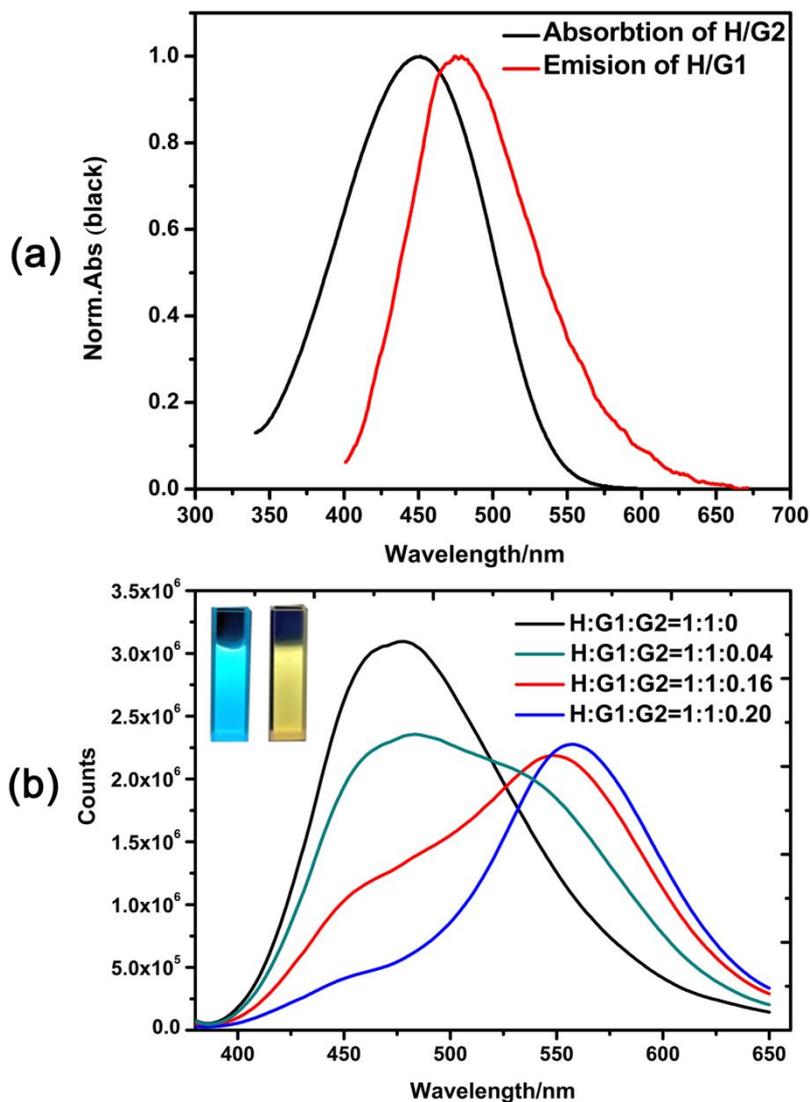
**Figure 2.** UV-vis spectra (a) and absorbance changes of **G1** at 345 nm (b) upon addition of **H** in an aqueous solution containing 3% DMSO ( $[\text{G1}] = 3.0 \times 10^{-5} \text{ M}$ ,  $[\text{H}] = 0\text{-}2.6 \times 10^{-4} \text{ M}$ , 25 °C).

It is well-known that  $\beta$ -CD could associate with adamantyl guests in aqueous solution. Then, the  $^1\text{H}$  NMR spectra was utilized by using  $\beta$ -CD and 1-adamantyl bromomethyl ketone (**ABK**) as model compound. The  $^1\text{H}$  NMR titration spectra for a fixed concentration of **ABK** upon incremental addition of  $\beta$ -CD showed the gradual

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4 downfield shifts of adamantyl protons signals (Figure S15, Supporting Information),  
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6 indicating the inclusion of the adamantyl moiety of **ABK** guest in the  $\beta$ -CD cavity.<sup>25</sup>  
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9 Compared with the free  $\beta$ -CD, the <sup>1</sup>H NMR spectra also showed that upon addition of  
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11 1.0 equiv. of **H**, the peaks of protons H<sub>a-c</sub> on **ABK** shifted downfield significantly ( $\Delta\delta$   
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13 = 0.09, 0.08 and 0.22 ppm for H<sub>a-c</sub>, respectively, Figure S16, Supporting  
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15 Information). Meanwhile, 2D NOESY NMR spectrum of equimolar **ABK** to **H** was  
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17 conducted to prove the formation of host–guest complex. The NOE (nuclear  
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19 Overhauser enhancement) correlations were observed between adamantyl protons of  
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21 **ABK** and  $\beta$ -CD moiety of **H**, corroborating that adamantyl moiety was included in  
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23  $\beta$ -CD's cavity to form host–guest complex (Figure S17, Supporting Information).  
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30 The host–guest complexes of **H/G1** and  $\beta$ -CD/**G1** were also studied by UV–vis  
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32 spectroscopy. From the absorption titration spectra, upon addition of  $\beta$ -CD to an  
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34 aqueous solution of **G1** with a fixed concentration, the absorbance peak at 345 nm of  
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36 **G1** experienced slightly red shift and the absorbance intensity was decreasing  
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38 gradually (Figure 2a). The binding constant for  $\beta$ -CD/**G1** complex was determined to  
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40 be  $(5.38 \pm 0.04) \times 10^3 \text{ M}^{-1}$  (Figure 2b). Compared to the  $\beta$ -CD/**G1** system, the  
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42 absorption spectra of **H/G1** showed the quite similar changes. These results revealed  
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44 that the adamantyl moiety of **G1** was included in the cavity of  $\beta$ -CD moiety of **H**. In  
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46 addition, the  $K_a$  value of **H/G1** was calculated to be  $(5.44 \pm 0.16) \times 10^3 \text{ M}^{-1}$ , which  
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48 was similar to the one of  $\beta$ -CD/**G2** complex (Figure S18, Supporting Information).  
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56 In addition, the spectroscopic titration experiments were also performed in D<sub>2</sub>O  
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4 containing 3% DMSO, showing quite similar molecular binding behaviors (Figures  
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6 S19-S21, Supporting Information).  
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9 It is well known that the fluorescence emission spectrum of donor should sufficiently  
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11 fall into the UV-vis absorption spectra of acceptor in an effective FRET process.  
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13 Theoretical calculation showed that the optimized structure of the inclusion  
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15 complexes between **H** and two guest molecules (**G1** and **G2**) is appropriate for FRET  
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17 by the molecular mechanics modeling (Figure S22, Supporting Information). As can  
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19 be seen in Figure 3a, upon excitation at 338 nm that corresponded to absorption band  
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21 of the host-guest complex of **H/G1**, the 1:1 supramolecular complex of **H/G1**  
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23 exhibited a strong fluorescence intensity centered around 475 nm in water, which was  
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25 well overlapped with the absorption band of **H/G2** complex in the range of 450–550  
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27 nm. To further investigate the FRET process of host-guest complexes based on the  
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29 macrocyclic dimer, fluorescence titration experiments were conducted in  
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31 aqueous solution. As shown in Figure 3b, with the stepwise addition of **G2** to the  
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33 **H/G1** (1:1 molar ratio), the fluorescence intensity of **H/G1** was gradually decreased  
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35 along with the enhancement of emission of **H/G2** when excited at 338 nm. Meanwhile,  
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37 the color that corresponded to fluorescence emission was accordingly changed from  
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39 blue to yellow. In the control experiments, either **H/G2** or free **G2** barely gave  
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41 fluorescence emission in the same experimental conditions ( $\lambda_{\text{ex}} = 338 \text{ nm}$ ; Figure S23,  
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43 Supporting Information). Furthermore, the energy-transfer efficiency was calculated  
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45 as high as 70.3%.  
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**Figure 3.** (a) Normalized absorption spectra of **H/G2** and emission spectrum of **H/G1**.

(b) Fluorescence spectra of **H/G1** ( $[\text{H}] = [\text{G1}] = 1.0 \times 10^{-4} \text{ M}$ ) in the solution of  $\text{H}_2\text{O}/\text{DMSO}$  (97:3) with different concentrations of **G2**. The concentrations of **G2** were 0,  $4.0 \times 10^{-6}$ ,  $1.6 \times 10^{-5}$ ,  $2.0 \times 10^{-5} \text{ M}$ , respectively. Inset: left, photographic images of **H/G1**, and right, **H/G1/G2** under UV light (365 nm) ( $[\text{H}] = [\text{G1}] = 1.0 \times 10^{-4} \text{ M}$ ,  $[\text{G2}] = 2.0 \times 10^{-5} \text{ M}$ ).

In conclusion, a newly macrocyclic dimer **H** bearing CD and CB moiety was synthesized via click chemistry. OMeCB[6] was chosen to construct this dimer

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4 instead of CB[6], because the solubility of parent CB[6] was rather limited in water.  
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6 Tetraphenylethylene modified with adamantyl moiety was synthesized to be  
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8 selectively trapped in the  $\beta$ -CD's cavity. After interaction with the host molecule **H**,  
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10 there is a strong blue emission centered at 478 nm. Then the **G2** molecule as a  
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12 receptor could be well encapsulated in the cavity of OMeCB[6] moiety in an aqueous  
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14 solution and the absorption spectrum had a good overlap with the donor emission  
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16 spectrum. Benefiting the good solubility of this conjugated dimeric host, a newly  
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18 intramolecular FRET system was constructed conveniently based on the  
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20 supramolecular host-guest strategy. Therefore, all the research results indicated that  
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22 novel macrocyclic dimer CB-CD-based host-guest complexation may be significant  
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24 for designing novel molecular sensors and devices and have potential application in  
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26 other fields such as materials and biology systems, including drug delivery, cell  
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28 imaging, and biosensors.  
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## 40 **Experimental Section**

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43 **Preparation of compound G1:** Compound **1**<sup>26</sup> (1.7 g, 4.86 mmol) and 1-adamantyl  
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45 bromomethyl ketone (1.25 g, 4.86 mmol) were dissolved in acetone (50 mL), and  
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47 potassium carbonate (2.02 g, 14.58 mmol) was added. The mixture was refluxed using  
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49 an oil bath over night. After cooling to room temperature, the solution was filtered,  
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51 and the filtrate was dried under reduced pressure to remove the solvent. The residue  
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53 was purified by column chromatography (silica gel, petroleum ether : CH<sub>2</sub>Cl<sub>2</sub> = 1:2,  
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55 v/v) to give compound **1** as white powder (2.42 g, 95% yield). <sup>1</sup>H NMR (400 MHz,  
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4 DMSO-*d*<sub>6</sub>, TMS): δ1.66 (m, 6H, H of adamantane), 1.82 (m, 6H, H of adamantane),  
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6 1.98 (s, 3H, H of adamantane), 4.98 (s, 2H, H of CH<sub>2</sub>), 6.60-6.62 (d, J = 8Hz, 2H, H  
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8 of benzene), 6.82-6.84 (d, J = 8 Hz, 2H, H of benzene) 6.93-7.18 (m, 14H, H of  
9  
10 of benzene); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, DMSO-*d*<sub>6</sub>, TMS): δ27.1, 35.8, 36.9, 44.5, 68.1,  
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12 113.7, 126.3, 127.6, 127.8, 130.5, 130.5, 130.6, 131.6, 143.3, 156.3, 208.8 ppm; MS  
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14 (MALDI) *m/z* : [M + H]<sup>+</sup> Calcd for C<sub>38</sub>H<sub>37</sub>O<sub>2</sub> 525.30; Found 525.34; [M + Na]<sup>+</sup> Calcd  
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16 for C<sub>38</sub>H<sub>36</sub>O<sub>2</sub>Na 547.26; Found *m/z* 547.31. Anal. Calcd for C<sub>38</sub>H<sub>36</sub>O<sub>2</sub>: C, 86.99; H,  
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18 6.92; O, 6.10. Found: C, 86.96; H, 6.90; O, 6.09.

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25 **Preparation of compound 3:** To a solution of **2**<sup>16</sup> (30 mg, 0.027 mmol) and N,  
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27 N'-dihexylviologen bromide salt (13.10 mg, 0.027 mmol) in anhydrous DMSO (2  
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29 mL), NaH (10 mg, 0.4 mmol) was added and stirred at room temperature for 15  
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31 minutes. propargyl bromide (0.5 mL, 5.8 mmol) was added subsequently at 0°C and  
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33 the reaction mixture was stirred at room temperature for 12 hours. The reaction was  
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35 then diluted with 50 mL diethyl ether and filtered. The remaining solid was triturated  
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37 with acetone (3 × 50mL) and dried under vacuum to give a yellow solid (15 mg,  
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39 72%).<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O): δ 1.78 (m, 24H), 3.01 (s, H), 4.38 (m, 12H),  
40  
41 4.50-4.54 (d, J = 16 Hz, 2H), 5.55 (m, 5H), 5.70 (m, 10H); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz,  
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43 D<sub>2</sub>O): δ 15.9, 16.5, 42.9, 44.0, 47.9, 48.1, 52.3, 70.8, 72.5, 77.2, 77.7, 78.0, 97.0,  
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45 155.7, 156.8 ppm; HRMS (MALDI) *m/z* : [M + Na]<sup>+</sup> Calcd for C<sub>47</sub>H<sub>54</sub>N<sub>24</sub>O<sub>13</sub>Na  
46  
47 1185.4200; Found 1185.4198. Anal. Calcd for C<sub>47</sub>H<sub>54</sub>N<sub>24</sub>O<sub>13</sub>: C, 48.54; H, 4.68; N,  
48  
49 28.90. Found: C, 48.52; H, 4.64; N, 28.87.

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58 **Preparation of compound H:** CuI (64.48 mg, 0.34 mmol) was added to a solution of  
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4 **3** (79.02 mg, 0.068 mmol) and **4**<sup>27</sup> (78.88 mg, 0.068 mmol) in dry DMF (10 mL), and  
5  
6 the reaction mixture was stirred at 80°C using an oil bath for 24 h under argon. After  
7  
8 cooling to room temperature, the mixture was filtered to remove any insoluble copper  
9  
10 salt, and the filtrate was evaporated under a reduced pressure to remove excess DMF.  
11  
12 The residue was purified by column chromatography (silica gel) with water/acetic  
13  
14 acid as eluent to give **H** as a white solid (101mg, yield 64%). <sup>1</sup>H NMR (400 MHz,  
15  
16 D<sub>2</sub>O): δ 1.68-1.90 (m, 24 H), 3.48-3.96 (m, 42 H), 4.25-4.52 (m, 14 H), 4.99-5.10 (m,  
17  
18 7 H), 5.52-5.77 (m, 15 H), 8.16 (s, H); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, D<sub>2</sub>O): δ 15.9, 16.5,  
19  
20 42.9, 44.1, 48.2, 51.4, 60.3, 70.4, 70.8, 71.8, 72.0, 72.8, 73.1, 77.8, 78.1, 81.3, 102.0,  
21  
22 156.3 ppm; MS (MALDI) *m/z* : [M + Na]<sup>+</sup> Calcd for C<sub>89</sub>H<sub>123</sub>N<sub>27</sub>O<sub>47</sub>Na 2344.796;  
23  
24 Found 2344.777. Anal. Calcd for C<sub>89</sub>H<sub>123</sub>N<sub>27</sub>O<sub>47</sub>: C, 46.02; H, 5.34; N, 16.28. Found:  
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26 C, 46.05; H, 5.35; N, 16.30.

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35 **Supporting Information:** Detailed synthesis, characterization data, Job's plots,  
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37 association constant, absorption and emission spectra, <sup>1</sup>H NMR spectra and  
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39 theoretical calculation. This material is available free of charge via the Internet at  
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41 <http://pubs.acs.org>.  
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52  
53 21861132001) for financial support.  
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