

**Molecular Taekwondo. 2. A New Calix[4]azacrown Bearing Two Different Binding Sites as a New Fluorescent Ionophore**

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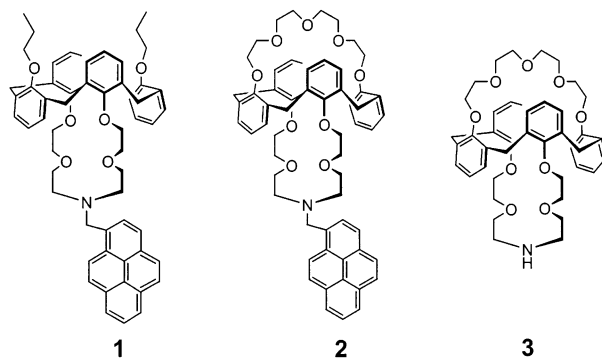
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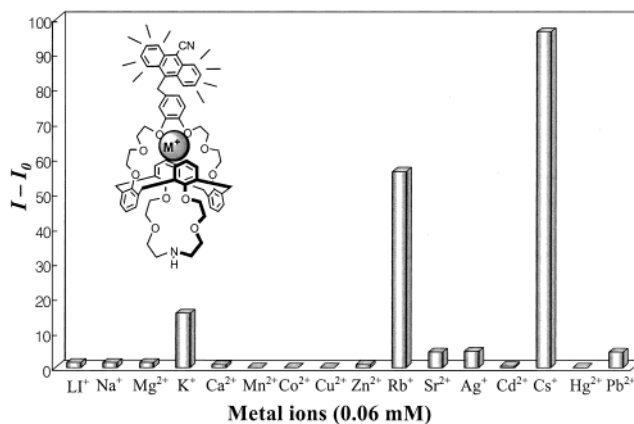
**Abstract:** Synthesis and binding studies of a new calixarene-based fluoroionophore were made. Calix[4]azacrown having an anthracenyl unit displayed large chelation-enhanced fluorescence effects with Cs<sup>+</sup>, Rb<sup>+</sup>, and K<sup>+</sup> over other metal ion tested. Interesting “molecular taekwondo” processes between Cs<sup>+</sup>-Cu<sup>2+</sup> and Cs<sup>+</sup>-Ag<sup>+</sup> pairs were monitored via fluorescent changes.

Calixarenes with appropriate appended groups are good candidates because they have been shown to be highly specific ligands, and their potential applications as sensing agents have received increasing interest.<sup>1,2</sup> On the other hand, fluoroionophores chemically communicate ion concentrations and are the subject of substantial investigation for metal ion analysis.<sup>3</sup> In fact, several calixarene-based fluorescent sensors have already been designed.<sup>4-7</sup>

Recently, we have synthesized new pyrene-armed calix[4]azacrowns as new fluorescent ionophores (Figure 1).<sup>8</sup> When metal ion is bound to either **1** or **2**, the metal ion itself can choose its better binding partner between the two different binding sites, such as crown ether and



**FIGURE 1.** Structure of compounds **1**–**3**.



**FIGURE 2.** CHEF effects of compound **4** (6.0 μM) with metal ions (100 equiv, 600 μM) in ethanol–dichloromethane (9:1, v/v) at 450 nm.

azacrown ligand. Furthermore, when K<sup>+</sup> ion was added to a solution containing **2** and Ag<sup>+</sup>, we observed a fluorescence quenching effect as the amount of K<sup>+</sup> ion increases. For example, complexation of K<sup>+</sup> into the crown ether site induced the decomplexation of Ag<sup>+</sup> from the azacrown site. We named this interesting “coming-in and kicking-out” process as a “molecular taekwondo” process.<sup>8</sup>

In a continuation of this work, we report herein the synthesis and binding studies of a new calix[4]arene derivative **4** containing two binding sites such as a crown ether and an azacrown ether. In this system, the selective binding properties toward metal ions and “molecular taekwondo” processes between Cs<sup>+</sup>-Cu<sup>2+</sup> and Cs<sup>+</sup>-Ag<sup>+</sup> pairs were easily monitored via fluorescence change.

Our synthesis began with 25,27-bis(5-chloro-3-oxapentylloxy)calix[4]arene (**5**), which was prepared following the published procedure.<sup>9</sup> Under a nitrogen atmosphere, treatment of **5** with *p*-toluenesulfonamide and Cs<sub>2</sub>CO<sub>3</sub> in DMF led to calix[4]monoazacrown *p*-toluenesulfonate (**6**) in 28% yield (Scheme 1). Calix[4]monoazacrown-5 (**7**) was obtained in 70% yield after tosyl group was removed using sodium amalgam. Finally, treatment of **7** with

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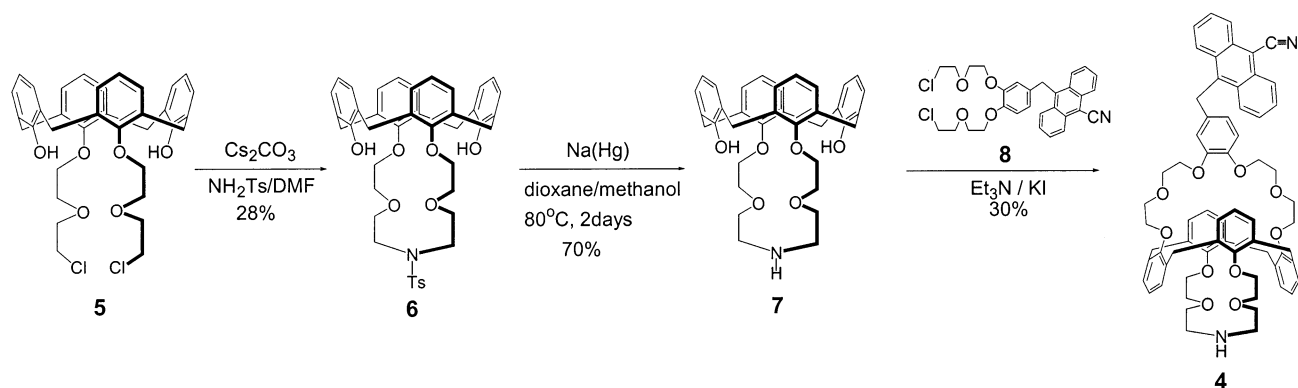
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## SCHEME 1. Synthesis of Compound 4

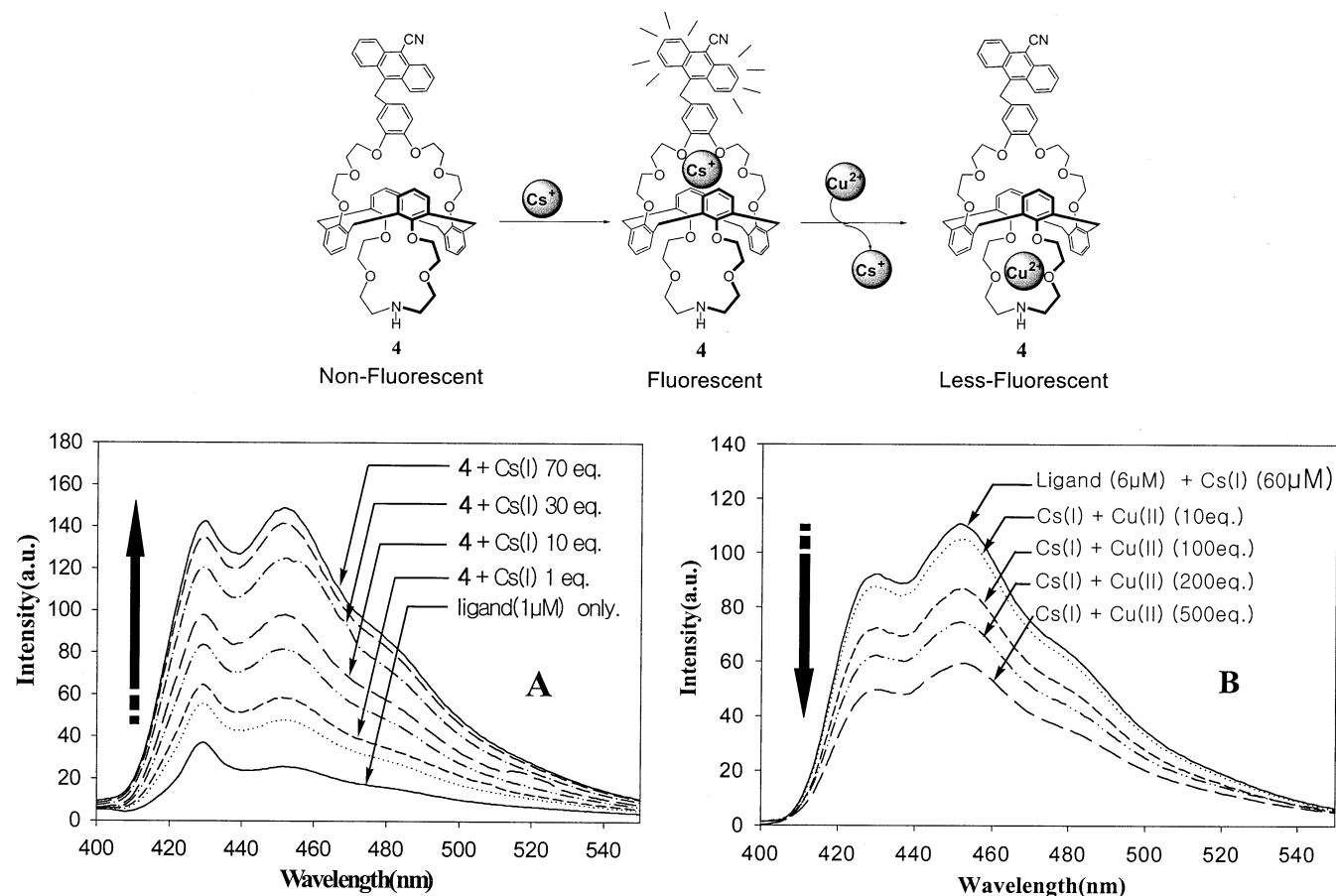


1,2-bis(5-chloro-3-oxa-1-pentyloxy)-4-(10-cyano-9-anthrylmethyl)benzene (**8**)<sup>6c</sup> gave compound **4** in 30% yield.

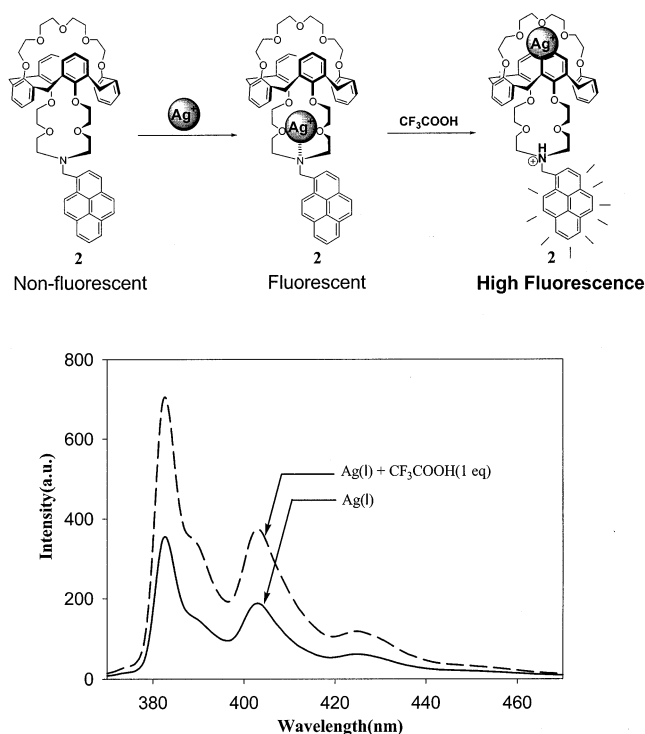
The perchlorate salts of  $\text{Ca}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Cs}^+$ ,  $\text{Cu}^{2+}$ ,  $\text{Hg}^{2+}$ ,  $\text{K}^+$ ,  $\text{Li}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Na}^+$ ,  $\text{Pb}^{2+}$ ,  $\text{Rb}^+$ ,  $\text{Sr}^{2+}$ , and  $\text{Zn}^{2+}$  were used to evaluate metal ion binding ability.<sup>10</sup> Using these metal ions (600  $\mu\text{M}$ , 100 equiv), **4** (6.0  $\mu\text{M}$ ) displayed large chelation-enhanced fluorescence (CHEF) effects with  $\text{Cs}^+$ ,  $\text{Rb}^+$ , and  $\text{K}^+$  in  $\text{EtOH}-\text{CH}_2\text{Cl}_2$  (9:1, v/v) (Figure 2).  $I_0$  is the fluorescence intensity in the absence of metal ion, and  $I$  is the intensity when 100 equiv of each metal ion was added. As illustrated in Dabestani's recent papers, in the absence of metal ions, fluorescence

is partially quenched by photoinduced electron transfer (PET) from the dialkoxybenzene moiety of the crown ring to the excited singlet state of 9-cyanoanthracene.<sup>6</sup> Upon complexation, only in the crown ether binding site, the oxygen lone pairs no longer participate in PET, causing the CHEF effect. From the fluorescence titration experiment, the association constants for  $\text{Cs}^+$  ion was estimated to be  $9.8 \times 10^5 \text{ M}^{-1}$  in  $\text{EtOH}-\text{CH}_2\text{Cl}_2$  (9:1, v/v).<sup>10</sup>

As illustrated in our previous report,<sup>8</sup> **1** displayed large CHEF effects upon the complexation with  $\text{Cu}^{2+}$ ,  $\text{K}^+$ ,  $\text{Pb}^{2+}$ , and  $\text{Rb}^+$ . On the other hand, **2** displayed similar CHEF effects with  $\text{Ag}^+$ ,  $\text{Co}^{2+}$ ,  $\text{Cu}^{2+}$ , and  $\text{Pb}^{2+}$ . Unlike **1**, **2** did



**FIGURE 3.** (a) Fluorescent emission spectra of **4** upon the addition of various amount of  $\text{Cs}^+$  in ethanol–dichloromethane (9:1, v/v) and (b) fluorescent emission spectra of titrations of compound **4** (6  $\mu\text{M}$ )· $\text{Cs}^+$  (100  $\mu\text{M}$ ) upon the addition of various amount of  $\text{Cu}^{2+}$  in ethanol–dichloromethane (9:1, v/v).



**FIGURE 4.** Fluorescence emission spectra of compound **2** ( $6 \mu\text{M}$ )· $\text{Ag}^+$  (10 equiv) upon the addition of  $\text{CF}_3\text{COOH}$  (1 equiv) in ethanol–dichloromethane (v/v, 9:1).

not show any CHEF effect with  $\text{K}^+$  and  $\text{Rb}^+$ . When metal ion is bound to **2**,  $\text{K}^+$  showed a better binding affinity with the crown ether moiety of **2**, and therefore, no CHEF effect has been observed. Productively compared, **4** showed large CHEF effects only with  $\text{Cs}^+$ ,  $\text{Rb}^+$ , and  $\text{K}^+$ , which are located in the crown ether site. Since we introduced a fluorophore in the crown ether site of **4**, the “molecular taekwondo” process was confirmed again in an opposite mode compared to **2**. Upon the addition of  $\text{Cs}^+$  to **4**, the CHEF effect was observed due to the inhibition of the PET mechanism (Figure 3). This CHEF effect also confirms that  $\text{Cs}^+$  is in the crown ether site. When  $\text{Cu}^{2+}$  ion was added to a solution containing **4** ( $6 \mu\text{M}$ ) and  $\text{Cs}^+$  (10 equiv), we observed a fluorescence quenching effect as the amount of  $\text{Cu}^{2+}$  ion increases (Figure 3). Complexation of  $\text{Cu}^{2+}$  into the azacrown ether site induced the decomplexation of  $\text{Cs}^+$  from the crown ether site. However, we could only observe partial decomplexations of  $\text{Cs}^+$  from the crown ether site of **4** under our experimental condition. The above observation was repeated using the  $\text{Cs}^+$ - $\text{Ag}^+$  pair.

Furthermore, when 1 equiv of trifluoroacetic acid was added into a solution of **2** and  $\text{Ag}^+$  (10 equiv), fluorescence emission intensity was further enhanced due to the protonation of benzylic amine (Figure 4). Interestingly, during this process,  $\text{Ag}^+$  moved to the crown ether moiety by intramolecular tunneling through the calix-tube. Following the couple of reports from Shinkai group<sup>11</sup>

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regarding the “molecular syringe” process in 1,3-alternate calix[4]azacrowns, Kim et al. recently reported<sup>12</sup> intramolecular  $\text{Ag}^+$  ion tunneling through the  $\pi$ -basic calix-tube in **3** (Figure 1). Upon the addition of trifluoroacetic acid to a solution of **3** and  $\text{Ag}^+$ ,  $\text{Ag}^+$  ion tunneling from the azacrown site to the crown ether site was observed using a dynamic  $^1\text{H}$  NMR technique. In our case, these processes can be easily monitored via fluorescent changes as well. These phenomena were also reproduced in **4**. When 1 equiv of  $\text{Cu}^{2+}$  or  $\text{Ag}^+$  was added to the solution of **4** ( $6 \mu\text{M}$ ) in dichloroethane–ethanol (1:1, v/v), there was not any change in fluorescent emission. Addition of trifluoroacetic acid to a solution containing only **4** did not induce any enhancement of its fluorescence emission intensity, either. On the other hand, the addition of trifluoroacetic acid (1.0 equiv) to these solution of either **4**· $\text{Cu}^{2+}$  or **4**· $\text{Ag}^+$  induced the CHEF effects, indicating that  $\text{Cu}^{2+}$  or  $\text{Ag}^+$  ions are located in the crown ether site by the electrostatic repulsion between metal ion and quaternary ammonium ion.

In conclusion, we report a synthesis and binding study of a new calixarene-based fluoroionophore. Among the metal ions examined, **4** displayed large CHEF effects with  $\text{Cs}^+$ ,  $\text{Rb}^+$ , and  $\text{K}^+$ . Also, interesting “molecular taekwondo” processes between  $\text{Cs}^+$ - $\text{Cu}^{2+}$  and  $\text{Cs}^+$ - $\text{Ag}^+$  pairs in **4** were easily monitored via fluorescent changes and productively compared with those of  $\text{Ag}^+$ - $\text{K}^+$  and  $\text{Cu}^{2+}$ - $\text{K}^+$  pairs in **2**. Furthermore, intramolecular metal ion tunnelings through  $\pi$ -basic calixtube upon the addition of trifluoroacetic acid were also easily monitored via fluorescent changes. Introduction of a second fluorophore on the azacrown ether site is under investigation.

## Experimental Section

**Synthesis. Calix[4]monoazacrown *p*-toluenesulfonate (6).** Under nitrogen, a mixture of *p*-toluenesulfonamide (0.53 g, 5.15 mmol),  $\text{Cs}_2\text{CO}_3$  (3.25 g, 23.5 mmol), and DMF (100 mL) was heated to  $80^\circ\text{C}$  for 30 min. 25,27-Bis(5-chloro-3-oxapentylloxy)-calix[4]arene (**5**) (5.00 g, 7.85 mmol) dissolved in DMF (20 mL) was added dropwise over a period of 3 h. After refluxing for 24 h, the mixture was dissolved in  $\text{CH}_2\text{Cl}_2$  (100 mL) and treated with 10% aqueous  $\text{NaHCO}_3$  (100 mL). The organic layer was washed with water (100 mL) and dried over anhydrous  $\text{MgSO}_4$  and filtered. Column chromatography using ethyl acetate as an eluent on silica gel gave **6** as a pale brownish solid in 28% yield: mp  $298\text{--}301^\circ\text{C}$ ; FAB MS  $m/z$  ( $\text{M}^+$ ) calcd 735.9, found 736.2. Anal. Calcd for  $\text{C}_{43}\text{H}_{45}\text{NO}_8\text{S}$ : C, 70.12; H, 6.11. Found: C, 70.15; H, 6.09.

**Calix[4]monoazacrown-5 (7).** Under nitrogen, to solution of 1,4-dioxane (100 mL) and methanol (20 mL) were carefully added calix[4]monoazacrown *p*-toluenesulfonate (1.0 g, 1.35 mmol), sodium hydrogen phosphate (0.42 g, 2.97 mmol), and 6%  $\text{Na}(\text{Hg})$  amalgam (3.9 g, 67.5 mmol). The reaction mixture was refluxed for 2 days at  $80^\circ\text{C}$ . After cooling to room temperature, the solvent was evaporated in vacuo.  $\text{CH}_2\text{Cl}_2$  (50 mL) and water (50 mL) were added, and the organic layer was separated. The  $\text{CH}_2\text{Cl}_2$  layer was washed twice with 10% aqueous  $\text{Na}_2\text{HPO}_4$  followed by drying over anhydrous  $\text{MgSO}_4$ . After filtration of magnesium sulfate, removal of the solvent in vacuo gave **7** as a white solid in 70% yield: mp  $181\text{--}183^\circ\text{C}$ ; FAB MS  $m/z$  ( $\text{M}^+$ ) calcd 581.7, found 582.3. Anal. Calcd for  $\text{C}_{36}\text{H}_{39}\text{NO}_6$ : C, 74.26; H, 6.70. Found: C, 74.29; H, 6.75.

**1,3-Alternate 25,27-[4-(10-Cyano-9-anthrylmethyl)-1,2-phenylenebis(5-dioxo-3-oxa-1-pentylloxy)]calix[4]azacrown-**

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**5 (4).** Under nitrogen, a mixture of calix[4]monoazacrown-5 (**7**) (0.4 g, 0.68 mmol), NaI (0.26 g, 1.73 mmol), Cs<sub>2</sub>CO<sub>3</sub> (3.59 g, 11.0 mmol), and 1,2-bis(5-chloro-3-oxa-1-pentyloxy)-4-(10-cyano-9-anthrylmethyl)benzene (**8**) (0.41 g, 0.76 mmol) in dry CH<sub>3</sub>CN (100 mL) was refluxed for 2 days. After cooling to room temperature, the solvent was evaporated in vacuo. CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and water (50 mL) were added, and the organic layer was separated. The CH<sub>2</sub>Cl<sub>2</sub> layer was washed twice with 10% aqueous NaCl solution followed by drying over anhydrous MgSO<sub>4</sub>. After filtration of magnesium sulfate, removal of the solvent in vacuo gave **4** as a yellow solid (30%), which was recrystallized from diethyl ether (30 mL): mp 217–220 °C; FAB MS *m/z* (M<sup>+</sup>) calcd 1047.2, found 1047.3. Anal. Calcd for C<sub>66</sub>H<sub>66</sub>N<sub>2</sub>O<sub>10</sub>: C, 75.63; H, 6.30. Found: C, 75.59; H, 6.35.

**General Procedure for Fluorescent Study.**

Stock solutions (1.00 mM) of those metal perchlorate salts were prepared using ethanol. A stock solution of **4** was prepared in dichloromethane (0.06 mM). Test solutions were prepared by placing 400 μL of the probe stock solution into a test tube, adding an appropriate aliquot of each metal stock, and diluting the solution to 4 mL with ethanol and dichloromethane. For all

measurements, excitation was at 390 nm; excitation and emission slit widths were both 3 nm.

Fluorescence titration experiments were performed using 6 μM of **4** and various amounts of cesium perchlorate in ethanol and dichloromethane (9:1, v/v). After calculating the concentrations of the complex form of **4** and free **4** from the fluorescence titration experiments, the association constant was obtained using the computer program ENZFITTER.<sup>10</sup>

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**Supporting Information Available:** Additional <sup>1</sup>H and <sup>13</sup>C NMR and IR data (Data S1–S3) for **4**, **6**, and **7**, respectively. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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