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New cavitand derivatives bearing four coumarin groups as fluorescent chemosensors for Cu^{2+} and recognition of dicarboxylates utilizing Cu^{2+} complex

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Abstract—New cavitand derivatives (**1**, **2**) bearing four coumarin groups were synthesized, and the binding properties of these cavitands towards metal ions were examined through their fluorescent changes. Cavitand **1** effectively recognized the Cu^{2+} ions among the metal ions examined. The recognition of cavitand **1**-Cu^{2+} with dicarboxlyates is also described.

The readily available calix[4]arene derivatives have been used as starting materials for the synthesis of metal selective ionophores.[1] On the other hand, it has been only a few years since cavitand derivatives were first used extensively as ionophores.[2] Cavitands are rather rigid and have enforced cavities compared with calix[4]arenes. Recent efforts to improve the yield of tetraboromocavitand[3] or tetrakis(bromomethyl)cavitand[4] have involved utilizing these intermediates for synthesizing various host compounds based on the cavitand moiety. Even though there are few reports regarding cavitand derivatives for metal ion recognition,[5] fluorescent cavitands as metal ion selective receptors have not been studied intensively.[6]

We report new cavitand derivatives (**1**, **2**) bearing four coumarin groups. The binding properties of these cavitands towards metal ions were also examined by their fluorescent changes. In particular, cavitand **1** effectively recognized Cu^{2+} ions among the metal ions examined. Furthermore, the cavitand **1**-Cu^{2+} complex displays fluorescent enhancements with dicarboxylates.

Both cavitands **1** and **2** were synthesized from the tetrahydroxy cavitand.[7] The tetrachloride **3** was synthesized using the procedure published elsewhere.[8] This intermediate was then reacted with coumarin 2 and NaI in acetonitrile to give cavitand **1**[9] in a 51% yield (Scheme 1). Treating the tetrahydroxy cavitand with 4-bromomethyl-6,7-dimethoxycoumarin in the presence of K_2CO_3 with subsequent purification by column chromatography using $CHCl_3$–MeOH (9:1, v/v), as an eluent, yielded cavitand **2**[10] in a 54% yield.

Ag^+, Ca^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Cs^+, Hg^{2+}, K^+, Li^+, Mg^{2+}, Mn^{2+}, Na^+ and Ni^{2+} ions (perchlorate salts) were used to evaluate the metal ion binding properties of compounds **1** and **2**. All fluorescent studies were carried out in acetonitrile–chloroform (4:1, v/v) using 1 μM of the compounds. Figure 1 shows the changes in the fluorescence emission of compound **1** upon the addition of various metal ions (100 equiv). The fluorescence spectra were obtained by excitation into the coumarin fluorophore at 357 nm, and both the excitation and emission slits were 1.5 nm. As shown in Figure 1, compound **1** had a large CHEQ effect *only* with Cu^{2+} among

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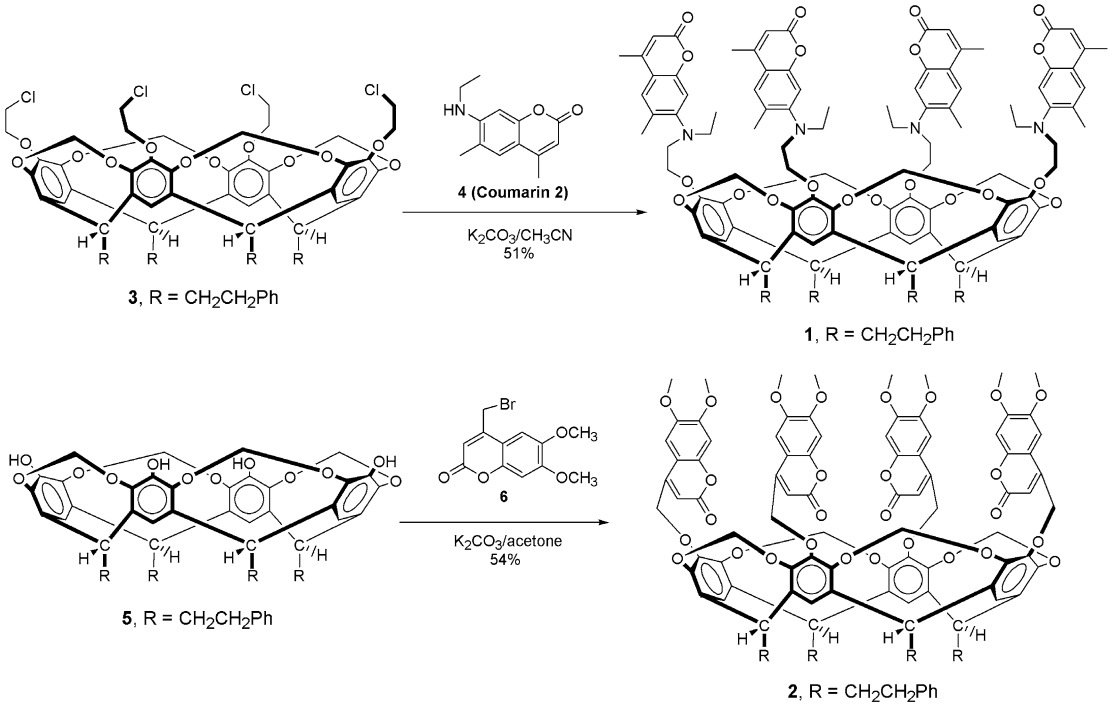


Scheme 1. Structures of cavitand **1** and **2**.

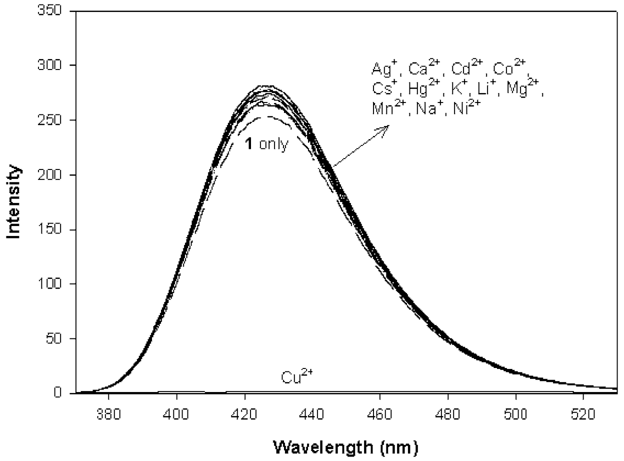


Figure 1. Fluorescence spectra of **1** (1 μM) upon the addition of various metal ions (100 equiv) in CH_3CN–$CHCl_3$ (4:1, v/v).

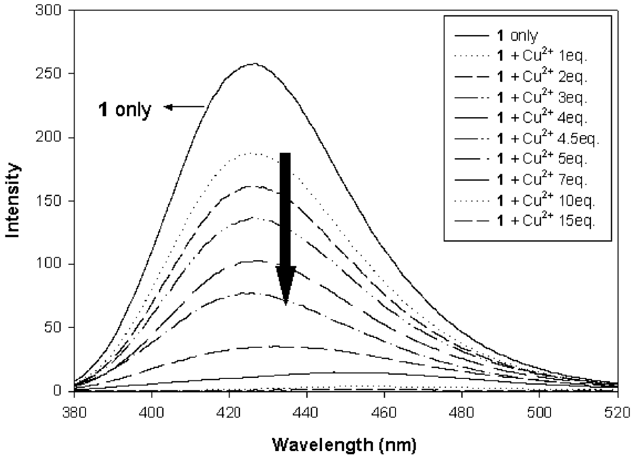


Figure 2. Fluorescence spectra of **1** (1 μM) upon the addition of $Cu(ClO_4)_2$ in CH_3CN–$CHCl_3$ (4:1, v/v).

the metal ions examined. An overall emission change of 200-fold was observed for Cu^{2+}. Figure 2 shows the fluorescent quenching effects of compound **1** upon the addition of Cu^{2+}. It was reported[11a] that intracomplex quenching takes place (via energy or electron transfer[11b]) when Cu^{2+} binds tightly to the host compound. Considerable red shifts (~30 nm) were observed as the amount of Cu^{2+} was increased (Fig. 2). The UV absorption spectra of compound **1** with Cu^{2+} also showed a similar red shift (~27 nm) in the same solvent system.

The selectivity of compound **1** towards Cu^{2+} was confirmed using the following experiments. First, the emission intensities of compound **1** with 1 μM Cu^{2+} in the presence of 1 mM of Pb^{2+}, Ag^{+} and Zn^{2+} ions were almost the same as that using 1 μM Cu^{2+} alone. Furthermore, there were no significant changes in the fluorescent spectra of the cavitand **1** when excess Pb^{2+} (1 mM) was present (Fig. 3). The job plot using the fluorescence changes indicated a 1:4 binding for compound **1** with Cu^{2+} (Fig. 4). Furthermore, in the ESI mass spectrum of compound **1** upon the addition of $Cu(ClO_4)_2$, a peak at *m*/*z* 280.3 (calculated value; 280.1) corresponding to $[\mathbf{1}+4Cu]^{8+}$ was observed (S-Figure 1). In the IR spectra, the peak at 1699.6, which corresponds to the characteristic ester carbonyl absorption, was shifted to 1696.5 upon the addition of $Cu(ClO_4)_2$ (4.2 equiv) (S-Figure 2). These IR data support that the carbonyl groups may not participate in binding with Cu^{2+}. Figure 5 shows proposed binding mode based on the job plot,

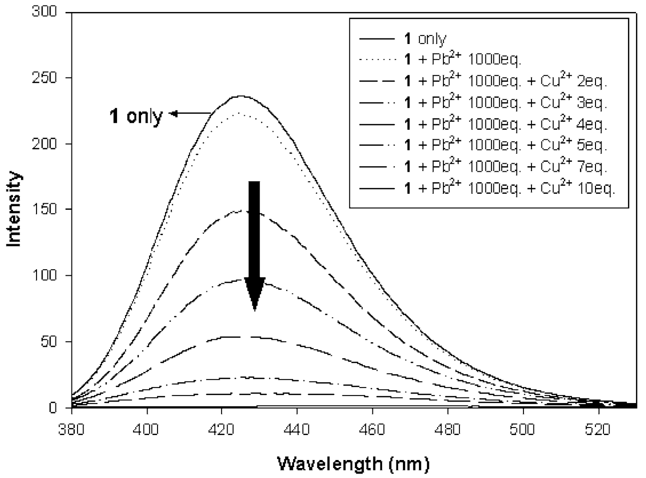


Figure 3. Fluorescence spectra of **1** (1 μM) upon the addition of $Cu(ClO_4)_2$ in the presence of 1 mM $Pb(ClO_4)_2$ in $CH_3CN–CHCl_3$ (4:1, v/v).

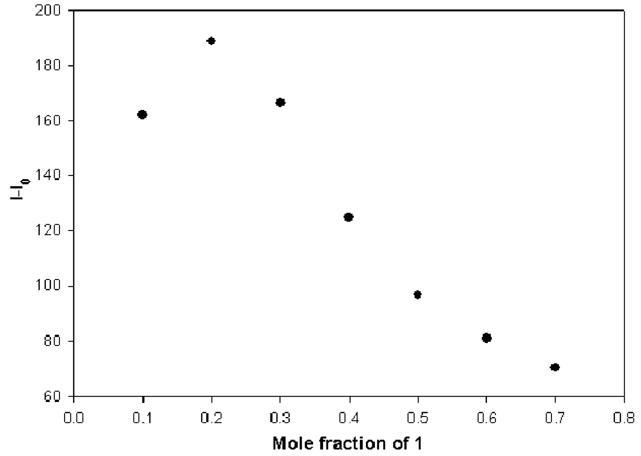
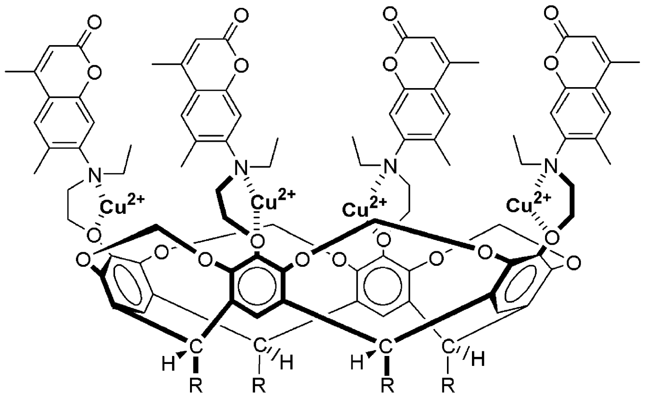


Figure 4. Job plot of **1** (1 μM) with $Cu(ClO_4)_2$ using fluorescent changes in $CH_3CN–CHCl_3$ (4:1, v/v).



1, R = CH_2CH_2Ph

Figure 5. Proposed binding mode of **1** with Cu^{2+}.

ESI mass and IR data. However, there is a possibility that one of the oxygen atoms in the OCH2O linker may participate in the binding with Cu^{2+}. From the fluorescence titration experiments, the K_d value with Cu^{2+} was observed to be ~3 μM.[12] Caivtand **2** also showed a selective fluorescence quenching effect with Cu^{2+} and slight fluorescence enhancement with several metal ions. However, in this case, the fluorescent quenching effect with Cu^{2+} was <10% (Fig. 6).

Recently, we reported a new cavitand bearing four imidazolium groups that displayed moderate selectivity with bis(tetrabutylammonium) 1,4-phenylenediacetate in DMSO.[13] The anion recognition of compound **1** (1 μM) in the presence of Cu^{2+} (5 μM) was also examined via its fluorescent changes. As shown in Figure 7, fluorescent enhancements were clearly observed as the amount of bis(tetrabutylammonium) 1,4-phenylenediacetate (**7**) was increased. The fluorescent intensity of **1**-Cu^{2+} upon the addition of excess dicarboxylate **7** was smaller than that of free host **1**. Similar fluorescent enhancements were also observed with bis(tetrabutylammonium) 1,3-adamantanedicarboxylate. From the

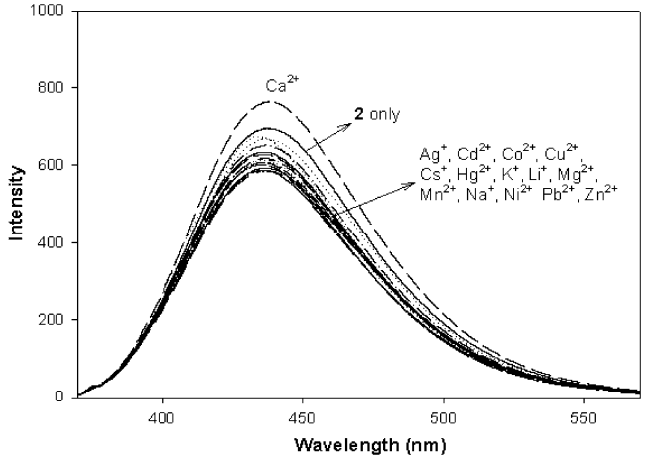


Figure 6. Fluorescence spectra of **2** (3 μM) upon the addition of various metal ions (500 equiv) in $CH_3CN–CHCl_3$ (4:1, v/v).

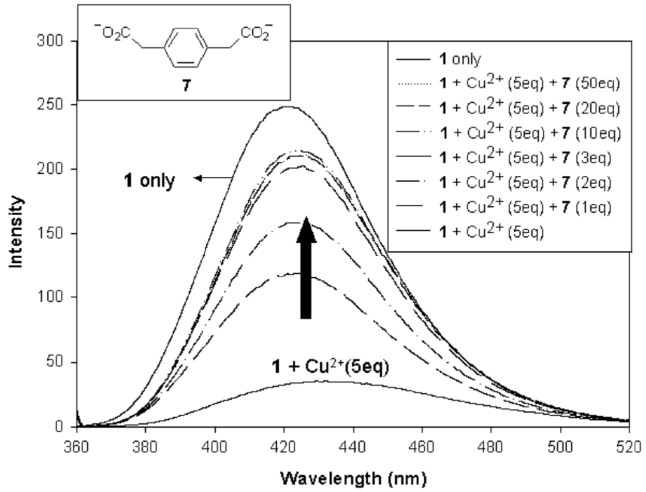


Figure 7. Fluorescence spectra of **1** (1 μM)-Cu^{2+} (5 μM) upon the addition of bis(tetrabutylammonium) 1,4-phenylenediacetate (**7**) in $CH_3CN–CHCl_3$ (4:1, v/v).

fluorescence titration experiments, the K_d values with 1,4-phenylenediacetate and 1,3-adamantanedicarboxylate were estimated to be 1.6 and 3.1 μM, respectively.[12]

In conclusion, two new cavitand derivatives (**1**, **2**) bearing four coumarin groups were synthesized. In particular, among the metal ions examined, cavitand **1** effectively recognized Cu^{2+} ions. The binding of this complex with dicarboxylates was further demonstrated via the fluorescent changes.

Acknowledgements

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Supplementary material

ESI mass spectra and IR spectra are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.02.087.

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9. Cavitand (**1**). Tetra(2-chloroethyloxy)cavitand **3** (120 mg, 0.1 mmol),[8] coumarin 2 (90 mg, 0.4 mmol) and K_2CO_3 (60 mg, 0.4 mmol) were dissolved in 20 mL of acetonitrile. After the addition of NaI (35 mg, 0.23 mmol) and Et_3N (100 μL, 0.8 mmol), the reaction mixture was refluxed for 48 h under N_2. After cooling to room temperature, the solvent was evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (3 × 10 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated. After the recrystallization from $CHCl_3$/hexane, further purification using Sephadex LH-20 column chromatography ($CHCl_3$/MeOH = 1:1, v/v) afforded **1** as a yellow powder (96 mg, 51%): mp 170–172 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.20 (m, 24H), 6.86 (s, 4H), 6.47 (s, 4H), 5.97 (br s, 4H), 5.88 (d, $J = 7.2$ Hz, 4H), 4.82 (t, $J = 7.7$ Hz, 4H), 4.42 (d, $J = 6.9$ Hz, 4H), 3.35 (t, $J = 7.0$ Hz, 8H), 3.22 (m, 8H), 2.34–2.69 (m, 16H), 2.35 (s, 12H), 2.18 (s, 12H), 1.34 (t, $J = 7.1$ Hz, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.5, 155.1, 153.2, 149.9, 148.7, 141.9, 139.1, 128.9, 128.7, 126.3, 125.4, 118.6, 109.9, 109.6, 96.6, 73.6, 39.5, 37.3, 34.8, 32.6, 31.9, 18.9, 17.3, 14.8; FAB MS $m/z = 1990$ ($M+H^+$).
10. Cavitand (**2**). Tetrol Cavitand **5** (100 mg, 0.1 mmol),[7] 4-bromomethyl-6,7-dimethoxy coumarin **6** (125 mg, 0.4 mmol) and K_2CO_3 (100 mg, 0.7 mmol) were dissolved in 20 mL of acetone. After the addition of NaI (35 mg, 0.23 mmol) and Et_3N (100 μL, 0.8 mmol), the reaction mixture was refluxed for 48 h under N_2. After cooling to room temperature, the solvent was evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (3 × 10 mL). The organic layer was dried over $MgSO_4$ and purified by column chromatography using $CHCl_3$/MeOH (9:1, v/v). 100 mg (54%) of **2** was obtained as a yellow solid: mp 177–180 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.20 (m, 20H), 6.95 (s, 4H), 6.87 (br s, 8H), 6.45 (s, 4H), 5.79 (d, $J = 7.0$ Hz, 4H), 5.14 (s, 8H), 4.84 (t, $J = 7.6$ Hz, 4H), 4.50 (d, $J = 7.0$ Hz, 4H), 3.95 (s, 12H), 3.90 (s, 12H), 2.39–2.67 (m, 16H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.0, 152.2, 150.7, 149.7, 148.3, 146.4, 143.8, 141.2, 139.0, 129.2, 128.9, 126.6, 114.3, 110.4, 109.6, 104.7, 100.3, 99.3, 70.2, 56.7, 56.2, 37.3, 34.4, 32.6; FAB MS $m/z = 1889$ ($M+H^+$).
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