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A new fluorogenic mono-ionizable calix[4]arene dansylcarboxamide as a selective chemosensor of soft metal ions, Tl^+ and Hg^{2+}

Vladimir S. Talanov, Ebony D. Roper, Nicole M. Buie and Galina G. Talanova*

Department of Chemistry, Howard University, 525 College Street, NW, Washington, DC 20059, United States

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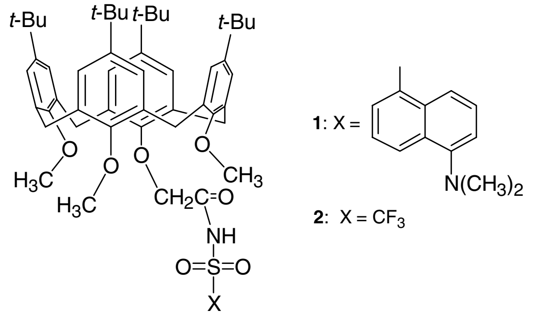
Abstract—A new fluorogenic calix[4]arene containing one pendent *N*-dansylcarboxamide group has been synthesized. The ligand demonstrates selective optical recognition of Tl^+ and Hg^{2+} in solvent extraction from aqueous solutions with high content of Na^+. Complexation of Tl^+ and Hg^{2+} produces contrasting changes in the fluorescence spectrum of this sensor. Partial cone is the dominant calixarene conformation in the complex with Tl^+.

The need for monitoring the levels of metal ion pollutants in the ecosystem encourages efforts of scientists in search for new methods of selective determination of such species. Fluorescent photometric reagents that consist of macrocyclic or chelating metal ion receptors with covalently attached fluorophores responsive to changes in the electron environment accompanying complex formation bear a lot of potential in terms of specificity and sensitivity.[1,2] (For the recent examples of Hg^{2+}-selective fluorogenic chelators, see Refs. 3,4.) Calixarene-based ligands providing wide spectrum of metal ion selectivities serve as convenient scaffolds for the design of such reagents.[5] In this context, multipurpose chemosensors that under different conditions may be used for detection of various analytes are of special interest. Thus, our group recently reported selective optical determination of micro-levels of Tl^+ and Cs^+ by a fluorogenic *1,3-alternate* calix[4]arene-bis(crown-6) ionophore containing one pendent proton-ionizable dansylamide group.[6] In continuation of our work on the design of fluorescent probes for hazardous unicharged metal ions, a new calix[4]arene-based receptor **1** has been synthesized. Analogously to its earlier published non-fluorogenic prototype, calix[4]arene *N*-(trifluoromethylsulfonyl)carboxamide **2**,[7] ligand **1** was expected to demonstrate extraction selectivity for Li^+ over other alkali metal cations (AMC). At the same time, **1** was envisioned to possess affinity for soft ions, for example, Tl^+. This mono-ionizable calixarene was deemed to be the most appropriate for binding of univalent cations. Nevertheless, probing of its capability for optical recognition of multicharged hazardous ionic species, such as Hg^{2+}, was undertaken as well. Herein, we present synthesis and preliminary complexation studies of **1** as a novel multipurpose fluorescent chemosensor of soft metal cations, Tl^+ and Hg^{2+}.



Synthesis of the fluorogenic calixarene **1** was performed as shown in Scheme 1.[8] Carboxylic acid **3** prepared by the earlier published procedure[9] was converted into the corresponding acid chloride and then reacted with dansylamide in the presence of NaH.

Complexing ability of **1** toward metal cations (M^{n+}) was evaluated in two-phase extraction system H_2O–$CHCl_3$ based on the magnitude of changes observed the ligand fluorescence spectrum upon the extraction.[10] The

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Keywords: Optical chemosensor; Fluorescence; Calix[4]arene; Thallium(I); Mercury(II).

* Corresponding author. Tel.: +1 202 806 4963; fax: +1 202 806 5442; e-mail: gtalanova@howard.edu

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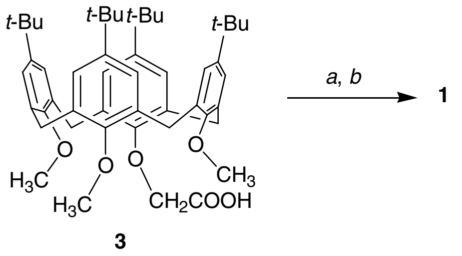

Scheme 1. Synthesis of **1**: Reagents and conditions: (a) $(COCl)_2$, CH_2Cl_2, rt; (b) dansylamide, NaH, THF, rt.

fluorescence spectrum of **1** in $CHCl_3$ showed an emission band at wavelength of 515 nm with excitation at 340 nm. (The spectrum remained essentially unchanged upon blank-extraction with deionized water.) Due to acidic nature of the NH-group in **1**, complex formation of this ionophore is expected to proceed via displacement of the proton by M^{n+}. As found earlier for other proton-ionizable calixarene and calix–crown dansylamides in aqueous MeCN solutions,[6,11] NH-group dissociation due to increasing pH or upon metal coordination results in hypsochromic shift of the ligand emission band ($\Delta\lambda_{em}$) with concomitant enhancement of the fluorescence intensity (I). This pattern of changes is rationalized in terms of increasing electron density on the adjacent 5-dimethylaminonaphthalene moiety. In order to assess the magnitude of $\Delta\lambda_{em}$ for ionization of **1** under the conditions of solvent extraction, aliquots of a 10.0 μM solution of this calixarene in $CHCl_3$ were contacted with aqueous Pr_4NOH[12] as well as AMC hydroxides (LiOH, NaOH, and KOH) at pH varying from 7.0 to 14.0, after which the fluorescence spectra of the organic phases were measured and compared with that for the blank-extraction of deionized H_2O. Extraction with Pr_4NOH produced no ligand ionization, since no noticeable deviation in the position and intensity of the emission band of **1** was evidenced. On the other hand, extraction of increasing concentrations of LiOH, NaOH, and KOH at pH > 9.0 resulted in a gradual hypsochromic shift of the λ_{em} (shown in Fig. 1 for NaOH; the limiting $\Delta\lambda_{em} = 53$ nm) due to the NH-proton displacement by the M^+. Based on these data, λ_{em} of 462 nm was considered as the emission maximum for the completely ionized ligand, $\mathbf{1}^-$. Increasing pH clearly facilitated complexation of AMC by proton-ionizable **1**. This becomes apparent from comparison of the presented (Fig. 1) emission spectra of **1** in $CHCl_3$ upon extraction of aqueous 1.0 M NaCl and same concentration NaOH (pH ~ 14.0). However, against expectations, **1** did not exhibit the Li/Na-selectivity, which was characteristic for the prototype **2**. In general, the optical sensing of AMC by **1** was non-discriminative: the ligand demonstrated comparable spectral response to interaction with LiOH, NaOH, and KOH under the analogous experimental conditions. Obviously, variation of the substituent in the *N*-(X-sulfonyl)carboxamide group from CF_3 (in **2**) to 5-dimethylaminonaphthyl (in **1**) was crucial to the complexation propensities of these calixarenes toward AMC.

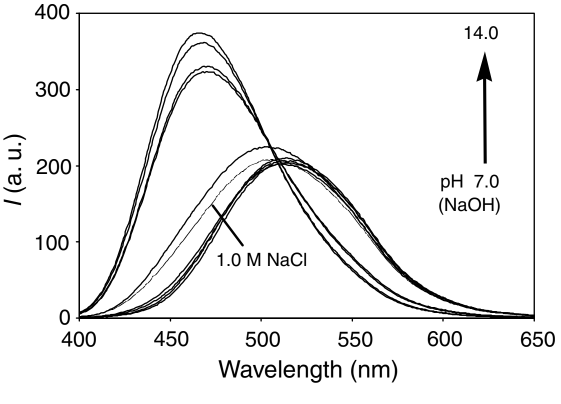

Figure 1. Evolution of the fluorescence emission spectrum of **1** in $CHCl_3$ upon extraction of aqueous NaOH solutions with increasing pH. For comparison purposes, the spectrum of **1** after the extraction of aqueous 1.0 M NaCl is shown as well. $C_1 = 10.0\,\mu M$; $\lambda_{ex} = 340$ nm.

The study of Tl^+[13] extraction into $CHCl_3$ by **1** was carried out from aqueous phase with pH maintained at 7.7 using sodium tetraborate (borax) buffer. Upon extraction of the buffered aqueous solutions in the absence of thallium, the emission maximum in the fluorescence spectrum of **1** was observed at 505 nm (Fig. 2). This value of λ_{em} indicated that the organic phase contained a non-ionized ligand **1** as well as its sodium complex, $Na^+\mathbf{1}^-$. With the formal concentration of Tl^+ (C_{Tl}) in the aqueous phase increasing from 0 to 1.00 mM, the emission band of 10.0 μM **1** in $CHCl_3$ showed further hypsochromic shift accompanied by enhancement of the fluorescence intensity, as may be seen in Figure 2a. Therefore, complexation of Tl^+ by **1** took place regardless of a large excess of Na^+ present in the buffered aqueous solution, which demonstrated an obvious preference of the dansyl-containing calixarene for binding of the soft over hard metal cation. In part, this phenomenon may be attributed to cation-π interactions[14,15] involving the calixarene aromatic cavity. With the ratio of thallium in the aqueous phase and ligand in the organic phase, C_{Tl}/C_1 about 1000, the emission maximum of the complex in $CHCl_3$ was observed at 462 nm, which corresponds to the λ_{em} of the anion $\mathbf{1}^-$. Uptake of Tl^+ by the calixarene was monitored in a dual-wavelength mode by changes in the ratio of the fluorescence intensities at λ_{em} of 462 and 505 nm (I_{462}/I_{505}). The graph of I_{462}/I_{505} versus C_{Tl} is shown in Figure 2b. The initial segment of this curve is linear (see the inset in Fig. 2b) and may be used as a calibration plot for determination of microconcentrations of Tl^+. Analysis of the fluorescence data performed as described elsewhere[16] confirmed that Tl^+ is extracted by **1** in 1:1 metal-to-ligand stoichiometry with the apparent extraction constant $\log K_{ex}^{app} = 5.59$.

Calix[4]arene moiety of **1** possesses conformational mobility due to the capability of three arene units bearing small-sized CH_3O-substituents for oxygen-through-the-annulus rotation. In the ^1H NMR spectrum of **1** in $CDCl_3$, all signals are extremely broad (as illustrated in Fig. 3) reflecting a fast interconversion between several possible ligand conformations.[17] It is known that during complex formation with a metal ion, a flexible

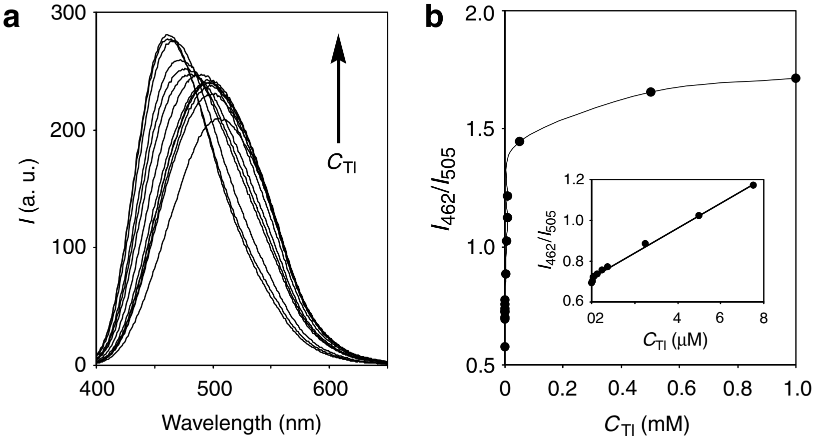

Figure 2. The effect of Tl^+ extraction on the fluorescence of **1** in $CHCl_3$: (a) changes in the emission spectrum of 10.0 μM **1** in $CHCl_3$ with the aqueous phase C_{Tl} increasing from 0 to 1.00 mM; (b) the dependence of I_{462}/I_{505} on C_{Tl}. Inset: the calibration plot for determination of microconcentrations of Tl^+. pH 7.7 (borax buffer); $\lambda_{ex} = 340$ nm.

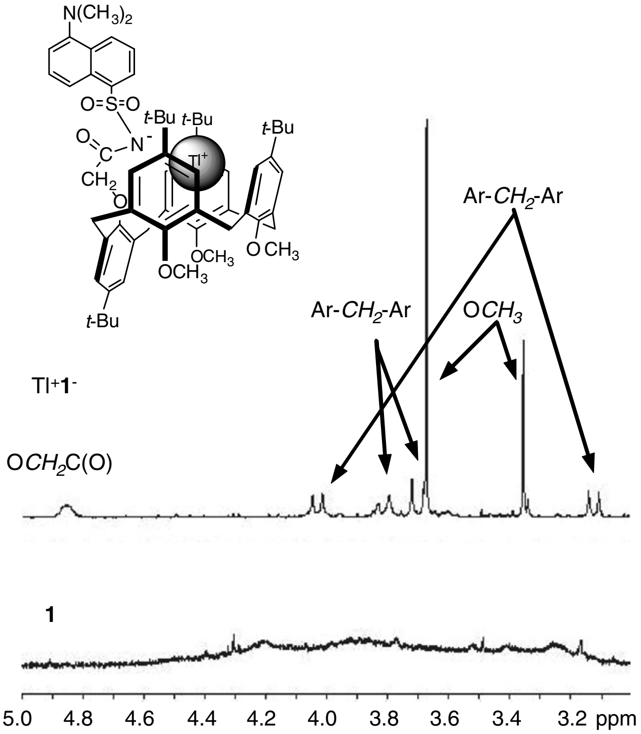

Figure 3. ^{1}H NMR spectra of **1** and Tl^+**1**$^-$ in $CDCl_3$ (400 MHz, 298 K) in the region of 3.0–5.0 ppm. (Solution of Tl^+**1**$^-$ was obtained by reaction of **1** with excess of thallium(I) acetate in $CDCl_3$.[18]).

calixarene tends to adopt the geometry, which is the most appropriate for accommodating the guest.[17] To find out the conformational preference of **1** in the complex with Tl^+, the ^{1}H NMR spectrum of Tl^+**1**$^-$ in $CDCl_3$ was studied.[18] As evident from comparison of the spectra for free **1** and Tl^+**1**$^-$ in Figure 3 where the region of 3.0–5.0 ppm is shown, metal coordination slows down the conformational exchange significantly, thus increasing the sharpness and resolution of the signals. Protons of methylene groups bridging the arene units (Ar–CH_2–Ar) in Tl^+**1**$^-$ produce two pairs of doublets. In one of these pairs, the two components are separated by a large distance (0.91 ppm), while the other two doublets are located close by (only 0.11 ppm apart). Such an arrangement of signals indicates that Tl^+**1**$^-$ contains both *syn*- and *anti*-oriented pairs of neighboring arene units. The pattern of signals for other groups of protons in the same region of the NMR spectrum, that is, two singlets for OCH_3 protons and a singlet for $OCH_2C(O)$ group are consistent with the partial cone (*paco*) conformation of the calix[4]arene with inverted arene moiety bearing pendent $OCH_2C(O)NHSO_2X$ group (sketched in Fig. 3). Appearance of the spectrum for *t*-Bu group protons (three singlets with the ratio of integral intensities of 1:1:2) as well as signals for the calixarene aromatic protons are in agreement with this suggested geometry. Overall, the ^{1}H NMR spectrum of Tl^+**1**$^-$ is similar to that reported earlier for Cs^+**2**$^-$ in which the same *paco* conformation was additionally confirmed using NOESY technique.[9] Apparently, a soft electron acceptor Tl^+ shapes the cavity of **1** in the geometry that allows for its π-coordination with the aromatic calixarene framework[19] as well as interaction with the ionized *N*-dansylcarboxamide group.

To probe the ability of the mono-ionizable calixarene for complex formation with soft multicharged metal ions, extraction of Hg^{2+} from Na^+-containing buffered aqueous solutions into $CHCl_3$ by 10.0 μM **1** was studied. With concentration of Hg^{2+} in the aqueous phase (pH 8.6, borax buffer) increasing from 0 to 0.50 mM, the λ_{em} of **1** exhibited a gradual bathochromic shift from 480 to 513 nm (Fig. 4) approaching the emission maximum of the non-ionized ligand. Supposedly, this phenomenon may be explained by substantially covalent character of Hg–N bond[20] in the complex thus formed. As evident from Figure 4, the bathochromic shift of the λ_{em} was accompanied by a decrease in the fluorescence intensity associated with photo-induced electron transfer (PET).[1,2] Interestingly, complexation of two soft metal cations, Tl^+ and Hg^{2+}, produced opposite effect on the fluorescence of **1**. Further studies of complex formation of **1** with Hg^{2+} are in progress.

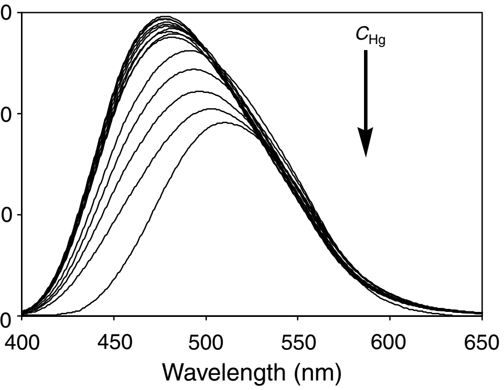

Figure 4. Variation of the fluorescence spectrum of 10.0 μM **1** in $CHCl_3$ upon extraction of Hg^{2+} from aqueous solutions with C_{Hg} increasing from 0 to 0.50 mM at pH 8.6 (borax buffer). $\lambda_{ex} = 340$ nm.

In conclusion, we have synthesized a new fluorogenic proton-ionizable calix[4]arene bearing one pendent *N*-dansylcarboxamide group on the lower rim. In extractions from aqueous solutions into $CHCl_3$, this ligand showed no discrimination of alkali metal cations, however, it provided selective optical sensing of soft metal ions, Tl^+ and Hg^{2+}, in the presence of a large excess of Na^+.

Acknowledgment

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8. Preparation of **1**, 25-*N*-(5′-dimethylaminonaphtalene-1′-sulfonyl)carbamoylmethoxy-26,27,28-trimethoxy-5,11,17,23-tetrakis(1,1-dimethylethyl)calix[4]arene. A solution of acid **3**[5] (0.50 g, 0.67 mmol) and oxalyl chloride (0.17 g, 1.34 mmol) in CH_2Cl_2 (15 mL) was stirred under N_2 at room temperature for 15 h and the volatiles were removed in vacuo to provide the corresponding acid chloride. A solution of the residue in THF (15 mL) was added to a mixture of the 5-dimethylaminonaphthalene-1-sulfonamide (dansylamide) (0.25 g, 1.00 mmol) and NaH (0.08 g, 3.34 mmol) in THF (10 mL). The mixture was stirred under N_2 at room temperature for 15 h. Then H_2O (1 mL) was added and the THF was evaporated in vacuo. CH_2Cl_2 (30 mL) and water (15 mL) were added to the residue. The organic layer was washed with 5% aqueous Na_2CO_3 and water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography on silica gel with gradient 0–3% MeOH in CH_2Cl_2 as eluent. The product was dissolved in CH_2Cl_2 and the solution was washed with 2 M aqueous HCl and water, dried ($MgSO_4$), and evaporated in vacuo to give **1** as a yellow solid. Yield 0.41 g (63%), mp 137–139 °C; ^1H NMR (400.13 MHz, $CDCl_3$, 298 K): 0.75–1.45 (br m, 36 H), 2.89 (s, 6 H), 2.9–4.7 (br m, 19 H), 6.5–7.3 (br m) + 7.17 (d, *J* 7.4) (9 H), 7.51 (br s) + 7.61 (t, *J* 8.3) (2 H), 8.25–8.65 (br m) + 8.62 (d, *J* 8.4) (3 H); MS (ESI): found 1003.542 $(M{+}Na)^+$ (calcd for $C_{61}H_{76}N_2NaO_7S$ 1003.527). Anal. Calcd for $C_{61}H_{76}N_2O_7S$: C 74.66, H 7.81, N 2.85. Found: C, 74.32; H, 7.91; N, 2.83.
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