Tetrahedron Letters 51 (2010) 5016–5019

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A new fluorogenic calix[4]arene *N*-dansylcarboxamide in the *cone* conformation for selective optical recognition of mercury(II)

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ARTICLE INFO

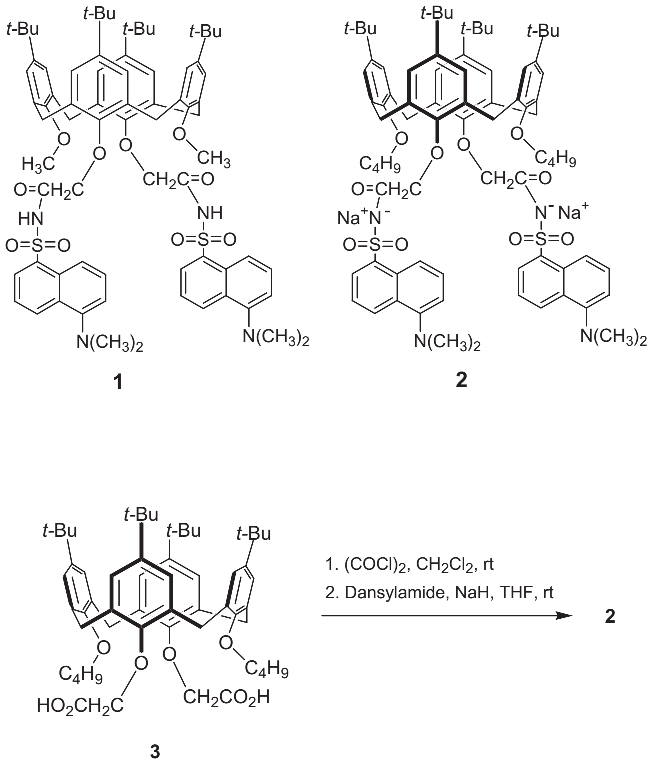
Article history:
Received 26 May 2010
Revised 15 July 2010
Accepted 15 July 2010
Available online 10 August 2010

Keywords:
Optical chemosensor
Mercury(II)
Fluorescence
Calix[4]arene
Cone conformation
Dansyl

ABSTRACT

A novel fluorogenic calix[4]arene dansylcarboxamide in the *cone* conformation has been synthesized as the disodium salt and employed in optical recognition of mercury(II). In extraction from aqueous solutions with high content of competing Na^+ (C_{Na+} ~0.1 M; pH 5.0, acetate buffer) into $CHCl_3$, the fluoroionophore allowed for detection of 8.0×10^{-7} M Hg^{2+} (1:1 complex; $K_{ex}^{app} = 2.6 \times 10^4$) with high selectivity over many other relevant metal ions.

Adverse health effects associated with exposure of humans to elevated amounts of Hg^{2+} in the environment are generally recognized. The US Environment Protection Agency and World Health Organization have set strict limits on the presence of this contaminant in water.[1] Accordingly, the development of new, efficient yet affordable methods for detection of mercury(II) has been attaining considerable attention among scientists. During the last decade, fluorogenic calix[4]arenes have emerged as a group of promising optical chemosensors of hazardous metal ions (see[2,3] for recent reviews). Thus, conformationally mobile ligand **1**[4] containing two pendent proton-ionizable dansylcarbamoyl groups was reported as a highly selective photometric reagent for determination of Hg^{2+} in acidic aqueous solutions both by solvent extraction[4] and in water–MeCN homogeneous mixtures.[5,6] It is known that flexible calix[4]arenes exist in solutions in equilibrium of different conformations and during complexation with metal cations, they tend to adopt the shapes which are the most appropriate for accommodation of the guests.[7] In particular, the *cone* was found to be one of the preferred geometries of **1** in its complexes with Hg^{2+}.[5,6] It was hypothesized that preorganization via synthesis of the calixarene scaffold of **1** in the *cone* conformation might yield a fluoroionophore with improved characteristics for mercury(II) sensing. Herein, we report synthesis and metal ion recognition studies of the novel fluorogenic calix[4]arene dansylcarboxamide **2** (shown below as the disodium salt) fixed in the *cone* conformation for selective detection of Hg^{2+}.



Scheme 1. Synthesis of the *cone* calixarene **2** (as the disodium salt).

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doi:10.1016/j.tetlet.2010.07.083

Calixarene **2** was synthesized as shown in Scheme 1.[8] First, the *cone* diacid **3** prepared by the earlier published procedure[9] was converted into the corresponding diacid chloride by treatment with oxalyl chloride. This conversion was verified by disappearance of the band at 1738 cm^{-1} ($\nu_{C=O}$) and emergence of a new band at 1813 cm^{-1} in the IR-spectrum of the crude product. The diacid chloride was further reacted with dansylamide in the presence of NaH. Compound **2** was isolated, purified and characterized as the disodium salt similarly to previously published procedure.[4,6]

It should be mentioned that typically, the non-ionized, NH-form of a *N*-dansylcarbamoyl calixarene derivative is readily obtained from the corresponding disodium salt by stripping its CH_2Cl_2 solution with aqueous HCl.[4,6] Indeed, upon treatment of salt **2** with 2 N HCl, the ^{1}H NMR spectrum of the resultant substance in $CDCl_3$ showed the signals anticipated for the desired NH-form of the *cone* ligand.[10] However, the spectrum also revealed a group of less intense signals (with the ratio of integral intensities for the two sets of about 8:1) that were rather broad and in part overlapping with the signals of the major set. (Interestingly, TLC chromatograms of the substance obtained in several different solvent systems showed only one spot). Although the molecular structure of the secondary compound could not be deduced unambiguously from the ^{1}H NMR spectrum of the acid-washed disodium salt **2**, this impurity might originate from partial degradation of the calixarene *N*-dansylcarboxamide. To probe this assumption, the acid-treated **2** was re-dissolved in CH_2Cl_2, washed with 5% aqueous Na_2CO_3 and its ^{1}H NMR spectrum in $CDCl_3$ measured. The obtained spectrum was identical to that of the original pure disodium salt **2**,[8] with no signs of any impurities. This fact signified total reversibility of Na^+ removal from **2** and allowed to rule out the ligand destruction during the acid stripping. Thus, the secondary product obtained along with the NH-form of **2** was suggested to be a monosodium salt of the *cone* calixarene. Subsequent attempts to obtain a pure NH-form of **2** by multiple runs of washing the disodium salt with 2 N HCl[11] and water were unsuccessful. Hence, during the synthesis, the *cone* calixarene **2** was discovered to possess an extremely high affinity for Na^+ which could not be removed from the substance entirely. Therefore, this fluoroionophore was obtained and characterized as a pure disodium salt, and it was further used in this form in Hg^{2+} recognition studies.

Structural examination of **2** by X-ray crystallography was performed.[12] Unfortunately, the crystal structure of this compound could not be resolved completely due to a disorder in the peripheral dansyl groups (see Supplementary data). However, a Na^+ ion situated in the lower-rim cavity formed by the calixarene pendent donor groups where it is coordinated with the four phenolic and two carbonyl oxygen atoms is evident in this structure (Fig. 1). Such a favorable coordination arrangement for Na^+, which is quite typical for sodium complexes of the *cone* calix[4]arene amides,[13] justifies strong binding of this metal cation with **2**.

The preliminary studies of optical recognition of Hg^{2+} and other metal cations by **2** were carried out under the conditions of solvent extraction from aqueous solutions (pH 5.0, 0.1 M sodium acetate buffer) into $CHCl_3$.[14] Despite the strong affinity of the *cone* calixarene for Na^+, extraction of Hg^{2+} from the aqueous phase with high sodium content was accompanied by significant changes in the fluorescence spectrum of **2** in $CHCl_3$. (It is worth of note at this point that the ability of a fluorescent reagent to detect mercury (II) in the presence of excess Na^+ abundant in water is crucial to practical applicability of such a chemosensor). A gradual quenching of the emission intensity (I) of 1.0×10^{-5} M **2** in $CHCl_3$ at essentially invariable wavelength of 468 nm (excitation at 340 nm) was observed with the aqueous mercury(II) concentration increasing from 0 to 1.0×10^{-3} M (Fig. 2a). This spectral response of the dansylamide-containing **2** to Hg^{2+} coordination is explained in terms of the photo-induced electron transfer (PET) within the complex.[4–6] Variation of the fluorescence intensity ($I_0 - I$) of **2** as a function of the aqueous-phase formal Hg^{2+} concentration (C_{Hg}) is illustrated in Figure 2b. As may be seen in this plot, extraction of 100 equiv of aqueous Hg^{2+} produced nearly 100% quenching of the fluorescence intensity of **2**. For comparison purposes, mercury(II) extraction by the conformationally mobile fluorogenic calixarene **1** was probed under the otherwise identical conditions.[15] It is evident from Figure 2b that for the same C_{Hg} in the presence of excess Na^+, the magnitude of fluorescence quenching demonstrated by the *cone* **2** was appreciably larger than that of the flexible prototype **1**. For the micro-levels of mercury in the aqueous phase, the dependence ($I_0 - I$) versus C_{Hg} for **2** is linear (shown in the inset in Fig. 2b) and it may be used as a calibration plot for Hg^{2+} determination.

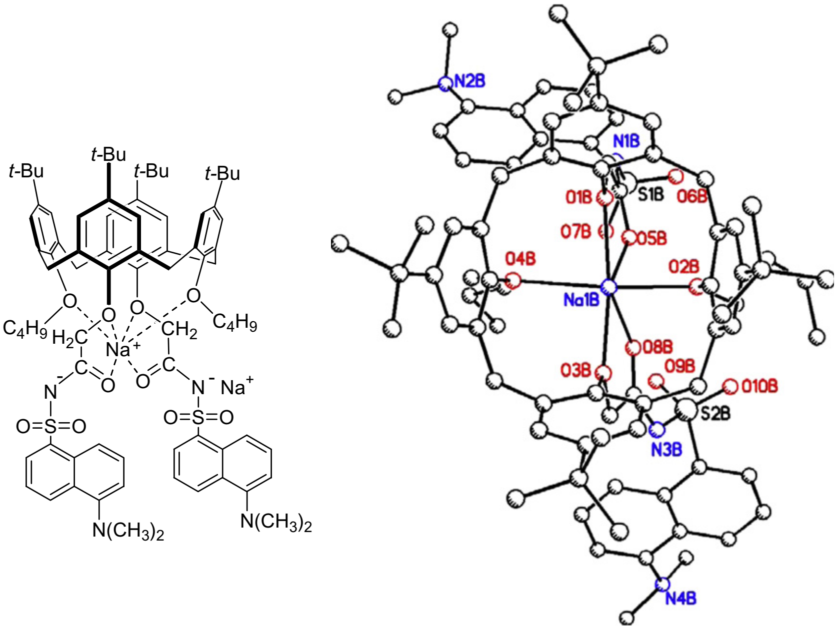

Figure 1. Crystal structure of **2** showing entrapped Na^+.

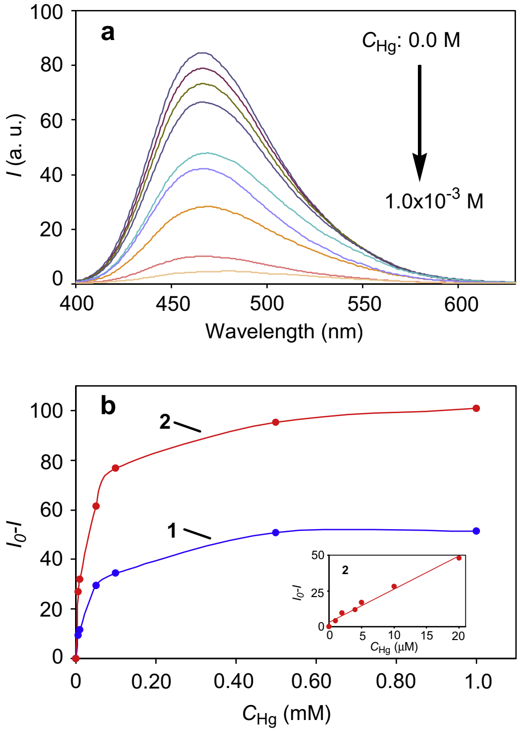

Figure 2. Changes in the fluorescence of **2** in $CHCl_3$ after extraction of increasing concentrations of Hg^{2+}: (a) evolution of the fluorescence emission spectrum of **2** in $CHCl_3$ upon mercury extraction; (b) the plot of $(I_0 - I)$ versus C_{Hg} for **2** (red) and **1** (blue); inset: the calibration plot for determination of micro-concentrations of Hg^{2+} with **2**. Organic phase: 1.0×10^{-5} M ligand in $CHCl_3$; aqueous phase: C_{Hg} (acetate) 0–1.0×10^{-3} M; pH 5.0, 0.1 M Na-acetate buffer. λ_{em} = 468 nm (**2**) and 489 nm (**1**); λ_{ex} = 340 nm; slit width 1.5 nm.

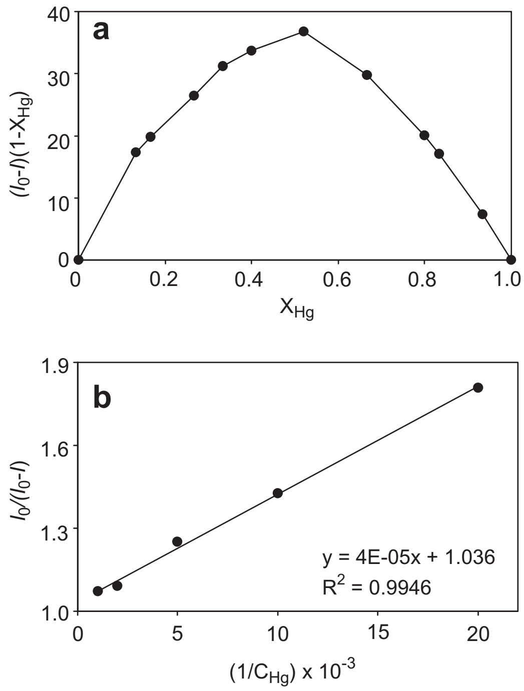

Figure 3. Extraction of aqueous Hg^{2+} (pH 5.0, 0.1 M Na-acetate buffer) by **2** in $CHCl_3$: (a) Job's plot for determination of Hg^{2+}-**2** extraction stoichiometry; (b) the plot for determination of K_{ex}^{app} ($C_2 = 1.0 \times 10^{-5}$ M). λ_{em} = 468 nm; λ_{ex} = 340 nm; slit width 1.5 nm.

The detection limit for Hg^{2+} in extraction from aqueous solutions (pH 5.0, 0. 1 M Na-acetate buffer) by 1.0×10^{-5} M **2** in $CHCl_3$ defined as three times the ratio of the standard deviation for the blank to the slope of the calibration plot[16] was found to be 8.0×10^{-7} M. Under the otherwise identical conditions, the detection limit for Hg^{2+} using the flexible analog **1** was 5.6×10^{-6} M. The stoichiometry of Hg^{2+} extraction by **2** was studied by the method of continuous variations. The Job's plot presented in Figure 3a exhibits a maximum at the molar fraction of mercury(II) (X_{Hg}) of 0.5, which is an indication of 1:1 metal-to-ligand complex formation. Therefore, the equilibrium for mercury(II) extraction by **2** (or Na_2L) may be presented as follows:

$$Hg^{2+}(aq) + Na_2L(org) \rightleftharpoons HgL(org) + 2Na^+(aq). \qquad (1)$$

Stability of the Hg^{2+}-**2** complex in the two-phase extraction system H_2O–$CHCl_3$ is characterized by the extraction constant, K_{ex}. Using the fluorescence spectroscopy data, the apparent extraction constant, K_{ex}^{app}, was determined similar to[17] from the modified Benesi–Hildebrand plot $I_0/(I_0 - I)$ versus $1/C_{Hg}$ (for $C_{Hg} \gg C_2$) (Fig. 3b) as the ratio of the intercept to the slope and it was found to be $2.6 \times 10.^4$ (As it could be expected, for Hg^{2+} extraction by **2** carried out in the absence of large excess of Na^+ in the aqueous phase, at pH 2.5 adjusted with dil. HNO_3, the K_{ex}^{app} increased to 1.3×10^5).

The ability of **2** for optical recognition of Hg^{2+} in the presence of a large excess of Na^+ demonstrated high selectivity of the ligand toward mercury(II) over sodium ion. For further assessment of Hg^{2+}-selectivity of the *cone* fluoroionophore, single-species[18] and competitive[19] extraction of different other metal ions (Pb^{2+}, Cd^{2+},

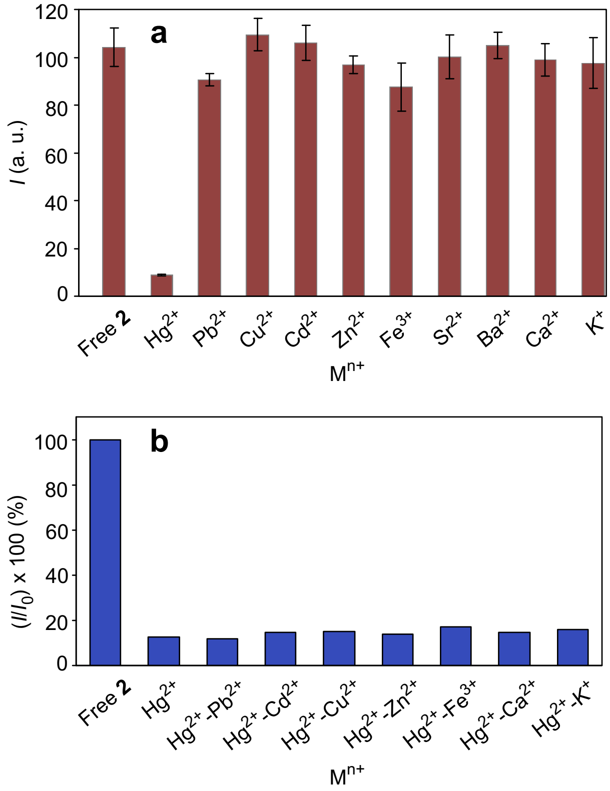

Figure 4. Selectivity of optical recognition of Hg^{2+} by 2: (a) fluorescence intensity of **2** in $CHCl_3$ upon single-species extractions of 100 equiv amounts of different metal ions from aqueous acetate solutions; (b) fluorescence intensity of **2** in $CHCl_3$ upon competitive extractions of Hg^{2+} and other metal ions from binary equimolar aqueous mixtures. Organic phase: 1.0×10^{-5} M **2** in $CHCl_3$; aqueous phase: $C_{Hg} = C_{Mn+} = 1.0 \times 10^{-3}$ M; pH 5.0, 0.1 M Na-acetate buffer. λ_{em} = 468 nm; λ_{ex} = 340 nm.

Cu^{2+}, Zn^{2+}, Fe^{3+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, and K^{+}) from aqueous 1.0×10^{-3} M acetate solutions (pH 5.0, 0. 1 M Na-acetate buffer) by 1.0×10^{-5} M **2** in $CHCl_3$ were studied. The results of these experiments are presented in Figure 4. It is obvious from Figure 4a that upon single-species extraction of various metal ions, M^{n+}, present in the aqueous phase in the amount of 100 equiv relative to **2** in $CHCl_3$, only uptake of Hg^{2+} produced dramatic change in the fluorescence intensity of the ligand, while other cations caused little or no effect. In addition, only insignificant interferences with optical recognition of Hg^{2+} by **2** were encountered during competitive extraction of this metal ion from binary aqueous mixtures with equimolar amounts of competing cations, M^{n+} (Fig. 4b).

In conclusion, this study showed that preorganization of the calixarene scaffold in the *cone* conformation preferred by the flexible *N*-dansylcarboxamide **1** in complexation with Hg^{2+} yielded the fluoroionophore **2** with improved sensorial characteristics towards this hazardous metal ion. Further investigation of Hg^{2+} recognition by **2** is in progress.

Acknowledgments

This work was supported by Howard University (Frederick Douglas Fellowship, P.D.), Government of the Republic of Botswana (BIUST Scholarship, P.D.), and Presidential Fellowship of Russian Federation (P.P.).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.083.

References and notes

1. The EPA maximum contaminant level (MCL) for Hg^{2+} in drinking water is 2 μg/L (US Environmental Protection Agency. National Primary Drinking Water Standards, 2009. Report EPA, 816-F-09-004). By the WHO requirements, concentration of Hg^{2+} should not exceed 1 μg/L (World Health Organization, Guidelines for Drinking-water quality, 3rd ed., Vol. 1, Geneva, 2004, p 188).
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7. For example including calix[4]arenes related to the compounds described herein, see Talanov, V. S.; Hwang, H.-S.; Bartsch, R. A. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1103–1108.
8. Preparation of **2**, disodium salt of 26,28-dibutoxy-25,27-bis(*N*-(5′-dimethylaminonaphtalene-1′-sulfonyl)carbamoylmethoxy)-5,11,17,23-tetrakis(1,1-dimethylethyl)-calix[4]arene in the *cone* conformation. To a solution of *cone*-diacid **3** (1.07 g, 1.22 mmol) in CH_2Cl_2 (5 mL), a small drop of DMF was added, then a solution of oxalyl chloride (0.93 g, 7.33 mmol) in CH_2Cl_2 (3 mL) was added dropwise, and the resulting mixture was stirred at room temperature for 24 h. Volatiles were removed in vacuo to provide the corresponding diacid chloride. A solution of the diacid chloride in THF (12 mL) was added to a mixture of 5-(dimethylamino)naphthalene-1-sulfonamide (dansylamide) (0.70 g, 2.81 mmol) and NaH (0.22 g, 9.27 mmol) in THF (10 mL), and the mixture was stirred under argon at room temperature for 15 h. Then H_2O (1 mL) was added and THF evaporated in vacuo. CH_2Cl_2 (50 mL) and H_2O (15 mL) were added to the residue, organic layer was washed with 5% aqueous Na_2CO_3 (40 mL) and water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography on silica gel with gradient 0–2% MeOH in CH_2Cl_2 as eluent. Compound **2** was obtained as a yellow solid, yield 1.32 g (78%), mp >280 °C (decomp.); IR (ν_{max}, cm^{-1}): 2957, 1579, 1479, 1121; ^{1}H NMR (400.13 MHz, $CDCl_3$, 295 K): 1.02 (t, *J* 7.4, 6H, CH_3), 1.07 (s, 18H, *t*-Bu), 1.16 (s, 18H, *t*-Bu), 1.34–1.44 (m, 4H, CH_2), 1.88–1.96 (m, 4H, CH_2), 2.87 (s, 12H, $N(Me)_2$), 3.31 (d, *J* 12.3, 4H, $ArCH_2Ar$), 3.95–4.00 (m, 4H, OCH_2), 4.28 (d, *J* 12.3, 4H, $ArCH_2Ar$), 4.43 (s, 4H, OCH_2O), 7.01 (s, 4H, ArH), 7.10 (s, 4H, ArH), 7.14 (d, *J* 7.0, 2H, ArH), 7.48–7.53 (m, 4H, ArH), 8.34 (dd, *J* 7.3, 1.2, 2H, ArH), 8.47 (d, *J* 8.6, 2H, ArH), 8.63 (d, *J* 8.6, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$, 298 K): 13.93, 18.86, 29.98, 31.15, 31.31, 33.93, 34.07, 45.40, 76.97, 77.88, 114.61, 121.17, 123.24, 125.58, 126.45, 127.05, 128.85, 129.61, 129.95, 130.07, 134.38, 134.54, 139.04, 146.93, 147.79, 148.53, 149.65, 151.27, 174.97. Anal. Calcd for $C_{80}H_{98}N_4Na_2O_{10}S_2 \cdot H_2O$: C, 68.45; H, 7.18; N, 3.99. Found: C, 68.38; H, 7.36; N, 3.87.
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10. *NH-form of* **2**: ^{1}H NMR (400.13 MHz, $CDCl_3$, 295 K): δ_H (400.13 MHz, $CDCl_3$, 295 K): 0.83 (s) + 0.84 (t, *J* 7.2) (24H, CH_3 + *t*-Bu), 1.13–1.23 (m, 4H, CH_2), 1.30 (s, 18H, *t*-Bu), 1.57–1.66 (m, 4H, CH_2), 2.89 (s, 12H, $N(CH_3)_2$), 3.21 (d, *J* 13.0, 4H, $ArCH_2Ar$), 3.78–3.84 (m, 4H, OCH_2), 4.36 (d, *J* 13.0, 4H, $ArCH_2Ar$), 4.76 (s, 4H, OCH_2CO), 6.47 (s, 4H, ArH), 7.06 (s, 4H, ArH), 7.19 (d, *J* 7.5, 2H, ArH), 7.59–7.64 (m, 4H, ArH), 8.49 (br d, *J* 8.6, 2H, ArH), 8.59–8.64 (br m, 4H, ArH), 10.58 (s, 2H, NH).
11. Stripping of **2** with a more concentrated HCl evidently results in protonation of the $N(CH_3)_2$ groups in the dansyl moieties which is accompanied by precipitate formation.
12. Crystals of **2** were obtained from CH_2Cl_2–CH_3OH solution by slow evaporation of the solvent. A colorless crystal of dimensions $0.16 \times 0.12 \times 0.04$ mm^3 was mounted on glass fiber using a small amount of epoxy cement. Data were collected on an Oxford Diffraction Gemini R CCD diffractometer. Crystallographic information for the complex (Supplementary Table S1), cif. file and an additional structure diagram (Supplementary Fig. S1) are presented in the Supplementary data.
13. For example, Baklouti, L.; Abidi, R.; Thuery, P.; Nierlich, M.; Asfari, Z.; Vicens, J. *J. Inclusion Phenom. Macrocycl. Chem.* **2001**, *40*, 323–325.
14. 3.0-mL samples of aqueous mercury(II) acetate (pH 5.0, 0.1 M Na-acetate buffer) of concentrations that varied from 0 to 1.0×10^{-3} M were extracted with equal volumes of 1.0×10^{-5} M **2** in $CHCl_3$. After extraction, the organic phases were separated and fluorescence spectra measured with a Shimadzu RF-5301 PC spectrofluorophotometer.
15. Herein, **1** was employed in Hg^{2+} extraction from the 0.1 M Na-acetate buffered aqueous solution both as a neutral ligand (the NH-form) and as the disodium salt obtained by treatment of neutral **1** in $CHCl_3$ with solid Na_2CO_3. The results of the two extraction experiments were in good agreement.
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18. Single-species extraction of different metal ions by **2** was carried out analogously to Ref. 13.
19. 3.0-mL samples of aqueous binary equimolar (1.0×10^{-3} M) mixtures of mercury(II) and competing metal ion (M^{n+}) acetates (pH 5.0, 0.1 M Na-acetate buffer) were extracted with equal volumes of 1.0×10^{-5} M **2** in $CHCl_3$. After extraction, the organic phases were separated and fluorescence spectra measured.