Jie Wang, Hongyu Guan*, Chunhua Ge, Ping Fan*, Xijuan Xing and Yunshan Shang

Azocalix[4]arene with three distal ethyl ester residues as a highly selective chromogenic sensor for Ca^{2+} ions

<https://doi.org/10.1515/hc-2017-0239>

Received December 6, 2017; accepted January 26, 2018; previously published online April 27, 2018

Abstract: Three azocalix[4]arenes with distal ethyl ester residues, 5-phenylazo-25,26,27-tris[(ethoxycarbonyl)methoxy]-28-hydroxycalix[4]arene (**2**), 5-(*o*-methylphenyl)azo-25,26,27-tris[(ethoxycarbonyl)methoxy]-28-hydroxycalix[4]arene (**3**), 5-(*p*-Methylphenyl)azo-25,26,27-tris[(ethoxycarbonyl)methoxy]-28-hydroxycalix[4]arene (**4**), were synthesized and their binding properties with metal ions were investigated by ultraviolet (UV)/visible spectroscopy. The chromogenic behavior of these compounds upon metal ion complexation indicates a specific selectivity toward Ca^{2+} ion in the presence of other cations tested. The stoichiometry of **3** to Ca^{2+} ion in the complex is 1:1 and the stability constant of the complex is $1.28 \times 10^4 \text{ M}^{-1}$.

Keywords: azocalix[4]arene; calcium ion; chromogenic sensor; ion recognition.

Introduction

Over the past two decades, significant efforts have been focused on the design and synthesis of chemosensors that are able to selectively recognize target molecules or ions, particularly those with color or fluorescent response functions [1–6]. Converting this recognition into an optical signal, a reaction process or a chemical species that could be observed and detected by the naked eye or with inexpensive equipment, is of interest [7–9]. Azocalixarenes have been reported to change color upon complexation with specific metal ions [10–13]. In many cases, the azo moiety is introduced into calixarenes at the upper rim to facilitate the monitoring of the binding process upon complexation.

Many studies on azocalixarene derivatives also involve the functionalization of the lower rim with metal-chelating groups, such as carboxylic acid, ester and other groups [14–18]. Other studies focus on azocalix[4]arenes functionalized with distal esters as chromogenic receptors [19–24].

An antracenylozo derivative was synthesized [19] and shown to undergo complexation with Eu^{3+} , Ag^+ and Cu^{2+} ions [20]. Subsequently, it was reported that this calixarene forms complexes with Ca^{2+} , Pb^{2+} , Sr^{2+} and Ba^{2+} ions as well, with a moderate selectivity toward Ca^{2+} ions [21]. On the other hand, it was reported that an azocalix[4]arene with four distal ester groups undergoes complexation with Ag^+ , Hg^+ and Hg^{2+} cations [22]. Similar azocalixarene species bearing diester groups on the lower rim were used for the selective extraction of Pd^{2+} ion in the presence of some other cations in hydrochloric acid solution [23]. Using the azocalixarenes as extractants made the extraction process visible. Additional applications have been reported [24].

Results and discussion

In an effort to synthesize azocalixarene species that exhibit unique chromogenic responses to specific metal ions, three new azocalix[4]arenes with distal ethyl ester groups on the lower rim, 5-phenylazo-25,26,27-tris[(ethoxycarbonyl)methoxy]-28-hydroxycalix[4]arene (**2**), 5-(*o*-methylphenyl)azo-25,26,27-tris[(ethoxycarbonyl)methoxy]-28-hydroxycalix[4]arene (**3**), 5-(*p*-methylphenyl)azo-25,26,27-tris[(ethoxycarbonyl)methoxy]-28-hydroxycalix[4]arene (**4**),

Scheme 1 Synthesis of calix[4]arenes **2–4**. Reagents and conditions: NaNO_2 /4N HCl, pyridine, 0°C , 5 h, aniline in acetone for **2**, *o*-toluidine in acetone for **3**, *p*-toluidine in acetone for **4**.

*Corresponding authors: Hongyu Guan and Ping Fan, College of Chemistry, Liaoning University, Shenyang 110036, People's Republic of China, e-mail: guanhongyu@lnu.edu.cn (H. Guan); pingfan@lnu.edu.cn (P. Fan)

Jie Wang, Chunhua Ge, Xijuan Xing and Yunshan Shang: College of Chemistry, Liaoning University, Shenyang 110036, People's Republic of China

Figure 1 Absorption spectra of **2** (A), **3** (B) and **4** (C) in the absence and the presence of various metal ions in acetonitrile.

were synthesized using methods inspired by Shinkai et al. [25] and Tóth et al. [26]. The synthesis of compounds **2–4** is illustrated in Scheme 1.

In acetonitrile, compounds **2–4** show a strong ultra-violet/visible (UV/Vis) absorption peak near 362 nm (Figure 1), which can be attributed to the $\pi\text{-}\pi^*$ transition of the -N=N- bond [21]. The binding properties of the three compounds with metal ions were investigated by monitoring UV/Vis spectral changes upon the addition of Na^+ , K^+ , Li^+ , Mg^{2+} , Ca^{2+} , Ba^{2+} , Fe^{3+} , Co^{2+} , Ni^{2+} , Zn^{2+} , Cd^{2+} , Hg^{2+} , Pb^{2+} , Mn^{2+} , Ag^+ , La^{3+} , Nd^{3+} , Eu^{3+} , Sm^{3+} and Cr^{3+} ions. With the exception of Ca^{2+} , addition of these ions does not significantly alter the absorption peaks of compounds **2–4**. Upon addition of Ca^{2+} to **2**, the intensity of absorption band at 362 nm decreases and a new band appears at 429 nm. The UV/Vis spectral changes for compounds **3** and **4** are similar to those observed for compound **2** (Figure 1).

These results indicate that compounds **2–4** possess a specific selectivity for Ca^{2+} ion. Compounds **2–4** may

Figure 2 Job's continuous variation plot for **3**- Ca^{2+} at 429 nm. ($[\text{3}] + [\text{Ca}^{2+}] = 1 \times 10^{-3}$).

Figure 3 Color of the solution of compound **4** (1.0×10^{-5} M) in the presence of various metal cations (4.0×10^{-5} M).

exist in two tautomeric forms containing azophenol and quinone-hydrazone moieties [12, 13, 27]. The metal complexation may induce a release of proton from the azophenol to the quinone-hydrazone function. When compounds **2–4** undergo complexation with Ca^{2+} ion, the formation of quinone-hydrazone tautomer results in the weakening of the double bond character of the azo moiety. As a result, the UV/Vis spectrum is altered, with the new band appearing at 429 nm.

The complexation ratio between azocalixarene **3** and Ca^{2+} was determined using a Job's plot (Figure 2). The experiment was conducted using a 429 nm wavelength. As can be seen, the maximum point is at a molar fraction of [azocalixarene **3**]/([azocalixarene **3**] + [Ca^{2+}]) of approximately 0.5, indicating a host-metal ion complex ratio of 1:1. The association constant for the **3**- Ca^{2+} complex in acetonitrile is $1.28 \times 10^4 \text{ M}^{-1}$ as determined by a Benesi-Hilderbrand plot [12, 28].

A color change is observed upon mixing the ligand **2**, **3** or **4** and Ca^{2+} cation. For example, when a dilute colorless solution of compound **4** is treated with Ca^{2+} (Figure 3), the solution becomes yellow. No color change is observed in the presence of other metal cations.

Conclusions

Azocalix[4]arenes **2–4** exhibit a remarkable selectivity toward complexation of Ca^{2+} ion, and the interaction is associated with a color change, suggesting possible applications as new chromogenic sensors for Ca^{2+} ion-sensing materials. The hydroxyl and distal ethyl ester units of azocalixarenes **2–4** take part in binding with Ca^{2+} ion, and the azo moiety is necessary for the color recognition of Ca^{2+} ion.

Experimental

Synthesis of compounds **2–4**

An ice-cold solution of NaNO_2 (0.90 g) in hydrochloric acid (4 M, 6 mL) was added to a solution of aniline, *o*-toluidine or *p*-toluidine

(0.86 mmol) in acetone (5 mL). The mixture was stirred for 20 min and then added to an ice-cold solution of calix[4]arene **1** (0.13 g, 0.19 mmol) in pyridine (8 mL) [25]. The colored mixture was stirred for 5 h at 0°C and then treated with hydrochloric acid (4 M, 50 mL). The resultant colored precipitate was subjected to chromatography on silica gel eluting with ethyl acetate/petroleum ether (1:5).

5-Phenylazo-25,26,27-tris[(ethoxycarbonyl)methoxy]-28-hydroxycalix[4]arene (2) Yield 20%; mp $199\text{--}201^\circ\text{C}$; IR (KBr): 3392, 2927, 1765 cm^{-1} ; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 1.26 (t, $J=7$ Hz, 3H, OCH_2CH_3), 1.34 (t, $J=7$ Hz, 6H, OCH_2CH_3), 3.32 (d, $J=13$ Hz, 2H, ArCH_2Ar), 3.47 (d, $J=13$ Hz, 2H, ArCH_2Ar), 4.14 (q, $J=7$ Hz, 2H, OCH_2CH_3), 4.29 (q, $J=7$ Hz, 4H, OCH_2CH_3), 4.41 (d, $J=13$ Hz, 2H, OCH_2CH_3), 4.51 (d, $J=15$ Hz, 2H, OCH_2COO), 4.66 (d, $J=15$ Hz, 2H, OCH_2COO), 4.97 (d, $J=13$ Hz, 2H, OCH_2COO), 5.13 (s, 2H, OCH_2COO), 6.56 (m, 6H Ar), 6.93 (t, $J=7$ Hz, 1H, Ar), 7.13 (d, $J=7$ Hz, 2H, Ar), 7.18 (s, 1H), 7.46 (m, 3H, Ar), 7.74 (s, 2H, Ar), 7.88 (d, $J=8$ Hz, 2H, Ar); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ 171.0 (CO), 169.2 (CO), 156.9, 155.9, 153.7, 153.0, 145.3, 135.8, 133.2, 132.0, 129.9, 129.5, 129.3, 129.0, 128.7, 128.4, 124.2, 123.8, 123.4, 122.3, 72.1 (OCH_2CO), 70.3 (OCH_2CO), 61.1 (s, OCH_2), 60.3 (OCH_2), 31.8 (CH_2), 31.0 (CH_2), 14.2 (CH_3). HR-MS. Calcd for M^+ : m/z 702.7054. Found: m/z 702.7060.

5-(*o*-Methylphenyl)azo-25,26,27-tris[(ethoxycarbonyl)methoxy]-28-hydroxy-calix[4]arene (3) Yield 30%; mp $192\text{--}194^\circ\text{C}$; IR (KBr): 3422, 2927, 1763 cm^{-1} ; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 1.27 (t, $J=7$ Hz, 3H, OCH_2CH_3), 1.34 (t, $J=7$ Hz, 6H, OCH_2CH_3), 2.72 (s, 3H, ArCH_3), 3.32 (d, $J=13.5$ Hz, 2H, ArCH_2Ar), 3.47 (d, $J=13.5$ Hz, 2H, ArCH_2Ar), 4.14 (q, $J=7$ Hz, 2H, OCH_2CH_3), 4.29 (q, $J=7$ Hz, 4H, OCH_2CH_3), 4.42 (d, 2H, ArCH_2Ar), 4.51 (d, $J=16$ Hz, 2H, OCH_2COO), 4.66 (d, $J=16$ Hz, 2H, OCH_2COO), 4.97 (d, $J=13.5$ Hz, 2H, ArCH_2Ar), 5.13 (s, 2H, OCH_2COO), 6.49–6.65 (m, 6H, Ar), 6.93 (t, $J=7$ Hz, 1H, Ar), 7.12 (d, $J=7$ Hz, 3H, Ar), 7.28 (m, 3H, Ar), 7.58 (d, $J=7$ Hz, 1H, Ar), 7.73 (s, 2H, Ar); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ 170.9 (CO), 169.1 (CO), 156.6, 155.7, 153.8, 151.1, 145.7, 137.0, 135.8, 133.2, 132.0, 131.0, 129.4, 129.3, 128.6, 128.3, 126.3, 124.1, 123.8, 123.3, 115.4, 72.2 (OCH_2CO), 70.2 (OCH_2CO), 61.0 (OCH_2), 60.2 (OCH_2), 31.7 (CH_2), 31.0 (CH_2), 17.5 (CH_3), 14.1 (CH_3). HR-MS. Calcd for M^+ : m/z 716.7320. Found: m/z 716.7311.

5-(*p*-Methylphenyl)azo-25,26,27-tris[(ethoxycarbonyl)methoxy]-28-hydroxycalix[4]arene (4) Yield 25%; mp $151\text{--}153^\circ\text{C}$; IR (KBr): 3410, 2978, 1733 cm^{-1} ; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 1.26 (t, $J=7$ Hz, 3H, OCH_2CH_3), 1.34 (t, $J=7$ Hz, 6H, OCH_2CH_3), 2.42 (s, 3H, ArCH_3), 3.31 (d, $J=13.5$ Hz, 2H, ArCH_2Ar), 3.46 (d, $J=13.5$ Hz, 2H, ArCH_2Ar), 4.14 (q, $J=7$ Hz, 2H, OCH_2CH_3), 4.29 (q, $J=7$ Hz, 4H, OCH_2CH_3), 4.40 (d, $J=13.5$ Hz, 2H, ArCH_2Ar), 4.50 (d, $J=15$ Hz, 2H, OCH_2COO), 4.65 (d, $J=15$ Hz, 2H, OCH_2COO), 4.96 (d, $J=13.5$ Hz, 2H, ArCH_2Ar), 5.13 (s, 2H, OCH_2COO), 6.47–6.63 (m, 6H, Ar-H), 6.93 (t, $J=7$ Hz, 1H, Ar-H),

7.03–7.14 (m, 3H, Ar), 7.29 (d, $J=8$ Hz, 2H, Ar–H), 7.72 (s, 2H, Ar), 7.78 (d, $J=7.5$ Hz, 2H, Ar); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 170.9 (s, CO), 169.0 (s, CO), 156.5 (s), 155.6 (s), 153.6 (s), 151.0 (s), 145.2, 140.2, 135.7, 133.1, 131.9, 129.6, 129.4, 129.2, 128.6, 128.3, 124.1, 123.6, 122.2, 70.9 (OCH₂CO), 70.2 (OCH₂CO), 61.0 (OCH₂), 60.1 (OCH₂), 31.6 (CH₂), 30.9 (CH₂), 21.3 (CH₃), 14.1 (CH₃). HR-MS. Calcd for M⁺: m/z 716.7320. Found: m/z 716.7383.

Acknowledgments: This work was supported by the National Natural Science Foundation of China (grant 21171081), the Science Foundation of Education Department of Liaoning Province (grant L2011007) and the Foundation of Project 211 for Innovative Talents Training, Liaoning University. The authors also thank the colleagues and students who participated in this work.

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