Synthesis of meso-2,2′-bipyridyl-substituted calix[4]arenes and their response to metal cations

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Abstract. A convenient synthetic approach to meso-substituted with 2,2′-bipyridine and 1-(pyridin-2-yl)isoquinoline residues calix[4]arenes is reported. This approach involves the reaction of generated in situ 2-lithio-calix[4]arene with 1,2,4-triazine precursor with the following aromatization of the obtained adduct, and the aza-Diels-Alder reaction of the 1,2,4-triazinyl-substituted calix[4]arene with 2,5-norbornadien or in-situ generated 1,2-dehydrobenzene. The UV/fluorescence response of thus obtained meso-pyridyl-substituted calix[4]arenes to metal cations is studied.

Keywords: calix[4]arene; 1,2,4-triazines; aza-Diels-Alder reaction; 2,2′-bipyridines; visual cations detection

Introduction

Calix[4]arenes and their derivatives are, probably, the mostly studied supramolecular hosts for various applications for analytical chemistry [1], materials science [2], as well as environmental [3] and medicinal [4] applications. By means the proper synthetic modification various calixarene derivatives bearing extra heterocyclic ligand units or other receptor units at the upper or lower rim were obtained to be used for the recognition/supramolecular extraction of inorganic [5] and organic cations [6], anions [7], as well as some neutral molecules [8]. In this article we wish to report a method for the preparation of meso-2,2′-bipyridyl-substituted calix[4]arenes and their response to metal cations.

Experimental part

$^1$H NMR spectra were recorded on a Bruker Avance-400 spectrometer (400 MHz), the internal standard was SiMe$_4$. Mass-spectra (ionization type — electrospray) were recorded on a MicrOTOF-Q II instrument from Bruker Daltonics (Bremen, Germany). Elemental analysis was performed on a Perkin Elmer
PE 2400 II CHN analyzer. Fluorescence spectra were measured on Horiba Fluoromax-4 spectrofluorometer. Absolute quantum yields were measured by using the integrating sphere. UV-spectra were measured on Shimadzu UV-1800 spectrometer. The starting meso-triazinyl-substituted calix[4]arenes were prepared as reported [9].

**Meso-2,2'-bipyridyl-substituted calix[4]arene (3).** In a 50 ml round-bottom flask to a solution of 2-(6-phenyl-3-(2-pyridyl)-1,2,4-triazin-5-yl)-25,26,27,28-tetramethoxycalix[4]arene 2 (0.106 g, 0.15 mmol) in 10 ml of o-xylene 2,5-norbornadiene (0.15 ml) was added and the resulting solution was heated at a temperature of 130–150 °C for 12 hours under the argon atmosphere. Then another 0.1 ml of 2,5-norbornadiene were added and the reaction mixture was heated for another 6 hours at a temperature of 130–150 °C. o-Xylene was distilled off under reduced pressure, and the column chromatography (eluent — ethyl acetate) resulted in the product 3 (Rf = 0.55). Yield 69 mg (0.097 mmol, 65%), mp >250°C. NMR 1H (CDCl3, δ, ppm): 8.64 (1H, d, J=4.9 Hz, H-6 (2-Py)), 8.43–8.51 (1H, dd, J=8.2 Hz, J=15.1 Hz, H-3 (Py)), 8.33–8.37 (1H, dd, J=2.7 Hz, J=8.2 Hz, H-4 (Py)), 7.67–7.76 (2H, m, H-3 (2-Py)), 7.44–7.47 (2H, m, H-5 (2-Py)), 7.22–7.33 (2H, m, Ph) 7.11–7.27 (5H, m, Ph), 6.90–6.97 (2H, m, Ph), 6.80–6.86 (2H, m, Ph), 6.67–6.77 (6H, m, Ph), 6.28, 5.70 (1H, s, C(2)H), 4.25–4.32, 4.12–4.17 (2H, m, ArCH2Ar), 3.72–3.77 (4H, m, 1H ArCH2Ar + 3H OMe), 3.65 (3H, s, OMe), 3.57 (1H, m, ArCH2Ar), 3.42–3.48 (4H, m, 1H ArCH2Ar + 3H OMe), 3.16 (3H, m, 3H OMe), 2.85 (1H, m, ArCH2Ar). Found: C 81.27%, H 6.15%. C48H42N2O4. Calculated: C 81.10%, H 5.96%.

**Meso-1-(pyridin-2-yl)isoquinolinyl-substituted calix[4]arene (4).** In a 100 ml three-necked flask equipped with a reflux condense 2-(6-phenyl-3-(pyridin-2-yl)-1,2,4-triazin-5-yl)-25,26,27,28-tetramethoxycalix[4]arene 0.142 g, 0.2 mmol) was dissolved and 0.1 ml of iso-amyl nitrite (0.7 mmol) in 40 ml of dry toluene was added at once. Under argon atmosphere the resulted solution was heated to a temperature of 105–110 °C, and a solution of anthranilic acid (96 mg, 0.7 mmol) in 20 ml of 1,4-dioxane was added to dropwise for 30 minutes with an intensive stirring the reaction mixture. After that the reaction was kept under such conditions for 60 minutes. The reaction mixture was than cooled down to room temperature and washed with a 30% aqueous alkali solution (4 times 50 ml each), the organic phase was separated, dried with an anhydrous sodium sulfate, filtered and the solvent was distilled off under reduced pressure. The product 4 was isolated by column chromatography (dichloromethane: ethyl acetate in a ratio of 4: 1, Rf = 0.85). Yield 10 mg (0.012 mmol, 6.0%), mp >250°C. NMR 1H (CDCl3, δ, ppm): 8.89 (1H, d, J=4.9 Hz, H-6 (2-Py)), 8.41–8.48 (1H, dd, J=8.2 Hz, J=15.1 Hz, H-3 (2-Py)), 8.79–8.88 (1H, dd, J=2.7 Hz, J=8.2 Hz, H-4 (2-Py)), 7.59–7.66 (2H, m, H-5 (2-Py), Ph), 7.46–7.55 (4H, m, Ph), 7.39–7.46 (3H, m, Ph), 7.08–7.18 (2H, m, Ph), 6.89–7.04 (2H, m, Ph), 6.83–6.88 (2H, m, Ph), 6.65–6.76 (5H, m, Ph), 6.57–6.64 (2H, m, Ph), 6.35, 5.96 (1H, s, C(2)H), 4.25–4.32, 4.12–4.17 (2H, m, ArCH2Ar), 3.72–3.77 (4H, m, 1H ArCH2Ar + 3H OMe), 3.65 (3H, s, OMe), 3.57 (1H, m, ArCH2Ar), 3.42–3.48 (4H, m, 1H ArCH2Ar + 3H OMe), 3.16 (3H, m, 3H OMe), 2.85 (1H, m, ArCH2Ar). Found: C 81.91%, H 5.77%. C52H44N2O4. Calculated: : C 82.08%, H 5.83%.
Studies of the interactions of calix-arenes 3–4 with cations
The studies of the interactions of compounds 3–4 with Zn$^{2+}$ and Cd$^{2+}$ cations were carried out at the concentrations of 3–4 of (1-9)$\cdot10^{-6}$ M (depending on the value of the absorption coefficient ($A \leq 0.1$)) in anhydrous freshly distilled THF. The concentrations of cations were $10^{-3}$–$10^{-4}$ M.

Results and discussion
A most common method for the introducing of (bi)pyridine moieties into the calix[4]arenes is the modification of upper or lower ring the calixarene core with oligopyridine-attached spacer groups by means of acylation, alkylation or condensation reactions [9–17]. As an alternative approach our group reported the direct modification of an upper ring of calix[4]arene moiety with 3-(2-pyridyl)-1,2,4-triazine-5(2$H$) — one residues [18]. For these modified calixarenes an effectiveness for their transport of La$^{3+}$ cations was confirmed. Additionally, we reported recently an effective synthetic approach to meso-substituted with 1,2,4-triazine moieties calix[4]arenes via direct modification of 5-H-1,2,4-triazines by the reaction with generated in situ 2-lithio-calix[4]arene and the following aromatization [9] (Scheme 1).

From another hand the 1,2,4-triazines are suitable precursors for the preparation of multi-substituted (bi)pyridine ligands/fluorophores via the inverse demand Diels-Alder/retro-Diels-Alder reaction sequence.

Scheme 1. Reagents and conditions: i) 1.6 M n-BuLi, TMEDA, THF, −78 °C, 1 h, then 25 °C overnight; ii) DDQ (1.2 eq.), THF, 25 °C, 0.5 h; iii) 2,5-norbornadiene, o-xylene, 130–150 °C, 18 h; iv) anthranilic acid, iso-amyl nitrite, 1,4-dioxane-toluene, 105–110 °C, 1.5 h.
with various dienophiles, such as 2,5-norbornadiene [20], enamines [21], acetylene equivalents [22] or aryne intermediates [23].

Keeping in mind all the mentioned above we decided to prepare new calix[4] arenes *meso*-substituted with (benzo) pyridine moieties and study their response to selected metal cations. To do that as a first step we prepared the corresponding *meso*-1,2,4-triazine-substituted calixarene 2 using the previously reported procedure [9]. As a next step the ID Diels-Alder reaction between 2 and 2,5-norbornadiene was carried out to afford smoothly *meso*-2,2’-bipyridyl-substituted calix[4] arene 3 in up to 65% yield (Scheme 1). The photophysical properties of calixarene 3 are presented below (Table 1).

The introduction of bipyridyl ligand/fluorophore on the periphery of calix[4] arene caused the change in the photophysical properties of product 3. Thus, in THF solution calixarene 3 has a strong absorbance band near 292 nm and an emission peak near 379 nm. Calculated absolute fluorescence quantum yield was 1.1%.

The response of calixarene 3 to Zn$^{2+}$ and Cd$^{2+}$ cations is shown below. Thus, in UV-spectra the addition of 1 eq. of these cations caused a strong decrease of the absorbance peak at 292 nm (Fig. 1).

The same trend was observed in the emission spectra. Thus, upon addition of 1 eq. of Cd$^{2+}$ or Zn$^{2+}$ a dramatic fluorescence quenching was observed along with the bathochromic shift of the emission maxima by 5–20 nm. It worth to mention that, the addition of Zn$^{2+}$ caused the stronger red-shift, while the addition of Cd$^{2+}$ caused stronger fluorescence quenching (Fig. 2).

As a last step the isoquinoline-substituted calixarene 4 was obtained by using the reaction between 2 and benzyne generated *in situ* as reported before [23]. The re-

### Table 1

| #  | $\lambda_{\text{abs max}}$ a, nm | $\lambda_{\text{em max}}$ b, nm | $\varepsilon_M$ (at $\lambda_{\text{abs max}}$, 10$^4$ M$^{-1}$·cm$^{-1}$) | Stokes shift, nm | $\Phi_f$ (%) c | $\lambda_{\text{ex}}$, nm d |
|----|---------------------------------|-------------------------------|-------------------------|-----------------|----------------|-----------------|
| C3 | 292                             | 379                           | 1.60                    | 113             | 1.1            | (292 nm)        |

a absorption maxima in THF at room temperature; b fluorescence maxima in THF at room temperature; c absolute photoluminescence quantum yield in THF; d excitation wavelength

![Fig. 1. UV-spectra of calixarene 3 in the presence of Cd$^{2+}$ and Zn$^{2+}$](image1.png)

![Fig. 2. Emission spectra of calixarene 3 in the presence of Cd$^{2+}$ and Zn$^{2+}$](image2.png)
action afforded as low as 6% of the desired calixarene 4, while the rest of the reaction mixture contains several non-identified products. In preliminary experiments in a solution of THF in the presence of even trace amounts of Cd$^{2+}$ calixarene 4 exhibited a dramatic fluorescence quenching. However, a lesser response to Zn$^{2+}$ was observed. In our opinion, these results confirm the influence of a nature of pyridine substituents in the meso-position of the calix[4]arene core on the fluorescence response of whole calixarene molecule to the selected metal cations.

**Conclusions**

In summary, meso-pyridyl- and meso-isoquinolinyl-substituted calix[4]arene ligands/fluorophores were prepared and their photophysical and coordination properties to metal cations were studied. For the obtained meso-pyridyl-calixarenes strong fluorescence turn-off response towards Zn$^{2+}$ and Cd$^{2+}$ cations was observed.

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**References**

1. Ludwig R. Calixarenes in analytical and separation chemistry. Fresenius J Anal Chem. 2000;367:103–28. doi:10.1007/s002160051611
2. Diamond D, Nolan K. Calixarenes: Designer Ligands for Chemical Sensors. Anal Chem. 2001;73:22A — 29A. doi:10.1021/ac012376g
3. Kumar R, Sharma A, Singh H, Suating P, Kim HS, Sunwoo K, Shim I, Gibb BC, Kim JS. Revisiting Fluorescent Calixarenes: From Molecular Sensors to Smart Materials. Chem Rev. 2019;119:9657–721. doi:10.1021/acs.chemrev.8b00605
4. Veber F, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem. 2002;45:2615–23. doi:10.1021/jm020017n
5. Dumazet-Bonnamour I, Halouani H, Oueslati F, Lamartine R. Calixarenes for metal cations extraction. C R Chim. 2005;8:881–91. doi:10.1016/j.crci.2005.02.004
6. Abraham W. Inclusion of organic cations by calix[n]arenes. J Incl Phenom Macro. 2002;43:159–74. doi:10.1023/A:1021288303104
7. Staffilani M, Hancock KSB, Steed JW, Holman KT, Atwood JL, Juneja RK, Burkhalter RS. Anion Binding within the Cavity of π-Metalated Calixarenes. J Am Chem Soc. 1997;119:6324–35. doi:10.1021/ja9702172
8. Atwood JL, Barbour LJ, Heaven MW, Raston CL. Association and orientation of C$_{70}$ on complexation with calix[5]arene. Chem Commun. 2003;3:2270–1. doi:10.1039/B306411P

9. Varaksin MV, Utepova IA, Chupakhin ON, Charushin VN. Synthesis of New meso-Substituted Heterocyclic Calix[4]arenes via S-N(H) Approach. Macroheterocycles. 2013;6:308–14. doi:10.6060/mhc131268c

10. Dalbavie JO, Regnouf-de-Vains JB, Lamartine R, Perrin M, Lecocq S, Fenet B. A Calix[4]arene-Based Bipyridine Podand as Versatile Ligand for Transition Metal Cations. Eur J Inorg Chem. 2002;4:901–9. doi:10.1002/1099-0682(200203)2002:4<901::AID-EJIC901>3.0.CO;2–9

11. Beer PD, Szemes F, Passaniti P, Maestri M. Luminescent Ruthenium(II) Bipyridine–Calix[4]arene Complexes as Receptors for Lanthanide Cations. Inorg Chem. 2004;43:3965–75. doi:10.1021/ic03499401

12. Dorta R, Shimon LJW, Rozenberg H, Ben-David Y, Milstein D. A New Ligand System Based on a Bipyridine-Functionalized Calix[4]arene Backbone Leading to Mono- and Bimetallic Complexes. Inorg Chem. 2003;42:3160–7. doi:10.1021/ic020643a

13. Beer PD, Martin JP, Drew MGB. Calix[4]arene cryptand and new 1,3-bis-pyridyl-, bipyridyl and -alkylthioether calix[4]arene designed to coordinate transition metal cations. Tetrahedron. 1992;48:9917–28. doi:10.1016/S0040-4020(01)92282–3

14. Regnouf-De-Vains JR, Lamartine R. Synthesis and Complexation Properties of a New Class of Receptors based on a cone-configurated tetra-p-(tert-butyl)calix[4]arene and bipyridyl subunits. Helv Chim Acta. 1994;77:1817–25. doi:10.1002/hlca.19940770713

15. Grigg R, Holmes JM, Jones SK, Norbert WDAJ. Luminescent pH sensors based on p-tert-butylicalix[4]arene-linked ruthenium(II) trisbipyridyl complexes. J Chem Soc, Chem Commun. 1994;2:185–7. doi:10.1039/C3994000185

16. Ulrich G, Ziessel R. Calixarene[4]-podands and barrel-shaped calixarene[4]-cryptands based on 5,5’-substituted-2,2’-bipyridine subunits. Tetrahedron Lett. 1994;35:6299–302. doi:10.1016/S0040-4039(00)73416–2

17. Regnouf-De-Vains JB, Lamartine R, Fenet B. Electrospray mass spectrometric evidence of calixarene p-quinone methide formation. Helv Chim Acta. 1998;81:661–9. doi:10.1002/(SICI)1096-9888(1998100)33:10<968::AID-JMS706>3.0.CO;2-M

18. Dalbavie JO, Regnouf-de-Vains JB, Lamartine R, Lecocq S, Perrin M. Complexation of cobalt(II) at the upper rim of two new calix[4]arene/bipyridine-based podands. Eur J Inorg Chem. 2000;4:683–91. doi:10.1002/(SICI)1099-0682(200004)2000:4<683::AID-EJIC683>3.0.CO;2-N

19. Beresnev DG, Itsikson NA, Chupakhin ON, Charushin VN, Kodess MI, Butakov AI, Rusinov GL, Morzherin YY, Konovalov AI, Antipin IS. One-step heterylation
at the upper rim of calix[4]arene with 1,2,4-triazin-5(2H) — ones. J Org Chem. 2006;71:8272–5. doi:10.1021/jo061069d

20. (a) Pabst GR, Sauer J. A new and simple ‘LEGO’ system for the synthesis of 2,6-oligopyridines. Tetrahedron Lett. 1998;39:6687–90. doi:10.1016/S0040-4039(98)01437–3; (b) Pabst GR, Schmid K, Sauer J. A new and simple ‘LEGO’ system for the synthesis of branched oligopyridines. Tetrahedron Lett. 1998;39:6691–4. doi:10.1016/S0040-4039(98)01438–5; (c) Pabst GR, Sauer J. The new and simple ‘LEGO’ system: Its application to the synthesis of superbranched oligopyridines. Tetrahedron Lett. 1998;39:8817–20. doi:10.1016/S0040-4039(98)02042–5; (d) Pfüller OC, Sauer J. The new and simple ‘LEGO’ system for the synthesis of thienyl substituted 2,6-oligopyridines. Tetrahedron Lett. 1998;39:8821–4. doi:10.1016/S0040-4039(98)02043–7; (e) Pabst GR, Pfüller OC, Sauer J. The new and simple ‘LEGO’ system: Its application for the synthesis of 6-oligopyridyl-1,5,12-triazatriphenylenes. Tetrahedron Lett. 1998;39:8825–8. doi:10.1016/S0040-4039(98)02044–9; (f) Pabst GR, Pfüller OC, Sauer J. The new and simple ‘LEGO’ System: Synthesis and reactions of ruthenium(II) complexes. Tetrahedron. 1999;55:8045–64. doi:10.1016/S0040-4020(99)00422–6; (g) Stanforth SP, Tarbit B, Watson MD. Synthesis of pyridine and 2,2′-bipyridine derivatives from the aza Diels — Alder reaction of substituted 1,2,4-triazines. Tetrahedron. 2004;60:8893–7. doi:10.1016/j.tet.2004.07.024

21. (a) Rykowski A, Branowska D, Kielak J. A novel one-pot synthesis of annulated 2,2′-bipyridine ligands by inverse electron demand Diels-Alder reaction of 5,5′-bi-1,2,4-triazines. Tetrahedron Lett. 2000;41:3657–9. doi:10.1016/S0040-4039(00)00436–6; (b) Branowska D, Rykowski A. Application of 1-vinylimidazole in Diels-Alder reaction of 5,5′-bi-1,2,4-triazines. Synlett. 2002:1892–4. doi:10.1055/s-2002-34880; (c) Branowska D, Kielak J. A facile synthesis of annulated 2,2′-bipyridine ligands with alkylsulfanyl and alkylsulfonyl substituents in the 6 and 6′ positions. Pol J Chem. 2003;77:1149–55. (d) Kozhevnikov DN, Kozhevnikov VN, Nikitina TV, Rusinov VL, Chupakhin ON, Neunhoeffer H. Synthesis of functionalised bipyridines by sequential nucleophilic substitution of hydrogen and cycloaddition in 1,2,4-triazine rings. Mendeleev Commun. 2002;12:30–2. doi:10.1016/j.mencom.2013.05.007; (b) Kopchuk DS, Kovalev IS, Khasanov AF, Zyryanov GV, Slepukhin PA, Rusinov VL, Chupakhin ON. A rational protocol for the synthesis of 1-(2-pyridyl)isoquinolines. Mendeleev Commun. 2013;23:142–4. doi:10.1016/j.mencom.2013.05.007; (b) Kopchuk DS, Nikonov IL, Zyryanov GV, Kovalev IS, Rusinov VL, Chupakhin ON. Preparation of 3-cyano-1-(2-pyridyl)isoquinolines by using aryne intermediates. Chem Heterocycl Compd. 2014;50:907–10. doi:10.1007/s10593-014-1545-9; (c) Kopchuk DS, Nikonov IL, Khasanov AF, Giri K, Santra S, Kovalev IS, Nosova EV, Gundala S, Venkatapuram P, Zyryanov GV, Majee A, Chupakhin ON. Studies on the interactions of 5-R-3-(2-pyridyl)-1,2,4-triazines with arynes: inverse demand aza-Diels-Alder reaction versus aryne-mediated domino process. Org Biomol Chem. 2018;16:5119–31. doi:10.1039/C8OB00847G