Polyhedron 77 (2014) 89–95

Contents lists available at ScienceDirect

Polyhedron

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

Lower rim substituted *p*-*tert*-butyl-calix[4]arene. Part 17. Synthesis, extractive and ionophoric properties of *p*-*tert*-butylcalix[4]arene appended with hydroxamic acid moieties

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ARTICLE INFO

Article history:
Received 30 January 2014
Accepted 8 April 2014
Available online 18 April 2014

Keywords:
Calix[4]arenes
Hydroxamic acids
Extraction
Ion-selective electrodes
Heavy metals

ABSTRACT

The synthesis and characterization of four *p*-*tert*-butylcalix[4]arene-hydroxamic acids are reported. The dependence of the metal ion binding, assessed by liquid–liquid extraction of the metal nitrates from water into dichloromethane in individual and competitive experiments, on the ligand structure, is presented. The results showed that those ligands could be successfully used in separation process of transition and heavy metals often present together. Two of the ligands were used as active materials in Pb-ion-selective membrane electrodes. The characteristics of these electrodes, in particular their selectivity coefficients for Pb^{2+} over other metal ions, are discussed.

1. Introduction

Naturally occurring compounds possessing hydroxamic acid moieties, known as siderophores, are produced by fungi and bacteria and act as sequestering agents for Fe^{3+} incorporation into microorganisms [1]. Their excellent binding properties found biomedical application in removal of Fe^{3+} and Al^{3+} from the body. It has been reported that siderophores show affinity also for other bivalent metal cations such as Pb^{2+}, Cu^{2+} or Ni^{2+} as well as UO_2^{2+} [1]. Calixarenes appended with hydroxamic acid groups could be regarded as synthetic siderophores and were mainly tested in solvent extraction experiments. They occurred to be excellent uranophiles [2–4], although they may efficiently extract transition and precious metal cations such as Fe^{3+}, Cu^{2+}, Zn^{2+}, Ni^{2+} and Pd^{2+} as well [5,6]. Solid-phase extraction of heavy metal ions using immobilized calix[4]arene-hydroxamic acids was also reported [7,8].

Heavy metals such as lead, cadmium, copper, nickel, cobalt, zinc or others, are present in our environment, mainly in wastewaters coming from various industries. These metals are easily accumulated in the human body, causing serious health disorders such as kidney and liver dysfunction, respiratory problems and bone disease. Therefore, the level of these toxic metals in natural and wastewaters needs to be monitored and controlled. However, the direct determination of their concentration level is frequently not sufficiently sensitive and the removal and separation of metal ions from their mixture is necessary.

Removal and separation of toxic heavy metals reduces the environmental impact and if they can be recovered in an economical way, it may generate some revenue for the industries. Therefore, the separation of metal ions, often present together, like Pb(II) and Cd(II) or Cu(II), Zn(II) and Ni(II), is a very important and challenging task and requires more and more selective ligands [9–11].

In this paper, we present the synthesis, characterization, extractive and ionophoric properties of four *p*-*tert*-butylcalix[4]arene hydroxamic acid derivatives (Fig. 1), among which, ligand **1** is reported here for the first time. These ligands differ by the number of functional groups attached to the calixarene framework (three or four arms) and by the substituents on the nitrogen atoms (R = H for **1** and **3**, R = CH_3 for **2** and **4**). Such structural changes are expected to influence binding properties of these compounds. Extraction experiments were carried out in individual and competitive conditions to evaluate the ability of these compounds to selectively separate heavy metal ions.

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http://dx.doi.org/10.1016/j.poly.2014.04.009
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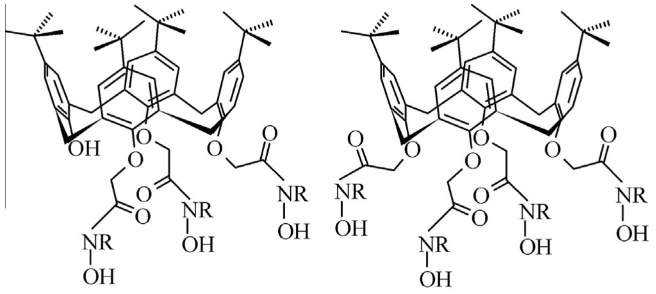

1 R = H **3** R = H

2 R = CH_3 **4** R = CH_3

Fig. 1. Chemical structures of the *p-tert*-butylcalix[4]arene hydroxamic acids synthesized and studied in this work.

Functionalized calixarenes play an important role as ionophores in the field of chemical sensors [12–14]. In the previous paper, ligands **2** and **4** were preliminary tested as Pb-ionophores in ion-selective membrane electrodes (ISEs) showing promising properties [15]. In this work, the results of the continued studies in this field are presented.

2. Experimental

2.1. General

TLC was performed on silica gel plates Merck 60 F_{254}. Melting points were measured and are uncorrected. ^{1}H NMR spectra were recorded in DMSO on a Varian instrument (200 or 500 MHz). IR spectra were obtained on a Mattson Genesis II spectrometer. Elemental analyses were performed on a Carlo Erba Instrument CHNS EA 1108-Elemental analyzer. The absorbances were measured by atomic absorption spectrometry with an air-acetylene flame (Varian-55).

The calibration curves were obtained by measuring the absorbance of several samples of known metal cation concentration under the same conditions as the unknown. Therefore, the metal concentration of the unknown sample could be calculated.

The EMF measurements were done on a 16 – channel LAWSON LAB potentiometer (16 EMF, USA).

2.2. Chemicals

p-tert-Butylcalix[4]arene, ethylbromoacetate, ethylchloroformate, triethylamine, DMSO, BaO, $Ba(OH)_2.8H_2O$, *N*-hydroxylamine hydrochloride ($NH_2OH.HCl$), *N*-methylhydroxylamine hydrochloride ($CH_3NHOH{\cdot}HCl$) were purchased from Aldrich; CH_3COOH and CH_3COONa were purchased from Prolabo and Merck, respectively.

For extraction experiments, the metal salts: $Ni(NO_3)_2{\cdot}6H_2O$, $Zn(NO_3)_2{\cdot}6H_2O$ (Fluka, purum), $Pb(NO_3)_2$, $Cd(NO_3)_2{\cdot}4H_2O$, $Fe(NO_3)_3{\cdot}H_2O$ (Merck, p.a.), $Cu(NO_3)_2{\cdot}3H_2O$ (Prolabo) and $Co(NO_3)_2{\cdot}6H_2O$ (Strem Chemicals) (analytical grade) were dried under vacuum at room temperature before use.

Poly(vinylchloride) (PVC, high molecular fraction), *o*-nitrophenyloctyl ether (NPOE) and the lipophilic salt, potassium tetrakis(*p*-chlorophenyl)borate (KT*p*ClPB), were purchased from Fluka (Selectophore). All aqueous salt solutions used for ISE studies: NaCl, KCl, $CaCl_2$, $ZnCl_2$, $CdCl_2$ (POCh all p.a. grade) and $Pb(NO_3)_2$ and $Cu(NO_3)_2$ (Aldrich) were prepared using ultrapure water from a Hydro-lab (RO) station (conductivity below 0.1 $\mu S\ cm^{-1}$).

The reagent grade organic solvents, dichloromethane (Fluka Analytical), ethyl ether (Fluka Analytical), acetone (Riedel-de-Haën), ethyl alcohol (Carlo Erba) were used without further purification. Tetrahydrofuran (THF) p.a. (from POCh) was dried and freshly distilled before use. Dimethylformamide (DMF) (from POCh) used in reactions was dried before use.

2.3. Synthesis

The four calix[4]arene-hydroxamic acids were prepared *via* the so-called mixed anhydrides method [16]. The intermediate compounds **I**–**IV** (Schemes 1 and 2) were synthesized according to the known procedures [17–19].

The tris-substituted calix[4]arene-hydroxamic acids (**1** and **2**) were prepared as follows (Scheme 1): calix[4]arene-triscarboxylic acid (**II**) was dissolved in dry CH_2Cl_2 (10 mL) and the solution was stirred and cooled to −10 °C. Subsequently, 3.2 equivalents of NEt_3 and 3.2 equivalents of ethyl chloroformate were added. The solution was stirred at −10 °C for 30 min. and then 18 equivalents of an appropriate hydroxylamine hydrochloride ($NH_2OH.HCl$ or $CH_3NHOH.HCl$, respectively) in 5 mL of CH_2Cl_2 were added. Before introducing amine hydrochloride to the reaction mixture, it was released from its hydrochloride form by adding the same equivalent of NEt_3. After 1 h, the mixture was diluted with CH_2Cl_2 (15 mL), washed with water (15 mL), then with 0.1 mol L^{-1} HCl (15 mL) and again with water (15 mL). The water phase was extracted twice with CH_2Cl_2 (30 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was crystallized from CH_2Cl_2/Et_2O mixture to give the pure products.

The tetrakis-substituted compounds (**3** and **4**) were prepared similarly by reacting calix[4]arene-tetra-carboxylic acid (**IV**) with 4.2 equivalents of ethyl chloroformate and 4.2 equivalents of triethyl amine. Subsequently, 24 equivalents of an appropriate hydroxylamine hydrochloride ($NH_2OH.HCl$ or $CH_3NHOH.HCl$, respectively) were added (Scheme 2).

2.3.1. 25-hydroxy-26, 27, 28-tris(N-hydroxycarbamoylmethoxy)-p-tert-butylcalix[4]arene (1)

$C_{50}H_{65}O_{10}N_3$; M.W. = 868.2 g/mol; m.p. = 188–190 °C; yield: 76%; IR ν_{max} (C═O) 1645 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): *cone* conformation, δ [ppm]: 0.96 (s, 18H, C–$(CH_3)_3$); 1.20 (s, 9H, C–$(CH_3)_3$); 1.22 (s, 9H, C–$(CH_3)_3$); 3.30 (d, 2H, Ar–CH_2–Ar, J = 13.67 Hz); 4.26 (d, 2H, Ar–CH_2–Ar, J = 13.67 Hz); 4.40 (d, 2H, Ar–CH_2–Ar, J = 13.19 Hz); 4.45 (d, 2H, Ar–CH_2–Ar, J = 13.19 Hz); 4.22 (s, 2H, –O–CH_2–CO); 4.41 (s, 4H, –O–CH_2–CO); 6.78 (s, 2H, Ar–*H*); 6.91 (s, 2H, Ar–*H*); 7.07 (s, 2H, Ar–*H*); 7.20 (s, 2H, Ar–*H*); 7.10 (s, 1H, N–*H*); 7.24 (s, 2H, N–*H*); 9.09 (s, 1H, O–*H*); 10.53 (s, 1H, O–*H*); 10.83 (s, 2H, O–*H*).

Experimental *Anal.* Calc. for $C_{50}H_{65}O_{10}N_3{\cdot}2H_2O$: C, 66.36; H, 7.63; N, 4.64. Found: C, 66.81; H, 7.45; N, 3.34%.

2.3.2. 25-Hydroxy-26,27,28-tris(N-methyl, N-hydroxycarbamoylmethoxy)-p-tert-butylcalix[4]arene (2)

$C_{53}H_{71}O_{10}N_3$; M.W. = 910.2 g/mol; m.p. = 217–221 °C; yield: 79%; IR ν_{max} (C═O) 1650 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): *cone* conformation, δ [ppm]: 0.94 (s, 18H, C–$(CH_3)_3$); 1.17 (s, 18H, C–$(CH_3)_3$); 3.14 (s, 9H, –N–CH_3); 3.18 (d, 2H, Ar–CH_2–Ar, J = 12.7 Hz); 3.22 (d, 2H, Ar–CH_2–Ar, J = 12.7 Hz); 4.37 (d, 2H, Ar–CH_2–Ar, J = 12.7 Hz); 4.54 (d, 2H, Ar–CH_2–Ar, J = 12.7 Hz); 4.95 (s, 6H, –O–CH_2–CO); 6.70 (s, 2H, Ar–*H*); 6.81 (s, 2H, Ar–*H*); 6.94 (s, 2H, Ar–*H*); 7.02 (s, 2H, Ar–*H*); 9.70 (s, 1H, O–*H*); 9.84 (s, 3H, O–*H*).

Experimental *Anal.* Calc. for $C_{53}H_{71}O_{10}N_3{\cdot}2H_2O$: C, 67.22; H, 7.93; N, 4.44. Found: C, 67.72; H, 7.70; N, 4.48%.