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Synthesis and characterization of heteroarylthio derivatives of 5,17-di-*tert*-butyl-11,23-diamido-25,27-diprotected calix[4]arene

Abstract: A series of 2-pyridylthio and 2-pyrimidinylthio derivatives of calix[4]arene have been synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR and MS.

Keywords: 4,6-dimethyl-2-pyrimidinethiol; diprotected calix[4]arenes; 2-pyridinethiol.

Introduction

In recent years, a variety of metal complexing ligands containing a calix[4]arene moiety have been designed and synthesized [1–5]. The complexation and extraction abilities of calix[4]arene derivatives appear to be highly dependent on the category and number of donor atoms and also on the conformation of the calix[4]arene backbone. Since Izatt and his colleagues [6] first reported the synthesis of calixarene ligands for the transport of alkali metal cations, many calix[4]arenes containing oxygen donor functions, such as ether, ester, amide and ketonic groups, have been synthesized as ligands for the main metal ions including Na^+, K^+, Ca^{2+}, Cs^+ [7–10]. The binding properties of calix[4]arene ligands bearing sulfur, nitrogen or selenium to the transition metal and soft metal ions have also been studied [11–14]. Hence, the introduction of different donor atoms and functional groups into calix[4]arene framework, to afford additional bonding sites to different metal ions and to improve the cation extraction capabilities of the host calix[4]arene, is of interest.

In this paper, we describe the design and synthesis of novel calix[4]arene derivatives bearing amido functions and heterocyclic groups as potential binding sites for the chemically and biologically important metal ions (Scheme 1).

Results and discussion

Compounds **1**–**3** were prepared following the literature procedures [15]. In the nitration step, the yield of the diprotected calix[4]arene with benzyl group at lower rim was lower than that of the ethyl and *n*-butyl derivatives, in agreement with the literature suggestion [16]. Dinitro derivatives were reduced to diamino derivatives **4** using $SnCl_2 \cdot 2H_2O$ in refluxing ethanol in almost quantitative yield. Dibromoacetylamino derivatives **5** were obtained by the reaction of bromoacetyl bromide with the appropriate diamino calix[4]arene in the presence of triethylamine in dichloromethane at room temperature according to the similar literature preparation [13]. Compounds **5** were then allowed to react with 2-pyridinethiol or 4,6-dimethyl-2-pyrimidinethiol in refluxing ethanol in the presence of KOH presented to give the target compounds **6** and **7**. The structural assignment for all new compounds was based on ESI-MS, ^{1}H NMR, ^{13}C NMR and IR spectroscopic analysis. The conformational characteristics of calix[4]arenes were conveniently estimated by ^{1}H and ^{13}C NMR spectroscopy [17, 18]. ^{1}H and ^{13}C NMR data show that compounds **6** and **7** exist in a single cone conformation. In particular, in their ^{1}H NMR spectra, a typical AB pattern is observed for methylene bridge $ArCH_2Ar$ protons and there is a $\Delta\delta$ separation of approximately 1 ppm between the *exo* and *endo* signals of geminal protons. Furthermore, the coupling constant for the splitting of $ArCH_2Ar$ protons is approximately 13 Hz. In the ^{13}C NMR spectra, the chemical shifts of the pertinent carbon atoms for the $ArCH_2Ar$ groups are observed near 32 ppm. These data are fully consistent with the conclusion that all these compounds adopt a single cone conformation.

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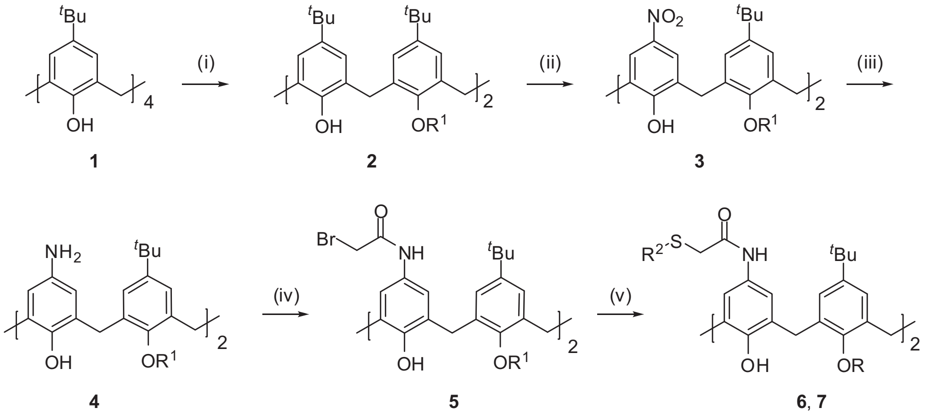

6a: R^1 = Et, R^2 = 2-pyridyl
6b: R^1 = ^{n}Bu, R^2 = 2-pyridyl
6c: R^1 = Bn, R^2 = 2-pyridyl
7a: R^1 = Et, R^2 = 4,6-dimethyl-2-pyrimidinyl
7b: R^1 = ^{n}Bu, R^2 = 4,6-dimethyl-2-pyrimidinyl
7c: R^1 = Bn, R^2 = 4,6-dimethyl-2-pyrimidinyl

Scheme 1 Reagents and conditions: (i) K_2CO_3, alkyl halide, MeCN, reflux 18 h; (ii) HNO_3, acetic acid, dichloromethane, room temperature, 6 h; (iii) $SnCl_2$, EtOH, reflux 16 h; (iv) bromoacetyl bromide, triethylamine, dichloromethane, room temperature; (v) KOH, 2-pyridinethiol or 4,6-dimethyl-2-pyrimidinethiol, ethanol, reflux 6 h.

Experimental

Melting points were measured on a Yanagimoto MP-500 apparatus and are uncorrected. The FT-IR spectra (KBr pellets) were measured on a BIO-RAD FTS3000 spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a Varian Inova 500 MHz and 125 MHz, respectively, at 298 K. Mass spectra were recorded on a LCQ Advantage MAX spectrometer. All reagents were commercially available and purified by standard methods prior to use. The synthesis of compounds 4-*tert*-butyl-calix[4]arene (**1**), 5,11,17,23-tetra-*tert*-butyl-25,27-diprotected calix[4]arene (**2**), 5,17-di-*tert*-butyl-11,13-dinitro-25,27-diprotected calix[4]arene (**3**) and 5,17-di-*tert*-butyl-11,13-diamino-25,27-diprotected calix[4]arene (**4**) have been described in the literature previously [15].

Synthesis of compounds 5

A solution of bromoacetyl bromide (2.2 mmol) in 20 mL CH_2Cl_2 was added dropwise over a period of 40 min to a solution of **4** (1.0 mmol) and 1.0 mmol of triethylamine in CH_2Cl_2 (20 mL) at room temperature and the mixture was stirred for 4 h. Water (50 mL) was then added and the aqueous layer was extracted with 100 mL CH_2Cl_2. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator. The residue was purified by silica gel column chromatography eluting with EtOAc/petroleum ether.

5,17-Di-*tert*-butyl-11,23-bis(bromoacetylamino)-25,27-diethoxycalix[4]arene (**5a**) Colorless solid; yield 84%; mp 235–239°C; IR: 3432, 2959, 2927, 2870, 1655, 1482, 1196, 1108 cm^{-1}; ^{1}H NMR: δ 8.28 (s, 2H), 7.86 (s, 2H), 7.19 (s, 4H), 6.95 (s, 4H), 4.31 (d, J = 13 Hz, 4H), 3.98 (b, 8H), 3.34 (d, J = 13 Hz, 4H), 1.71 (m, 6H), 1.09 (s, 18H); ^{13}C NMR: δ 163.0, 150.8, 150.4, 147.8, 132.9, 129.4, 128.6, 126.0, 120.8, 76.8, 34.4, 32.4, 31.9, 31.5, 19.6. ESI-MS: Calcd for $C_{44}H_{52}Br_2N_2O_6$: m/z 864.7, found: m/z 865.8 (M+1)$^+$.

5,17-Di-*tert*-butyl-11,23-bis(bromoacetylamino)-25,27-dibutoxycalix[4]arene (5b) Colorless solid; yield 87%; mp 231–236°C; IR: 3399, 2960, 2931, 2871, 1656, 1483, 1195, 1106 cm^{-1}; ^{1}H NMR: δ 8.29 (s, 2H), 7.81 (s, 2H), 7.20 (s, 4H), 6.96 (s, 4H), 4.32 (d, J = 13 Hz, 4H), 4.00 (m, 8H), 3.24 (d, J = 13 Hz, 4H), 2.04 (m, 4H), 1.70–1.78 (m, 4H), 1.11 (m, 24H); ^{13}C NMR: δ 162.9, 150.8, 150.4, 147.8, 132.9, 129.4, 128.6, 126.0, 120.8, 76.0, 34.4, 32.4, 31.9, 31.5, 30.0, 19.6, 14.3. ESI-MS: Calcd for $C_{48}H_{60}Br_2N_2O_6$: m/z 920.8, found: m/z 921.8 (M+1)$^+$.

5,17-Di-*tert*-butyl-11,23-bis(bromoacetylamino)-25,27-dibenzyloxycalix[4]arene (5c) Colorless solid; yield 86%; mp 216–223°C; IR: 3390, 2960, 2867, 1662, 1481, 1248, 1106 cm^{-1}; ^{1}H NMR: δ 7.90 (s, 2H), 7.61 (m, 4H), 7.55 (s, 2H), 7.38 (m, 6H), 7.20 (s, 4H), 6.87 (s, 4H), 5.02 (s, 4H), 4.24 (d, J = 13 Hz, 4H), 4.01 (s, 4H), 3.29 (d, J = 13 Hz, 4H), 1.00 (s, 18H); ^{13}C NMR: δ 162.7, 150.7, 150.1, 147.7, 129.8, 129.8, 129.0, 128.8, 118.9, 136.8, 132.2, 127.6, 125.9, 123.2, 120.7, 77.9, 34.1, 31.9, 31.7, 31.3. ESI-MS: Calcd for $C_{54}H_{56}Br_2N_2O_6$: m/z 988.8, found: m/z 990.0 (M+1)$^+$.

Synthesis of compounds 6 and 7

KOH (5.5 mmol) was added to a solution of pyridine-2-thiol or pyrimidine-2-thiol (5.5 mmol) in ethanol (30 mL) and the suspension was stirred at 50°C until a solution was formed. Then, the appropriate bis(bromoacetylamino)-calix[4]arene **5** (2.5 mmol) was added and the mixture was stirred under reflux for an additional 6 h. The solvent was removed under reduced pressure and the residue was taken up in ethyl acetate (50 mL) and washed with brine (60 mL) three times. After drying with anhydrous magnesium sulfate, ethyl acetate was removed and the crude product was purified by flash chromatography eluting with a mixture of petroleum ether (bp 60–90°C) and ethyl acetate.

5,17-Di-*tert*-butyl-11,23-bis[(2-pyridylthio)acetylamino]-25,27-diethoxycalix[4]arene (6a) Colorless solid; yield 80%; mp 259–261°C; IR: 3441, 2927, 2845, 1679, 1565, 1488, 1198, 1028 cm^{-1}; ^{1}H NMR: δ 9.51 (s, 2H), 8.48 (s, 2H), 8.45 (d, *J* = 5 Hz, 2H), 7.48 (t, *J* = 5.5 Hz, 2H), 7.20 (d, *J* = 5 Hz, 2H), 7.07 (s, 4H), 7.04 (t, *J* = 5.5 Hz, 2H), 6.99 (s, 4H), 4.32 (d, *J* = 13 Hz, 4H), 4.12 (m, 4H), 3.80 (s, 4H), 3.30 (d, *J* = 13 Hz, 4H), 1.70 (t, *J* = 7.5 Hz, 6H), 1.11 (s, 18H); ^{13}C NMR: δ 167.6, 158.3, 150.5, 136.9, 149.0, 147.7, 134.0, 130.7, 130.1, 126.0, 122.8, 120.6, 120.2, 72.2, 35.1, 34.3, 32.1, 31.5, 15.6; ESI-MS: Calcd for $C_{54}H_{60}N_4O_6S_2$: m/z 924.4, found: m/z 925.4 (M+1)$^+$.

5,17-Di-*tert*-butyl-11,23-bis[(2-pyridylthio)acetylamino]-25,27-dibutoxycalix[4]arene (6b) Colorless solid; yield 79%; mp 259–263°C; IR: 3432, 2962, 2876, 1668, 1559, 1482, 1414, 1242, 1031 cm^{-1}; ^{1}H NMR: δ 9.47 (s, 2H), 8.45 (d, *J* = 5 Hz, 2H,), 8.43 (s, 2H), 7.49 (t, *J* = 5.5 Hz, 2H), 7.21 (d, *J* = 5 Hz, 2H), 7.07 (s, 4H), 7.05 (t, *J* = 5.5 Hz, 2H), 6.99 (s, 4H), 4.32 (d, *J* = 13 Hz, 4H), 4.12 (m, 4H), 3.81 (s, 4H), 3.30 (d, *J* = 13 Hz, 4H), 2.03 (m, 4H), 1.75–1.78 (m, 4H), 1.28 (m, 6H), 1.11 (s, 18H); ^{13}C NMR: δ 167.6, 158.3, 149.0, 137.0, 120.6, 150.5, 147.7, 134.0, 130.7, 130.1, 126.0, 122.8, 120.3, 72.2, 35.1, 34.4, 32.1, 31.8, 31.5, 20.4, 15.6. ESI-MS: Calcd for $C_{58}H_{68}N_4O_6S_2$: m/z 980.5, found: m/z 981.4 (M+1)$^+$.

5,17-Di-*tert*-butyl-11,23-bis[(2-pyridylthio)acetylamino]-25,27-dibenzyloxycalix[4]arene (6c) Colorless solid; yield 70%; mp 107–109°C; IR: 3369, 2957, 2853, 1682, 1560, 1481, 1454, 1286, 1124 cm^{-1}; ^{1}H NMR: δ 9.48 (s, 2H), 8.46 (d, *J* = 5 Hz, 2), 7.72 (s, 2H), 7.58–7.60 (m, 5H), 7.47 (t, *J* = 5.5 Hz, 2H), 7.38 (m, 5H), 7.21 (d, *J* = 5 Hz, 2H), 7.11 (s, 4H), 7.03 (t, *J* = 5.5 Hz, 2H), 6.96 (s, 4H), 5.00 (s, 4H), 4.21 (d, *J* = 13 Hz, 4H), 3.84 (s, 4H), 3.22 (d, *J* = 13 Hz, 4H), 1.02 (s, 18H); ^{13}C NMR: δ 167.3, 158.3, 150.0, 136.7, 122.6, 149.5, 148.8, 147.5, 132.8, 129.9, 128.9, 125.8, 119.9, 128.9, 128.1, 78.2, 34.9, 34.1, 31.8, 31.3. ESI-MS: Calcd for $C_{64}H_{64}N_4O_6S_2$: m/z 1048.4, found: 1049.4 (M+1)$^+$.

5,17-Di-*tert*-butyl-11,23-bis[(4,6-dimethyl-2-pyrimidinylthio)acetylamino]-25,27-diethoxycalix[4]arene (7a) Colorless solid; yield 76%; mp 142–144°C; IR: 3441, 2927, 2845, 1689, 1565, 1488, 1198, 1028 cm^{-1}; ^{1}H NMR: δ 8.96 (s, 2H), 8.39 (s, 2H), 7.17 (s, 4H), 6.96 (s, 4H), 6.78 (s, 2H), 4.31(d, *J* = 13 Hz, 4H), 4.11 (m, 4H), 3.84 (s, 4H), 3.29 (d, *J* = 13 Hz, 4H), 2.47 (s, 12H), 1.68 (t, *J* = 7.5 Hz, 6H), 1.11 (s, 18H); ^{13}C NMR: δ 170.3, 167.1, 167.1, 149.3, 150.5, 147.7, 133.7, 130.4, 129.9, 126.0, 120.2, 116.7, 72.2, 35.8, 34.3, 32.1, 31.5, 24.2, 15.5. ESI-MS: Calcd for $C_{56}H_{66}N_6O_6S_2$: m/z 982.5, found: m/z 1005.6 (M+Na)$^+$.

5,17-Di-*tert*-butyl-11,23-bis[(4,6-dimethyl-2-pyrimidinylthio)acetylamino]-25,27-dibutoxycalix[4]arene (7b) Colorless solid; yield 81%; mp 128–131°C; IR: 3329, 2960, 2872, 1686, 1584, 1483, 1266, 1196 cm^{-1}; ^{1}H NMR: δ 8.97 (s, 2H), 8.28 (s, 2H), 7.11 (s, 4H), 6.92 (s, 4H), 6.78 (s, 2H), 4.28 (d, *J* = 13 Hz, 4H), 3.96 (t, *J* = 7 Hz, 4H), 3.86 (s, 4H), 3.28 (d, *J* = 13 Hz, 4H), 2.47 (s, 12H), 2.05 (m, 4H), 1.67–1.69 (m, 4H), 1.26 (m, 6H), 1.07 (s, 18H); ^{13}C NMR: δ 170.3, 167.6, 167.0, 150.5, 149.8, 147.5, 133.2, 130.0, 129.3, 126.0, 120.3, 116.7, 76.8, 35.6, 34.3, 32.3, 32.0, 31.5, 24.2, 19.5, 14.3. ESI-MS: m/z: Calcd for $C_{60}H_{74}N_6O_6S_2$: m/z 1038.5, found: m/z 1056.5 (M+H_2O)$^+$.

5,17-Di-*tert*-butyl-11,23-bis[(4,6-dimethyl-2-pyrimidinylthio)acetylamino]-25,27-dibenzyloxycalix[4]arene (7c) Colorless solid; yield 81%; mp 115–118°C; IR: 3249, 2965, 2882, 1678, 1596, 1489, 1257, 1186 cm^{-1}; ^{1}H NMR: δ 9.16 (s, 2H), 7.60 (s, 2H), 7.59 (m, 5H), 7.37–7.38 (m, 5H), 7.13 (s, 4H), 6.92 (s, 4H), 6.83 (s, 2H), 5.00 (s, 4H), 4.22 (d, *J* = 13 Hz, 4H), 3.88 (s, 4H), 3.22 (d, *J* = 13 Hz, 4H), 2.47 (s, 12H), 1.01 (s, 18H); ^{13}C NMR: δ 170.5, 167.8, 167.1, 149.8, 150.9, 150.4, 148.5, 130.4, 130.1, 129.3, 128.5, 119.0, 137.4, 133.5, 128.6, 124.9, 124.2, 121.7, 76.3, 35.8, 34.6, 32.9, 32.0, 24.3. ESI-MS: Calcd for $C_{66}H_{70}N_6O_6S_2$: m/z 1106.5, found: m/z 1124.6 (M+H_2O)$^+$.

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