Novel synthesis of calix[n]arene amide supramolecular receptor

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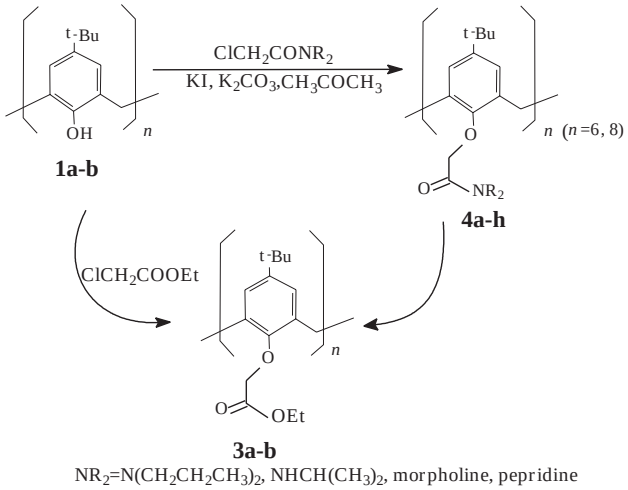
In the system of K_2CO_3/KI/acetone, eight *p*-tert-butylcalix[*n*]arene amide products (*n* = 6, 8) were prepared by the O-alkylation of calixarenes with *N, N*-dialkyl α-chloroacetamides in high yields (HNR_2 = dipropylamine, isopropylamine, pepridine, morphine). These amide products can also be synthesised by the amination reaction of the correspond ethyl calix[n]aryl acetates.

Keywords: calixarene, amide, ester, alkylation, supramolecular chemistry

Calixarenes are currently enjoying considerable interest in the field of supramolecular chemistry because their derivatives can form inclusion complexes with cations or with neutral molecules.[1] For this purpose calixarenes are readily converted into a wide variety of derivatives at the lower rim and the upper rim of the calix unit.[2] In past decades, *p*-tert-butylcalix[4]arenes have mostly been used as a platform for the preorganisation of the building site due to their small size,[3] while the larger calix[n]arenes (*n* =6, 8) appear more suitable to play the role of a molecular receptor and have attracted much attention in recent years.[4-5] Because of their importance as ionophores, the introduction of ester and amide groups in calix[4]arenes through the alkylation reaction has been studied in most detail and is being explored to larger calixarene system with more and more examples.[6] Our interest is to extend and to develop some new functionalized calix[*n*]arenes (*n* = 6, 8) to give a supramolecular system. In this study, we describe the synthesis of some amide derivatives of *p*-tert-butylcalix[*n*]arenes (*n* = 6, 8).

The general synthetic method to the tetrakisdiethylamide of *p*-tert-btuylcalix[4]arene,[7] which is probably one of the most studied calixarene ligands and other amide analogs,[8-10] is the o-alkylation reaction of calixarene using *N,N*-dialkyl α-chloroacetamide as alkylating reagent, which usually give satisfactory results. In our study we also chose this synthetic strategy. The alkylating reagents are *N*-alkyl or *N,N*-dialkyl chloroacetate **2a–d**, which were prepared from the reaction of chloroacetyl chloride with isopropylamine, dipropylamine, morphine and pepridine. As in the case of *p*-tert-butylcalix [4]arene, the alkylation reaction was carried out as follows: a mixture of *p*-butylcalix[*n*]arenes **1a–b** (*n* = 6, 8) and N-substituted chloroacetamide **2a–d** was refluxed in K_2CO_3/KI/acetone system for several days. In order to obtain completely alkylated amide products, at first the larger molar ratio of chloroacetamide must be used. Second, by adding some potassium iodide, the more reactive iodoacetamide was formed *in situ*, which accelerated the speed of the reaction. Third, a much longer reaction time is necessary. The reaction system was usually refluxed for more than five days, even if the *p*-tert-butylcalixarene had disappeared by (TLC monitor). After work up, the very pure completely-alkylated products **4a–h** were separated with little difficulty in good yields. Their structure was confirmed by their IR and ^{1}H NMR spectra. All eight amides products **4a–h** give very similar IR spectra with slight peak differences. In the IR spectra, the original OH absorption band at 3300–3600cm^{-1} in calixarenes **1a–b** disappeared; all compounds show one very strong band at 1642–1661cm^{-1}, due to the carbonyl absorption of amide. In their ^{1}H NMR spectra, the signal of the methylene bridge in the calix unit ($ArCH_2Ar$) usually shows one, rather broad peak; while the signal of OCH_2CO shows a multiple band, sometimes overlapping with the peaks of other group such as NCH_2 and OCH_2. Thus it is difficult to determine the conformation of the products. The tert-butyl group in **4e** and **4f** clearly shows two single peaks, which means the six or eight tert-butyls exist in different positions and indicates that more than one configuration isomers exist.[7] In amides **4a–d** the signal of the tert-butyl group overlaps heavily with the isopropyl group or propyl group and gives the mixed absorption peaks, which are difficult to assign. Unfortunately, no good quality crystals for X-ray structural analysis have been grown, precluding definitive structural determination. The study of these calixarene amides as ionophores and supermocular receptors is under way. Preliminary extraction experiments show that amide **4e** presents high extracting capability for Fe^{2+} and **4h** presents high selectivity for Na^+.



Scheme 1

Encouraged by our study of calix[4]resorcinarene amide derivatives, which can be easily synthesised by the direct amination of esters, we developed a second method for the preparation of *p*-tert-butylcalix[*n*]arene amides **4a–h**. The *p*-tert-butylcalix[*n*]arene **1a–b** were first alkylated with ethyl α-bromoacetate by the published method to yield the ethyl calix[*n*]aryl acetates **3a–b** (80–87%). The **3a** or **3b** compound was then refluxed with a large excess molar ratio of amine such as dipropylamine, isopropyiamine, morphine, and pepridine, respectively in a mixture of ethanol and toluene for about 24 hours. After workup the desired amide products **4a–h** were prepared in very high yields (80–96%), and gave the same characterisation data as for samples prepared by the first synthetic method. In our opinion, for the preparation of the calixarene amide derivatives this indirect two-step synthetic method is superior to the direct alkyation paths, which do not need to prepare *N, N*-dialkyl α-chloroacetamides.

Experimental

Melting points were taken on a hot-plate microscope apparatus and are not corrected. IR spectra were obtained on a Nicolet FT-IR 740 spectrometer (KBr disc). ^{1}H NMR spectra were recorded with a

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Bruker AV-600 spectrophotometer at 600 MHz with $CDCl_3$, as solvent and TMS as internal standard. Dipropylamine, isopropylamine, peperidine and morpholine are commercial chemical reagents and used as received. Solvents (acetone, alcohol and ether) were purified by standard techniques. *p*-tert-Butylcalix[*n*]arenas **1a–b** (*n* = 6, 8)[11], ethyl calix[*n*]aryl acetate **3a–b** (*n* = 6, 8)[12] and *N*, *N*-dialkyl α-chloroacetamides[13] **2a–d** were prepared according to the published methods. TLC monitored the reaction process.

General procedure for the alkylation of calixarenes with N, N-dialkyl a-chloroacetamides*:* A mixture of p-tert–butylcalix[*n*] arene **1a–b** (*n* = 6, 8, 1.0 mmol), K_2CO_3 (30.0 mmol, 4.19g) and KI (8.0 mmol, l.47g) in acetone (80ml) was heated to reflux for 2 hours under an atmosphere of dinigrogen. Then N, N-dialkyl chloroacetamide (24.0 mmol) was added by syringe. The suspension was refluxed for 5–6 days. The solid was removed by filtration. The orange solution was evaporated under reduced pressure to yield the oily residue, which was extracted twice with chloroform (60ml). The volatile material was removed again under reduced pressure and the residue was titrated with alcohol to give white solid, which was recrystallized with ethanol to afford the product.

5,11,17,23,29,35-hexakis(tert-butyl)-37,38,39,40,41,42-hexakis [N,N-dipropylaminocarbonyl]methoxycalix[6]arene **(4a)**: White solid, 79.3%. M.p. 251–253°C. IR : ν = 2964(vs), 2910(s), 2859(m), 1661(vs), 1471(s), 1358(m), 1182(s), 1089(m),1034(m) cm^{-1}. ^1H NMR: δ = 0.95–1.33 (m, t-Bu, CH_2CH_3, 114H); 3.97–4.39 (m, NCH_2, OCH_2, $ArCH_2Ar$, 48H); 6.83–7.15 (m, Ar-H,12H) ppm.

5,11,17,23,29,35,41,47-Octakis(tert-butyl)-49,50,51,52,53,54,55,56-octakis[N,N-dipropylaminocarbonyl]methoxycalix[8]arene **(4b)**: White solid, 56.6%. M.p. 264–266°C. IR : ν = 2964(s), 2929(vs), 2859(s), 1661(vs), 1478(s), 1365(m), 1203(s), 1119(m), 1055(m) cm^{-1}. ^1H NMR: δ = 0.97–1.27 (m, *t*-Bu, CH_2CH_3, 152H); 4.07–4.50 (m, NCH_2, OCH_2, $ArCH_2Ar$, 64H); 6.93–7.24 (m, Ar-H, 16H) ppm.

5,11,17,23,29,35-hexakis(tert-butyl)-37,38,39,40,41,42-hexakis [N-iso-propylaminocarbonyl]methoxycalix[6]arene **(4c)**: White solid, 80.4%. M.p. 253–255°C. IR : ν = 2957(s), 2858(m), 1654(vs), 1534(s), 1470(s), 1358(m), 1182(s), 1034(s) cm^{-1}. ^1H NMR: δ = 0.91–1.27 (m, *t*-Bu, $CH(CH_3)_2$, 90H); 3.63–4.44 (m, $CH(CH_3)_2$,OCH_2, $ArCH_2Ar$, 30H); 6.73–7.15 (m, NH, Ar-H, 18H) ppm.

5,11,17,23,29,35,41,47-Octakis(tert-butyl)-49,50,51,52,53,54,55,56-octakis[N-iso-propylaminocarbonyl]methoxycalix[8]arene **(4d)**: White solid, 71.4%. M.p. 254–256°C. IR : ν = 2957(s), 2858(m), 1647(vs), 1470(s), 1428(m), 1104(s), 1020(s) cm^{-1}. ^1H NMR: δ = 0.83–1.35 (m, *t*-Bu, $CH(CH_3)_2$, 120H); 3.61–3.68 (m, $CH(CH_3)_2$, 8H); 4.03–4.42 (m, OCH_2, $ArCH_2Ar$, 32H); 6.59 (m, NH, 8H); 6.87, 7.19 (s, s Ar-H,16H) ppm.

5,11,17,23,29,35-Octakis(tert-butyl)-37,38,39,40,41,42-hexakis [N-morpholinocarbonyl]methoxycalix[6]arene **(4e)**: White solid, 70.7%. M.p. 276–278°C. IR : ν = 2957(s), 2910(m), 2858(m), 1647(vs), 1470(s), 1428(m), 1266(m), 1182(m), 1104(s), 1020(s) cm^{-1}. ^1H NMR: δ = 0.89 (m, 27H, $C(CH_3)_3$); 1.30 (m, 27H, $C(CH_3)_3$); 2.70–3.00 (bs, 24H, $N(CH_2)_2$); 3.65–3.95 (m, 24H, $O(CH_2)_2$); 4.19 (s, 12H, $ArCH_2Ar$); 4.35-4.80 (br, 12H, OCH_2CO); 6.56–6.65 (m, 12H, ArH) ppm.

5,11,17,23,29,35,41,47-Octakis(tert-butyl)-49,50,51,52,53,54,55,56-octakis[N-morpholinocarbonyl]methoxycalix[8]arene **(4f)**: White solid, 76.3%. M.p. 275-276°C. IR : ν = 2957(s), 2910(m), 2865(m), 1661(vs), 1632(vs), 1477(s), 1358(m), 1111(s), 1020(m) cm^{-1}. ^1H NMR, δ = 0.85 (s, *t*-Bu, 36H); 1.34 (s, t-Bu, 36H); 3.74–4.67 (m, NCH_2CH_2O, $ArCH_2Ar$, OCH_2, 96H); 6.61, 7.22 (s, s, Ar-H, 16H) ppm. 4.35–4.80 (bs, 12H, OCH_2CO) ppm.

5,11,17,23,29,35-Octakis(tert-butyl)-37,38,39,40,41,42-hexakis [N-piperidinecarbonyl]methoxycalix[6]arene **(4g)**: White solid, 85.8%. M.p. 275–276°C. IR: ν = 2950(s), 2851(m), 1639(vs), 1470(s), 1435(s), 1358(m), 1245(m), 1182(s), 1006(s) cm^{-1}. ^1H NMR: δ = 1.26 (s, 54H, *t*-Bu); 1.53–1.61 (m, 12H, $CH_2\underline{CH_2}CH_2$); 2.61 (m, 24H, $CH_2CH_2CH_2$); 3.00–4.28 (m, 48H, NCH_2, $ArCH_2Ar$, OCH_2); 7.00-7.29 (m, 12H, Ar-H) ppm.

5,11,17,23,29,35,41,47-Octakis(tert-butyl)-49,50,51,52,53,54,55,56-octakis[N-pepridinecarbonyl]methoxycalix[8]arene **(4h)**: White solid, 95.8%. M.p. 258–260°C. 2950(s), 2851(m), 1639(vs), 1470(s), 1435(s), 1358(m), 1245(m), 1182(s), 1006(s) cm^{-1} ^1H NMR: δ =1.26 (br, 72H, *t*-Bu); 1.53–1.62 (m, 16H, $CH_2\underline{CH_2}CH_2$); 2.61 (m, 32H, $CH_2CH_2CH_2$); 3.00–4.30 (m, 64H,NCH_2, $ArCH_2Ar$, OCH_2,); 6.99–7.28 (m, 16H, Ar-H) ppm.

General procedure for the amination of ethyl calix[n]aryl acetate with amines: A solution of ethyl calix[n]aryl acetate **3a–b** (*n* = 6, 8, 0.50mmol) and amine (10ml) in ethanol (15ml) and toluene (15ml) was refluxed for 24 h under an atmosphere of dinitrogen. The organic solvent and excess of amine were removed under reduced pressure. The oily residue was titrated with alcohol to give a white solid, that was recrystallised with ethanol to afford the desired amide product, which give similar melting point and ^1H NMR data to that of the sample prepared by the alkylation method.

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