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# Synthesis and complexation properties of *N,N′*-bis(calix[4]arenoxyacetyl)hydrazine derivative

**Elena A. Alekseeva,* Aleksandr P. Luk'yanenko and Andrei I. Gren**

*A. V. Bogatsky Physico-Chemical Institute, National Academy of Sciences of Ukraine, 65080 Odessa, Ukraine.*
*Fax: +38 0482 65 2012; e-mail: Alyeksyeyeva@rambler.ru*

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**Heating of *p-tert*-butylcalix[4]arene bearing acethydrazide moiety at the lower rim in MeCN or Pr$^i$OH (EtOH) affords the corresponding *N,N′*-bis(calix[4]arenoxyacetyl)hydrazine derivative. The hydrazinolysis of mono(methoxycarbonylmethoxy)-*p-tert*-butylcalix[4]arene in benzene or refluxing biscalixarene hydrazide in benzene in the presence of hydrazine hydrate produces the mixture of 1,2- and 1,3-(*N,N′*-diacetylhydrazine)-*p-tert*-butylcalix[4]arenes.**

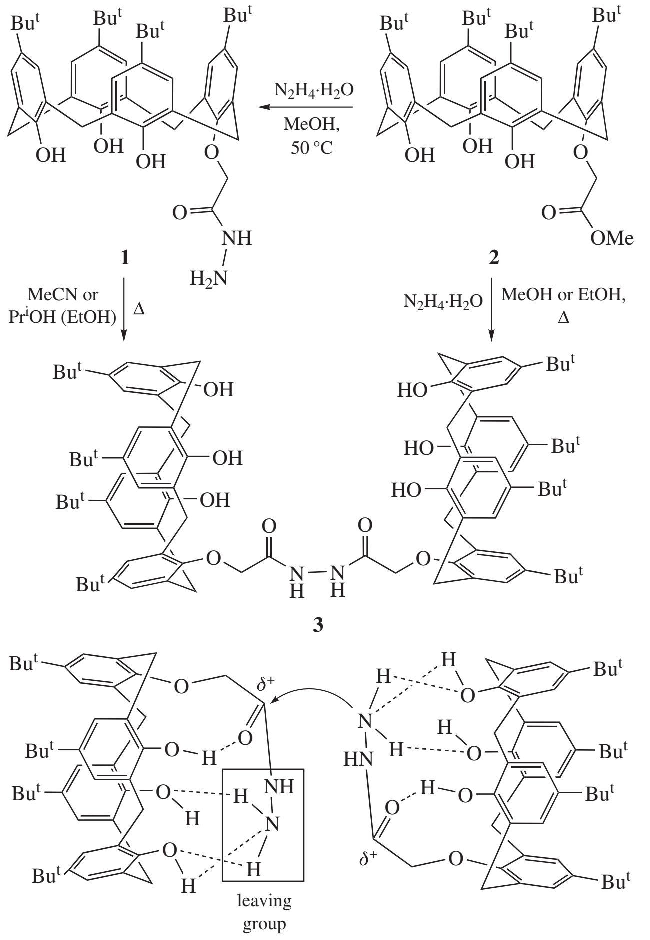
Calixarenes are the popular platforms for design of molecular receptors. Their modification with carbonyl oxygen and simultaneously with the soft donor atoms such as nitrogen brings about additional effective binding sites in these molecules.[1,2] Calix[4]arenes with various nitrogen-containing groups at the lower rim were prepared recently from acylhydrazide derivatives.[3–5] Synthesis and complexation properties of calix[4]arenes and thiacalix[4]arenes derivatized with four acylhydrazide groups were also described.[6–9]

However, calix[4]arenes bearing only one hydrazide group, which seem promising for the synthesis of other unsymmetrical nitrogen derivatives were not investigated. Herein, we report on the preparation of calix[4]arene having one acethydrazide moiety at the lower rim and some its properties.

The *p-tert*-butylcalix[4]arene derivative **1** (Scheme 1) was obtained by hydrazinolysis of the corresponding methyl ester **2** in methanol at 50 °C. Its formation was proved by FAB mass spectrometry in negative ions. All attempts to obtain pure compound **1** by recrystallization either from ethyl or isopropyl alcohols or MeCN (rather than column chromatography) led to another nitrogen containing compound which was identified by FAB mass spectrometry and $^1$H NMR spectroscopy as a hydrazide dimer **3** in which both calixarene moieties adopt cone conformation. The biscalixarene hydrazide **3** was also obtained in almost quantitative yield when hydrazinolysis of ester **2** was carried out in EtOH at higher temperature, or by refluxing of suspension of pure monohydrazide **1** in acetonitrile.

Noteworthy, such a dimerization is typical only of compounds with three unsubstituted OH groups at the lower rim. The prolonged refluxing of analogous 1,3-bis(hydrazinocarbonylmethoxy)-*p-tert*-butylcalix[4]arene derivative either in MeCN or Pr$^i$OH results in solidifying of the reaction mixture, whose mass spectrum exhibits signals with *m*/*z* within the high-mass region (over 1500). At the same time, no changes were observed in case of calixarenes with one or two $OCH_2C(O)NHNH_2$ groups, when the rest phenol hydroxyls are alkyl- or benzyl-etherified. Apparently, such a susceptibility of compound **1** to form dimer **3** can be caused by the participation of OH groups and hydrazide fragments in the intramolecular hydrogen bond that can increase the fugacity of the hydrazine group (see Scheme 1).

The hydrazinolysis of ester **2** in benzene with excess of hydrazine hydrate (30 equiv.) as well as refluxing of dimer **3** in benzene in the presence of few drops of hydrazine hydrate led to the mixture of two *N,N′*-diacylhydrazine derivatives **4** and **5** (1:3) in the distorted cone conformation of the calixarene moiety, and unsubstituted *p-tert*-butylcalix[4]arene (Scheme 2).[†] The mechanism of this reaction involving ether C–O bond cleavage is intriguing. Anyway we may admit, that basis hydrazine molecule plays main role in this process. Calixarene phenolic OH groups



**Scheme 1**

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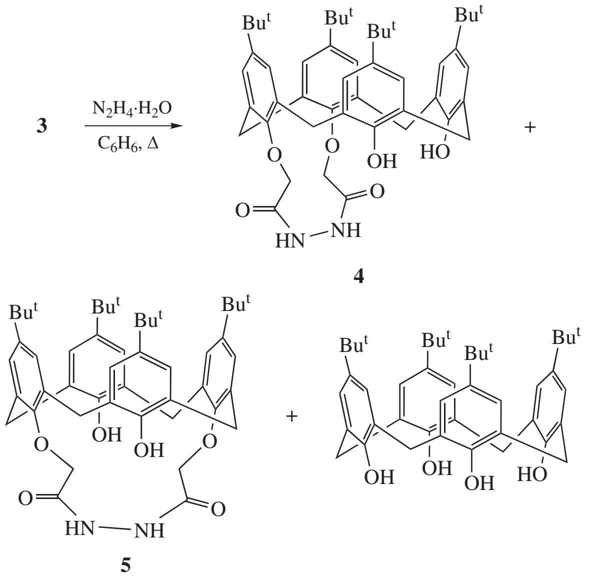
[†] $^1$H NMR spectra were recorded in $CDCl_3$ on a Bruker AVANCE DRX 500 (500 MHz) spectrometer, using TMS as internal standard. FAB-mass spectra were recorded on VG 70-70EQ with Xe atom beam (8 kV) using *m*-nitrobenzyl alcohol as a matrix. Ultraviolet titration experiments were performed on Specord M 40 and Hitachi U3210 spectrometers using $2\times10^{-5}$ M solutions of ligands in MeOH–$CHCl_3$ (5:1) and various concentrations of metal salts [NaCl, KCl, $SrCl_2$, $CuCl_2$, $ZnCl_2$, $NiCl_2$, $MgCl_2$, $FeCl_3$, $AgNO_3$, $Al(NO_3)_3$, $Pb(OAc)_2$] in MeOH–$CHCl_3$ (5:1). UV spectra of the mixtures undergo changes at 230–330 nm.



**Scheme 2**

participating in intramolecular hydrogen binding are attacked by base and then they are transformed into phenoxide anions. Therefore, the intramolecular Williamson reaction seems possible.

In order to consider the presence of 'soft' donor atoms in molecules of new receptors we examined the capability of calix[4]arenes **3** and **5** to coordinate at some metal cations by UV titration in methanol–chloroform (5:1) solutions. The resulting spectral changes were analyzed by SIRKO program.[10] The values of the corresponding stability constants, as log$\beta$, and stoichiometries of the complexes are given in Table 1.

**Table 1** Stability constants and stoichiometries of the complexes of ligands **3** and **5** with metal cations.

| Ligand | Cation, log$\beta$±0.01 (L:M ratio) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $Na^+$ | $K^+$ | $Ag^+$ | $Sr^{2+}$ | $Zn^{2+}$ | $Cu^{2+}$ | $Ni^{2+}$ | $Mg^{2+}$ | $Pb^{2+}$ | $Fe^{3+}$ | $Al^{3+}$ |
| **3** | 3.57<br>3.05<br>(1:2) | 4.28<br>4.87<br>(1:2) | 9.7<br>(1:1) | 5.86<br>(1:1) | 7.57<br>(1:1) | 6.22<br>(1:1) | 9.03<br>(1:1) | 3.88<br>(1:1) | 8.9<br>(1:1) | 10.8<br>(1:1) | 11.0<br>(1:1) |
| **5** | 4.05<br>(1:1) | 3.8<br>(1:1) | 8.4<br>(1:1) | 5.13<br>(1:1) | 7.05<br>(1:1) | 5.41<br>(1:1) | | 3.67<br>(1:1) | —[a] | —[a] | —[a] |

[a] No evidence changes in spectrum.

Contrary to our expectations, the polytopic properties were not discovered for biscalixarene **3** in the most cases with exception of the 1:2 complexes with sodium and potassium cations. Similar values of stability constants for complexes of both compounds **3** and **5** with Cu, Zn and Sr cations make us assume that *N*,*N'*-diacylhydrazine sites of calixarene molecule contributed mainly into the cation binding. The formation of ionic compounds in case of interaction of dimer **3** with triple-charged Fe and Al cations due to the replacement of protons of hydroxy groups with cation may cause more stability of the complexes, which was observed as relatively high stability constants. Such an assumption was confirmed by the appearance of peaks in the FAB mass spectra of complexes of calixarene **3** with $Al^{III}$ and $Fe^{III}$ cations corresponding to $[\mathbf{3}+M-1]$ and $[\mathbf{3}+M-2]$.

In conclusion, preparation of *N*,*N'*-diacylhydrazine-bridged calix[4]arene monomers and dimer represent an interesting case in chemistry of such a class of compounds. A high affinity of the compounds obtained to some transition metal cations and the possibility to form binuclear complex with alkali metal cations with participation of biscalixarene *N*,*N'*-diacylhydrazine make them promising ligands for practical purposes.

*Online Supplementary Materials*

Supplementary data associated with this article (synthesis and characteristics of compound **1**) can be found in the online version at doi:10.1016/j.mencom.2012.09.012.

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*Compound* **3**. *Method A*. $N_2H_4 \cdot H_2O$ (10 mmol, 0.5 ml) was added to a suspension of ester **2** (1 mmol, 0.72 g) in ethanol (50 ml). The mixture was refluxed for 5 h and cooled. The precipitate was filtered off, dissolved in $CHCl_3$ and washed with water (3×50 ml). After evaporation of the solvent, the crude product was crystallized from acetonitrile. Yield 90%.

*Method B*. Suspension of monohydrazide **1** (1 mmol, 0.72 g) in MeCN (50 ml) was refluxed for 15 min and cooled down. The precipitate which was an individual substance was filtered off and dried at 100–120 °C. Mp 305–307 °C. $^1$H NMR, $\delta$: 1.18 (s, 18 H, Bu$^t$), 1.21 (s, 36 H, Bu$^t$), 1.25 (s, 18 H, Bu$^t$), 3.42 (d, 4 H, $ArCH_2Ar$, *J* 13.4 Hz), 3.54 (d, 4 H, $ArCH_2Ar$, *J* 13.4 Hz), 4.26 (d, 4 H, $ArCH_2Ar$, *J* 14.4 Hz), 4.33 (d, 4 H, $ArCH_2Ar$, *J* 14.4 Hz), 4.82 (s, 4 H, $CH_2O$), 6.90 (d, 4 H, ArH), 7.02 (s, 4 H, ArH), 7.08 (d, 4 H, ArH), 7.10 (s, 4 H, ArH), 9.47 (s, 4 H, OH), 9.95 (s, 2 H, OH), 11.45 (s, 2 H, NH). Found (%): C, 78.40; H, 8.24; N, 2.05. Calc. for $C_{92}H_{116}O_{10}N_2$ (%): C, 78.37; H, 8.29; N, 1.99. FAB-MS, *m/z*: 1409 $(M+H)^+$.

*Compounds* **4** *and* **5**. Solution of ester **2** (1 mmol, 0.79 g) and $N_2H_4 \cdot H_2O$ (30 mmol, 1.25 ml) in benzene (100 ml) was refluxed for 10 h. The solution was washed with water (3×50 ml) and concentrated *in vacuo* to leave a residue which was dissolved in minimum $CHCl_3$. The precipitate of unsubstituted *p-tert*-butylcalix[4]arene was filtered off and the filtrate was concentrated. The individual products were separated by preparative TLC (MeOH–$CHCl_3$, 3:1) to afford **4** (15%) and **5** (37%). Alternatively, refluxing of **3** (0.35 mmol, 0.5 g) in benzene (20 ml) in the presence of few drops of $N_2H_4 \cdot H_2O$ for 30 min gave compound **5** as the main product.

For **4**. $^1$H NMR, $\delta$: 1.20 (s, 9 H, Bu$^t$), 1.23 (s, 9 H, Bu$^t$), 1.24 (s, 9 H, Bu$^t$), 1.25 (s, 9 H, Bu$^t$), 3.43 (d, 1H, $ArCH_2Ar$, *J* 13.45 Hz), 3.52 (d, 2 H, $ArCH_2Ar$, *J* 13.69 Hz), 4.13 (d, 1H, $ArCH_2Ar$, *J* 14.43 Hz), 4.18 (d, 1H, $ArCH_2Ar$, *J* 13.69 Hz), 4.29 (d, 2 H, $ArCH_2Ar$, *J* 13.94 Hz), 4.34 (d, 1H, $ArCH_2Ar$, *J* 13.45 Hz), 4.72 (s, 4 H, $OCH_2$), 7.02 (d, 2 H, ArH), 7.04 (d, 2 H, ArH), 7.08 (d, 1H, ArH), 7.1 (d, 1H, ArH), 7.12 (d, 2 H, ArH), 9.40 (br. s, 1H, OH), 9.48 (br. s, 1H, OH), 10.45 (s, 2 H, NH). Found (%): C, 75.71; H, 7.89; N, 3.74. Calc. for $C_{48}H_{60}N_2O_6$ (%): C, 75.76; H, 7.95; N, 3.68. FAB-MS, *m/z*: 761 $(M+1)^+$.

For **5**. $^1$H NMR, $\delta$: 1.21 (s, 9 H, Bu$^t$), 1.23 (s, 18 H, Bu$^t$), 1.26 (s, 9 H, Bu$^t$), 3.58 (d, 4 H, $ArCH_2Ar$, *J* 13.69 Hz), 4.19 (d, 4 H, $ArCH_2Ar$, *J* 13.45 Hz), 4.69 (s, 2 H, $OCH_2$), 4.77 (s, 2 H, $OCH_2$), 6.99 (d, 2 H, ArH), 7.04 (s, 2 H, ArH), 7.08 (d, 2 H, ArH), 7.1 (s, 2 H, ArH), 9.51 (br. s, 2 H, OH), 10.37 (br. s, 2 H, NH). Found (%): C, 75.70; H, 7.90; N, 3.74. Calc. for $C_{48}H_{60}N_2O_6$ (%): C, 75.76; H, 7.95; N, 3.68. FAB-MS, *m/z*: 761 $(M+1)^+$.

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