Journal of Inclusion Phenomena and Macrocyclic Chemistry (2007) 58:169–172
DOI 10.1007/s10847-006-9139-5

Synthesis and Extraction Property of Novel Thiacalix[4]biscrown: Thiacalix[4]-1, 3-2,4-aza-biscrown

FAFU YANG[1,*], CUIYU HUANG[1], HONGYU GUO[1], JIANRONG LIN[1] and QI PENG[2]
[1]*College of Chemistry and Materials, Fujian Normal University, Fuzhou, 350007, P.R. China;* [2]*State Key Laboratory of Structural Chemistry, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, Fuzhou, 350002, P.R. China*

(Received: 18 April 2006; in final form: 7 August 2006)

Key words: amino acid, aza, cation, extraction, synthesis, thiacalix [4]biscrown

Abstract

The novel thiacalix[4]-1,3-2,4-aza-biscrown **3** in 1,3-alternate conformation, was facilely prepared by "1 + 2" cyclocondensation of *p-tert*-butylthiacalix[4]arene tetrahydrazide derivative **2** with *o*-phthalaldehyde in yield of 78%. The liquid–liquid extraction experiment showed that compound **3** was excellent receptor for zwitterionic α-amino acids and soft cations Ag^{+} and Hg^{2+}. The extraction percentage of methionine was as high as 78%.

Introduction

Thiacalixarene, which have four sulfur atoms in calixarene skeleton, attracted much research interest recently because the presence of sulfur atoms results in many novel features compared with "classical" calixarenes, such as easy chemical modification, different size and more flexible conformational behavior, different complexation ability with sulfur contribution [1]. Specially, many attentions have been paid to thiacalixcrowns because the crown chains not only anchor the conformation effectively but also construct new *tri*-dimension cavities which usually exhibit excellent recognizing abilities for guests. In 2002, Vicens *et al.* [2] and Bitter *et al.* [3] synthesized the first example of thiacalix[4]crowns. From then on, a series of full-oxygen thiacalix[4]monocrowns or thiacalix[4]biscrowns and their binding properties for metal cations were reported [4–7]. Narumi *et al.* also reported a thiacalix[4]crown carboxylic acid with recognition abilities for enantiomeric primary amines and amino esters [8]. Lately, Lhoták *et al.* synthesized the first thiacalix[4]-1,2-3,4-*aza*-biscrowns in cone conformation [9], and Csokai reported an inherently chiral thiacalix[4]arene derivatives capped by carboxamide bridges [10], but no complexation properties of them were presented. Nevertheless, comparing with "classical" calixcrowns, many research fields of thiacalixcrowns are still unknown. In this paper, we wish to report the synthesis of first example of thiacalix[4]-1,3-2,4-aza-biscrown in 1,3-alternate conformation and its excellent complexation property for zwitterionic α-amino acids and soft metal cations.

Experimental

Melting points were uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker-ARX 500 instrument, using TMS as reference. ESI-MS spectra were obtained from DECAX-30000 LCQ Deca XP mass spectrometer. Elemental analyses were performed at Vario EL III Elemental Analyzer. The UV–Vis measurements were performed on Varian UV–Vis spectrometer. *p-tert*-Butylthiacalix[4]arene tetraethyl acetate **1** in 1,3-alternate conformation was prepared according to published method [11]. The organic and inorganic reagents, except special instruction, were analytical grade or chemical grade without further purification.

Synthesis of thiacalix[4]arene tetrahydrazide derivative **2**

Under N_2 atmosphere, a mixture of *p-tert*-butylthiacalix[4]arene tetraethyl acetate **1** (1.1 g, 1 mmol) and 1 ml hydrazine hydrate (content of 80%, 0.8 g, 16 mmol) was stirred and refluxed in 40 ml toluene/methanol (1:1, *V*/*V*) for 12 h. TLC detection showed the materials were disappeared. After distilling off the solvent, the residue was treated with 20 ml distilled water and precipitation was formed. The precipitation was filtered and recrystallized by $MeOH/H_2O$. The compound **2** was obtained as white powder in yield of 92%.

* Author for correspondence. E-mail: yangfafu@fjnu.edu.cn

Compound **2**: m.p. 168–170 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.28 [s, 36H, $C(CH_3)_3$], 3.49 (bs, 4 H, NH), 4.59 (s, 8H, OCH_2CO), 7.37(s, 8 H, NH_2), 7.43 (s, 8H, ArH). ESI-MS: m/z 1031.7 (MNa^+, 100%). Anal. calcd for $C_{48}H_{64}N_8S_4O_8$(1008.99); C, 57.13; H, 6.39; Found: C, 57.05; H, 6.45.

Synthesis of thiacalix[4]-1,3-2,4-aza-biscrown **3**

Under N_2 atmosphere, a mixture of compound **2** (0.3 g, 0.3 mmol) and *o*-phthalaldehyde (0.1 g, 0.75 mmol) was stirred and refluxed in 50 ml $CHCl_3$/MeOH (1:1, V/V) for 24 h. 0.2 ml acetic acid was added as catalyst. TLC detection showed the materials were disappeared. After distilling off the solvent, the residue was treated with 10 ml MeOH and refrigerated for 5 h till the precipitation was separated out fully. The precipitation was filtered and recrystallized by $CHCl_3$/MeOH. Compound **3** was obtained as white crystal in yield of 78%.

Compound **3**: m.p. 198–201 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.04 [s, 36H, $C(CH_3)_3$], 3.72 (bs, 4 H, NH), 4.76∼4.89 (m, 8H, OCH_2CO), 7.39 (s, 8H, ArH in calix skeleton), 7.73, 7.87, 8.25, 8.38 (bs, each 2H, ArH in bridging chains); 9.75 (bs, 4 H, CH = N). ESI-MS: m/z 1206.9 (MH^+, 100%). Anal. calcd for $C_{64}H_{68}N_8S_4O_8$(1205.18): C, 63.73; H, 5.69; Found C, 63.68; H, 5.78.

Results and discussion

Synthesis of p-tert-butylthiacalix[4]-1,3-2,4-aza-biscrown

The synthetic route was shown in Figure 1. The *p-tert*-butylthiacalix[4]arene tetraethyl acetate **1** in 1,3-alternate conformation was prepared by reacting *p-tert*-butylthiacalix[4]arene with $BrCH_2COOEt$ in Cs_2CO_3/acetone system according to published method [11]. By the aminolysis of compound **1** with excess of hydrazine hydrate in toluene–methanol, compound **2** was synthesized in almost quantitative yield. Further reacting compound **2** with *o*-phthalaldehyde using acetic acid as catalyst in diluted condition, thiacalix[4]-1,3-2,4-*aza*-biscrown **3** was obtained by "1 + 2" condensation mode in yield of 78%. The separate procedures were simple and the total yield was as high as nearly 70%.

In literature, Bitter *et al.* [2–7] synthesized the full-oxygen thiacalix[4]-biscrowns by condensation thiacalix[4]arene with polyethylene glycol ditosylate directly. Due to the flexible conformation and weak selectivity of thiacalix[4]arene, the yields of these thiacalix[4]-biscrowns were not high and the work-up was troublesome with chromatographic column. The thiacalix[4]-1,2-3,4-aza-biscrown reported by Lhoták *et al.* [9] was accomplished by reacting cone conformational thiacalix[4]arene tetraethyl acetate with α,ω-diamine, but the yield was less than 36% because several byproducts in other bridging modes were produced. In this paper, the *p-tert*-butylthiacalix[4]arene tetraethyl acetate **1** in 1,3-alternate conformation was chose as material, which successfully avoid the other intramolecular bridging modes (such as 1,2-bridging) in next cyclocondensation. On the other hand, the "1 + 2" cyclocondensation was fulfilled by the Schiff-base reaction, which was easily accomplished in high yield. As a result, the novel thiacalix[4]-1,3-2,4-aza-biscrown **3** in 1,3-alternate conformation was facilely prepared in simple separate procedure and high yield. To the best of our knowledge, compound **3** was the first example of thiacalix[4]-1,3-2,4-aza-biscrown in 1,3-alternate conformation.

Structure and conformation of p-tert-butylthiacalix[4]-1,3-2,4-aza-biscrown

The structures of new compounds **2** and **3** were characterized by FAB-MS spectra, elemental analyses, ^{1}H NMR spectra. The ^{1}H NMR spectrum of **1** was in accord with the reported 1,3-alternate conformation [11]. The ^{1}H NMR spectrum of **2** showed a singlet for the *tert*-butyl groups, a singlet for the aromatic protons and a singlet for OCH_2CO, which indicated that compound **2** adopted 1,3-alternate conformation or cone conformation. Considering that compound **2** was the derivative of compound **1**, we speculated it also adopted 1,3-alternate conformation. This deduction was also

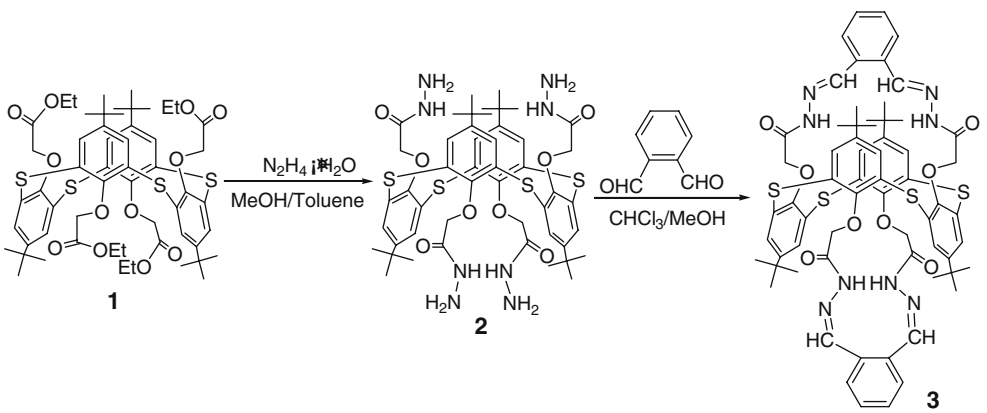

Figure 1. Synthesis route of compound **3**.

supported by the conformation of compound **3**. In the ESI-MS spectrum of compound **3**, the clear MH^+ base peak at 1206.9 definitely suggested that the "1 + 2" cyclocondensation was accomplished. Thus, compound **3** possessed two possible bridging modes: thiacalix[4]-1,3-2,4-biscrown or thiacalix[4]-1,2-3,4-biscrown. Bitter *et al*. [3, 4, 6] and Lhoták *et al*. [9] had reported that thiacalix[4]-1,3-2,4-biscrown showed a singlet for the aromatic protons of calixarene skeleton in 1,3-alternate conformation, but thiacalix[4]-1,2-3,4-biscrown exhibited a pair of doublets for the aromatic protons of calixarene skeleton in cone conformation or 1,2-alternate conformation. The ^1H NMR spectrum of compound **3** showed a singlet for the aromatic protons of calixarene skeleton, which certainly indicated that compound **3** adopted 1,3-2,4-*bis*-bridging mode in 1,3-alternate conformation. This result was also in accordance with the speculation that compound **2** adopted 1,3-alternate conformation. As regards the structure of C = N bonds in compound **3**, it was difficult to determine their conformations due to the complicated signals of aromatic protons in bridging chains, which might indicate that the C = N bonds possess mixed structures of *trans*-form and *cis*-form.

Extraction studies for cations and α-amino acids

It is well known that the cavity of calix-*aza*-crowns could bind soft metal cations according to the "soft and hard acids and bases" concept, ammonium ion and anions (such as carboxylate) by hydrogen bond action. Comparing with the reported thiacalix[4]-1,2-3,4-*aza*-biscrown in cone conformation, novel thiacalix[4]-1,3-2,4-*aza*-biscrown **3** in 1,3-alternate conformation possessed two tri-dimension cavities of calix-aza-crowns which not only had the potential for complexing guests using the two cavities independently, but also a single guest using two cavities cooperatively. To evaluate the binding ability of novel host **3**, two-phase solvent extraction for series of metal cations and α-amino acids were carried out.

The extraction percentages of series of cations with hosts **3** from water into $CHCl_3$ at room temperature were summarized in Table 1 (similar structural full-oxygen thiacalix[4]-1,3-2,4-biscrown-5 **4** [4] as referenced compound). The full-oxygen thiacalix[4]-1,3-2,4-bis-crown-5 **4** was reported to show poor extraction ability for Ag^+ due to the co-operation between the ethylene glycol bridge and the bridging sulfur atoms was not possible [4]. However, our experimental results clearly showed that the novel host **3** showed very outstanding extraction ability for Ag^+ and Hg^{2+} but poor extraction ability for alkali metals cations. Considering the similar structures of compounds **3** and **4**, the outstanding extraction ability of compound **3** for Ag^+ and Hg^{2+} could be attributed to the introduction of the *aza*-groups in bridging chains.

The extraction percentages of series of zwitterionic α-amino acids from water into $CHCl_3$ were summarized in Table 2 (see Fig. 2). As expected, novel host **3** exhibited good extraction ability towards tested α-amino acids. The extraction percentage for methionine was as high as 78%. It was worthy of noting that the extraction ability of thiacalix[4]crowns for zwitterionic α-amino acids was studied for the first time, and the extraction percentage of compound **3** was outstanding among all kinds of calixarene derivatives, although some calixarene derivatives [13], especially, aqueous miscible or hydrophilic calixarene derivatives containing carboxylic acids [14, 15], phosphonates [16] or sulphonate [17] were reported to bind amino acids or amino acid esters. These extraction result of compound **3** indicated that thiacalix[4]biscrown were an effective receptors not only for metal cations, but also for bioorganic molecules, such as amino acids.

Table 1. Extraction percentage (E%) of picrate salts from water into $CHCl_3$ at room temperature[a]

Hosts	E%				
	Na^+	K^+	Cs^+	Ag^+	Hg^{2+}
3	3.5	5.1	7.5	81.7	72.2
4[b]	8	11	5	3	/

[a]According to the reported picrate extraction method [12], 2.00 ml of 0.005 M receptor solution in $CHCl_3$ was shaken (20 min) with 2.00 ml of 0.005 M picrate salt solution in triple distilled H_2O and the percentage extraction was measured from the resulting absorbance at 380 nm in $CHCl_3$. Control experiments showed that no picrate extraction occurred in the absence of the calixarene derivatives. Average of thrice independent experiment was carried out.
[b]These data quoted from reference [4].

Conclusion

By reacting *p-tert*-butylthiacalix[4]arene tetrahydrazide derivative **2** in 1,3-alternate conformation with *o*-phthalaldehyde, the first example of thiacalix[4]-1,3-2,4-aza-*bis*-crown **3** was prepared by in "1 + 2" condensation mode. Comparing with the previous synthetic

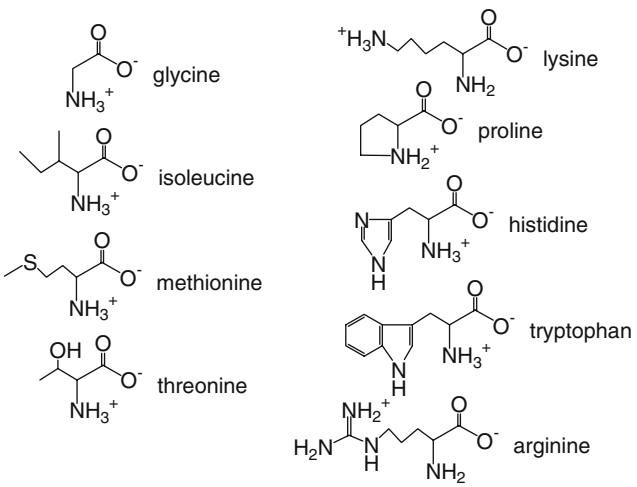

Figure 2. List of zwitterionic amino acids.

Table 2. Extraction percentages (E%) of α-amino acids from water into $CHCl_3$ [a]

Host	E%								
	Gly	Iso	Met	Thr	Lys	Pro	His	Try	Arg
3	30.4	41.2	78.2	47.7	37.4	32.3	11.6	22.9	19.3

[a]The extraction experiment was performed by the same method as described in Table 1. The concentrations of amino acids after extraction were assessed by classical ninhydrin tests [18]. Control experiments showed that the extraction percentage for amino acids was less than 0.3% in the absence of the host.

methods of thiacalix[4]-biscrowns, the separate procedure of this synthetic route was simple and the yield was high. The liquid–liquid extraction experiments showed that compound **3** was excellent receptor for zwitterionic α-amino acids and soft cations Ag^+ and Hg^{2+}. The extraction percentage for methionine was as high as 78%. These extraction results indicated that the thiacalix[4]biscrown were an effective receptors not only for metal cations, but also for bioorganic molecules, such as amino acids.

Acknowledgments

Financial supports from the National Natural Science Foundation of China (No. 20402002) and Fujian Natural Science Foundation of China (No. E0220002).

References

1. P. Lhotak: *Eur. J. Org. Chem.* **8**, 1675 (2004).
2. V. Lamare, J.F. Dozol, P. Thuéry, M. Nierlich, Z. Asfari, and J. Vicens: *J. Chem. Soc., Perkin Trans 2*. **15**, 1920 (2001).
3. A. Grün, V. Csokai, G. Parlagh, and I. Bitter: *Tetrahedron Lett*. **43**, 4153 (2002).
4. F.W.B. van Leeuwen, H. Beijleveld, H. Kooijman, A.L. Spek, W. Verboom, and D.N. Reinhoudt: *Tetrahedron Lett*. **43**, 9675 (2002).
5. V. Csokai, B. Balázs, G. Tóth, G. Horváth, and I. Bitter: *Tetrahedron* **60**, 12059 (2004).
6. V. Csokai, A. Grün, G. Parlagh, and I. Bitter: *Tetrahedron Lett*. **43**, 7627 (2002).
7. V. Csokai, A. Grün, B. Balázs, G. Tóth, G. Horváth, and I. Bitter: *Org. Lett*. **6**, 477 (2004).
8. F. Narumi, T. Hattori, N. Matsumura, T. Onodera, H. Karagiri, C. Kabuto, H. Kameyama, and S. Miyano: *Tetrahedron* **60**, 7827 (2004).
9. V. Šťastný, I. Stibor, H. Petříčková, J. Sýkora, and P. Lhoták: *Tetrahedron* **61**, 9990 (2005).
10. V. Csokai, A. Simon, B. Balázs, G. Tóth, and I. Bitter: *Tetrahedron* **62**, 2850 (2006).
11. H. Akdas, G. Mislin, E. Graf, M.W. Hosseini, and A.D. Cian: *J. Fischer: Tetrahedron* **40**, 2113 (1999).
12. F. Arnaud-Neu, E.M. Collins, M. Deasy, G. Ferguson, S.J. Harris, B. Kaitner, E. Marques, M.J. Schwing-Weill, and E.M. Seward: *J. Am. Chem. Soc*. **111**, 8681 (1989).
13. L. Mutihac, H.J. Buschmann, R.C. Mutihac, and E. Schollmeyer: *J. Incl. Phenom. Macrocylic Chem*. **51**, 1 (2005).
14. T. Oshima, K. Inoue, and K. Uezu: *Analytica Chimica Acta*. **509**, 137 (2004).
15. T. Oshima, M. Goto, and S. Furusak: *J. Incl. Phenom. Macrocylic Chem*. **43**, 77 (2002).
16. I.S. Antipin, I. Stoikov, and E.M. Pinkhassik: *Tetrahedron Lett*. **38**, 5865 (1997).
17. E.D. Silva and A.W. Coleman: *Tetrahedron* **59**, 7357 (2003).
18. G.Z. Fang and N. Liu: *Anal. Chim. Acta*. **445**, 245 (2001).