

Synthesis and cations complexation of dumbbell shaped biscalix[4]-1,3-aza-crown with rigid thiourea-bridge

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Abstract By reacting calix[4]-1,3-aza-crown **2** with 1,4-phenyl diisothiocyanate in “1 + 2” condensation mode, the novel dumbbell shaped biscalix[4]-1,3-aza-crown **3** with rigid thiourea-bridge was conveniently prepared in yield of 85%. Its structure and conformation were characterized by elemental analyses, ESI-MS, ^1H NMR and ^1H - ^1H COSY techniques. The complexation properties of compound **3** were investigated by liquid-liquid extraction experiments and ^1H NMR titration experiments. The results showed that compound **3** has excellent complexation abilities for soft cations and outstanding extraction selectivity for Ag^+ . The Ag^+/Na^+ and $\text{Ag}^+/\text{Hg}^{2+}$ extraction percentage of host **7** were as high as 43.2 and 16.9, respectively. ^1H NMR titration experiments revealed the 1:2 stoichiometry of receptor **3**- Ag^+ complex was formed.

Keywords Biscalix[4]crown · Thiourea · Dumbbell · Complexation · Ag^+

Introduction

It is well known that calixarenes and their derivatives are macrocyclic molecules possessing interesting complexation abilities towards target molecules or ions. Many researches were involved in design and syntheses of different kinds of receptor molecules with defined

cavities by using calix[4]arenes as a key structural motif [1–3]. Double calix[4]arenes were prepared as examples of higher order molecular architectures in the recent past [4–7]. For examples, Beer et al. reported a biscalix[4]arene with carboxylic groups which exhibited excellent complexation for UO_2^{2+} [8]. Stibor and Lhoták et al. synthesized a biscalix[4]arene-based ditopic hard/soft receptor for K^+/Ag^+ complexation [9]. Nabeshima et al. reported biscalix[4]arenes with homotropic and heterotropic complexation abilities [10]. Prados et al. reported a biscalix[4]arene with the complexation for Fullerene [11]. Aeduini et al. reported the self-assembly of a double calix[6]arene with oriented channels [12]. Tuntulani et al. synthesized a calix[4]quinones derived from double calix[4]arenes with electrochemical properties [13]. Our groups also reported a series of biscalix[4]arenes with interesting complexation properties [14–17]. From these literatures, it could be concluded that the biscalixarenes were usually constructed by bridging at their upper rims (“head-to-head” type), lower rims (tail-to-tail type) or upper-lower rims (“head-to-tail” type) through one or more spacers. And the complexation properties of biscalix[4]arene were mainly decided not only by the structure of biscalix[4]arene but also by the characteristic of functional groups of bridging chains. Lately, we reported a dumbbell shaped biscalix[4]crown with soft carbochain-bridge, which showed interesting complexation abilities for anions [18]. In this paper, we synthesized another type of dumbbell shaped biscalix[4]arene with rigid thiourea-bridge, in which the two calixarene units were linked on the crown ether moieties of calix[4]-1,3-aza-crown by 1,4-phenyl dithiourea. The novel biscalix[4]arene **3** not only was facilely prepared in high yield but also exhibited high selective complexation ability towards Ag^+ .

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Experimental

Melting points are uncorrected. ^1H NMR spectra were recorded in CDCl_3 on a Bruker-ARX 500 instrument, using TMS as reference. ESI-MS spectra were obtained from DECA-30000 LCQ Deca XP mass spectrometer. Elemental analyses were performed at Vario EL III Elemental Analyzer. The UV-Vis measurements in extraction experiment were performed on Varian UV-Vis spectrometer. Cation concentrations in competitive extracting experiments were measured with Thermo Intrepid XSP Radial ICP-OES. All solvents were purified by standard procedures.

The synthesis of p-tert-butylcalix[4]-1,3-aza-crown (**2**)

The mixture of compound **1** (1 mmol) and diethylenetriamine (5 mmol), in 100 mL of toluene/methanol ($V:V = 1:1$) was stirred and refluxed. TLC detection indicated the disappearance of compound **1** in 12 h. The solvent was evaporated and the residue was purified by SiO_2 chromatographic column (100–200 mesh, acetone as eluent). Compound **2** was obtained as white powder in 53% yield. m.p. 188–189 °C (literature [19]: 183–185 °C), ^1H NMR (500 MHz, CDCl_3) δ : 1.00 (s, 18 H, $\text{C}(\text{CH}_3)_3$), 1.25 (s, 18 H, $\text{C}(\text{CH}_3)_3$), 3.42 (4 H, $J = 13.5$ Hz, ArCH_2Ar), 3.73 (bs, 4 H, NCH_2), 4.02 (4 H, $J = 13.5$ Hz, ArCH_2Ar), 4.19 (bs, 4 H, CONCH_2), 4.46 (bs, 4 H, OCH_2CO), 6.88–7.65 (m, 11 H, ArH, and NH), 8.58 (bs, 2 H, OH). MS m/z (%): 831.8 (M^+ , 100). Anal. calcd for $\text{C}_{52}\text{H}_{69}\text{O}_6\text{N}_3$: C 75.06, H 8.36; found C 75.01, H 8.43.

The synthesis of dumbbell shaped bis-calix[4]-1,3-aza-crown (**3**)

The mixture of compound **2** (1 mmol) and 1,4-phenyl diisothiocyanate (0.55 mmol) in 15 mL of CHCl_3 was stirred and refluxed for 2 h. Evaporation of the solvent obtained crude product. The recrystallization from petroleum ether (60–90 °C) gave a white powder **3** in 85% yield. Compound **3**: m.p. 208–210 °C. ^1H NMR (500 MHz, CDCl_3) δ ppm: 1.01 [s, 36 H, $\text{C}(\text{CH}_3)_3$], 1.28 [s, 36 H, $\text{C}(\text{CH}_3)_3$], 3.42 (d, 8 H, $J = 13.5$ Hz, ArCH_2Ar), 3.77 (bs, 8 H, NCH_2), 4.08 (d, 8 H, $J = 13.5$ Hz, ArCH_2Ar), 4.22 (bs, 8 H, NCH_2), 4.58 (s, 8 H, OCH_2CO), 6.89 (s, 8 H, ArH), 7.09 (s, 8 H, ArH), 7.49 (s, 4 H, ArH), 7.58 (s, 4 H, OH), 8.69 (bs, 2 H, NHCS), 8.73 (s, 4 H, NHCO), MS m/z (%): 1878.6 (MNa^+ , 100). Anal. calcd for $\text{C}_{112}\text{H}_{142}\text{O}_{12}\text{N}_8\text{S}_2$: C 72.46, H 7.71, N 6.04; found C 72.51, H 7.68, N 6.11.

Noncompetitive extracting experiment of metallic picrates

According to the reported method [18], 3 mL of chloroform solution containing calixarene derivatives (2.0×10^{-5} M) and 3 mL of aqueous solution containing a metallic picrate (2.0×10^{-5} M) were placed in a flask. The mixture was shaken for 5 min and stored for 2 h at room temperature. The extraction ability was not affected by further shaking, indicating that the equilibrium had been attained within 2 h. The aqueous phase was separated and subjected to the analysis by UV absorption spectrometry in near 357 nm. The extracting percentage ($E\%$) was determined by the decrease of the picrate concentration in the aqueous phase: $E\% = \{([\text{Pic}]_{\text{blank}} - [\text{Pic}]_{\text{water}}) / [\text{Pic}]_{\text{blank}}\} \times 100$, where $[\text{Pic}]_{\text{blank}}$ denoted the picrate concentrations in the aqueous phase after extraction with pure chloroform, and $[\text{Pic}]_{\text{water}}$ denoted the picrate concentrations in the aqueous phase after extraction with chloroform solution containing calixarene derivatives as extractants. Average of twice-independent experiments was carried out. Control experiments showed that no picrate extraction occurred in the absence of the calixarene derivatives.

Competitive extracting experiments of metallic cations

Competitive extraction experiments were performed with equal volumes (10 mL) of an aqueous solution of an equimolar mixture of picrate salts (Na^+ , K^+ , Cs^+ , Zn^{2+} , Cd^{2+} , Pb^{2+} , Co^{2+} , Ni^{2+} , Hg^{2+} and Ag^+ , 2.0×10^{-5} M each) and a CHCl_3 solution (10 mL) of the hosts (2.0×10^{-5} M) were mixed in a stoppered flask and vigorously shaken for 15 min. The solution was stored for 2 h. This was repeated 3 times, then the solutions were left standing for 24 h until phase separation was complete. The relative concentrations of the cations in the aqueous phase were determined by ICP-OES. Quantification was made by using a standard solution containing a mixture of picrate salts (Na^+ , K^+ , Cs^+ , Zn^{2+} , Cd^{2+} , Pb^{2+} , Co^{2+} , Ni^{2+} , Hg^{2+} , and Ag^+). A blank experiment without added host was carried out under similar experimental conditions.

^1H NMR complexation experiments

Solution of receptor **3** was prepared at a concentration of 5×10^{-3} M in CDCl_3 . The initial ^1H NMR spectrum was recorded. and aliquots of Ag^+ (ClO_4^-) in the same solvent, were added by a microsyringe from a solution made such that from 0.5 molar equiv to 3.0 molar equiv were added in 20 μL , and the ^1H NMR spectrum was recorded.

Results and discussion

Syntheses and characterization

The synthetic route was depicted in Scheme 1. Compound **1** was obtained in yield of 85% by reacting *p*-*tert*-butylcalix[4]arene with ethyl bromoacetate in K_2CO_3 /dry acetone system according to the published procedures [20]. But we failed to prepare compound **2** by ammonolysis reaction of compound **1** with diethylenetriamine in mol ratio of 1:3 according to the reported procedures [17]. Most materials were not reacted even the reaction time was prolonged to 48 h. We found that compound **2** could be synthesized when mol ratio was raised to 1:5. Although some intermolecular bridging products were also produced under this ratio, compound **2** was easily separated by chromatographic column in moderate yield of 53%. By refluxing compound **2** with 1,4-phenyl diisothiocyanate in $CHCl_3$, a novel dumbbell shaped biscalix[4]arene **3** with thiourea-bridge was obtained in “1 + 2” condensation mode, and the yield was as high as 85% with simple separated procedure of recrystallization. The yield was far higher than that of other previous reported biscalix[4]arenes [3–13]. It was worthy of noting that biscalixarene **3** was novel dumbbell shaped biscalix[4]arene with rigid thiourea-bridge on the crown ether moieties of biscalix[4]crown.

The structure and conformation of compound **3** were confirmed by 1H NMR, ESI-MS, 1H – 1H COSY spectrum and elemental analysis. Only molecular base peak at 1878.6 (MNa^+) in ESI-MS spectrum indicated that “1 + 2” condensation was accomplished thoroughly. 1H NMR spectrum of compound **3** showed two singlets (1:1) for the *tert*-butyl groups, two singlets (1:1) for ArH and a pair of doublet (1:1) for the methylene protons of the calix[4]arene skeleton, which revealed that biscalix[4]arene **3** adopt high symmetric structure and cone conformation of calixarene units.

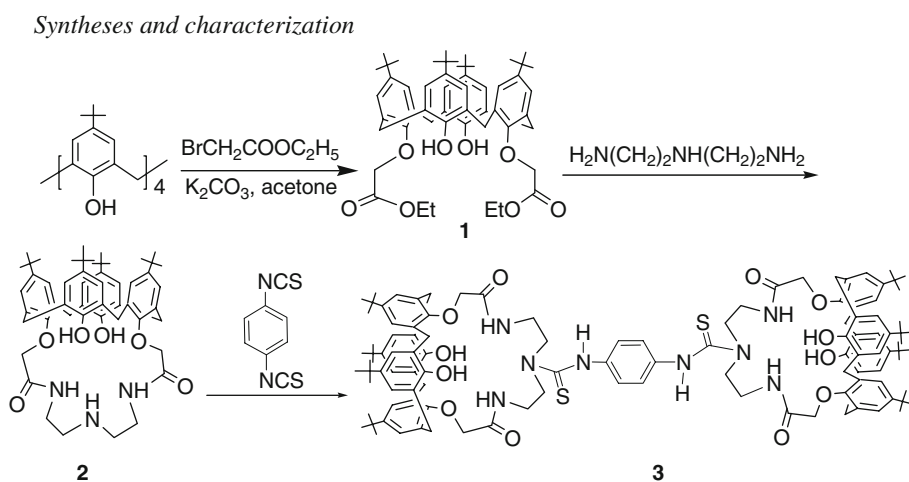
In order to confirm the structure and conformation of compound **3** further, the 1H – 1H COSY spectrum was done to study the coupling relationship of H atom. The result was showed in Scheme 2. The coupling signals of $^1H(\delta_H 3.77)$ – $^1H(\delta_H 4.22)$ and $^1H(\delta_H 3.77)$ – $^1H(\delta_H 8.73)$ were ascribed to protons of $NHCH_2CH_2-NHCH_2CH_2$ and $NHCH_2CH_2-NHCH_2CH_2$ on linking chain. The coupling signals of $^1H(\delta_H 3.42)$ – $^1H(\delta_H 4.08)$ was ascribed to protons of $ArCH_2Ar$ on calixarene skeleton. All these coupling signals of 1H – 1H COSY spectrum certainly further supported the cone conformation and high symmetric structure of biscalix[4]arene **3**.

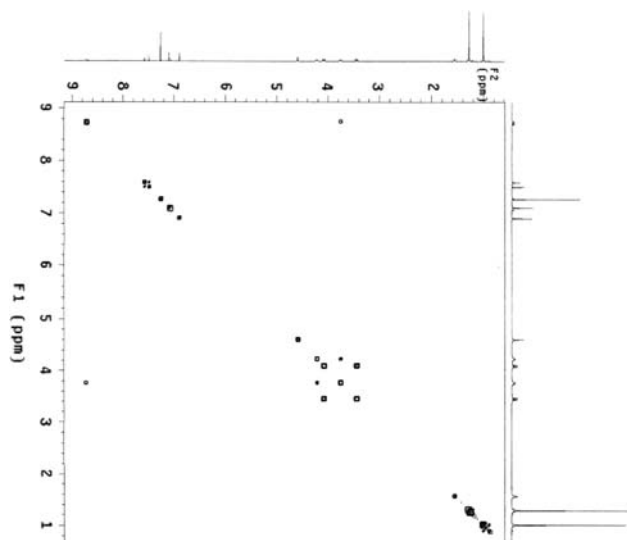
Complexation studies for cations

Examination of the CPK molecular models revealed that novel biscalix[4]arene **3** were highly preorganized for binding guests. NH and S were excellent electron donation functional group for binding metal cations. The noncompetitive complexation abilities of compound **2** and **3** towards a series of metal cations were studied by two phase extraction experiment ($H_2O/CHCl_3$) of metal cation picrate salts. The results were summarized in Fig. 1. Novel biscalix[4]arene **3** exhibited higher extraction percentage for cations, especially for soft cations, than that of calix[4]crown **2**. These extraction results might be explained by that two calixarene units and the thiourea group of compound **3** improved complexation abilities, especially, for Ag^+ and Hg^{2+} greatly. On the other hand, the soft cations complexation abilities of compound **3** were much higher than that for hard cations, which were accordance with the “soft and hard acids and bases” concept. The highest Ag^+ extraction percentage was as high as 60.3%.

To assess the competitive extraction selectivity of compound **3**, competitive solvent extractions experiments from aqueous solutions into chloroform were performed. The extraction percentages (%E) were summarized in

Scheme 1 The synthetic route of dumbbell shaped biscalix[4]-1,3-aza-crown **3**





Scheme 2 ^1H - ^1H COSY spectrum of bisicalix[4]arene **3**

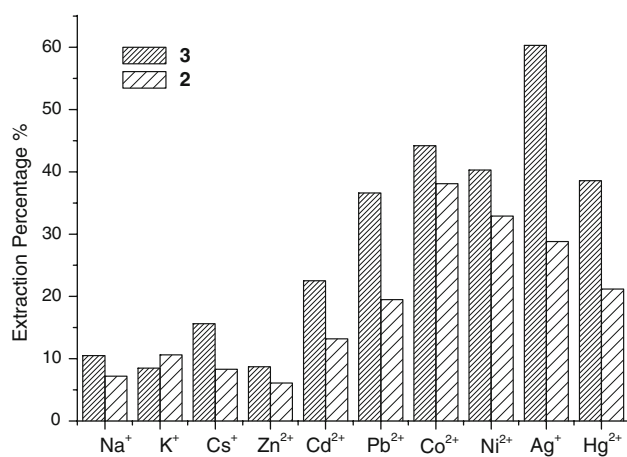


Fig. 1 The extraction percentage of compounds **2** and **3** for metallic cations

Table 1 (the competitive extraction selectivity of compound **2** was studied as reference). It can be seen that, in the competition experiments, the extraction abilities towards the competing metallic ions showed similar capability order of noncompetitive extraction experiment: soft metallic cations \gg hard metallic cations. Although the extraction percentages were lower than that of noncompetitive extraction experiment, however, the extraction selectivities in competition experiments were far higher than that of noncompetitive experiment. For example, the

Table 1 Competitive extracting percentages (%E) of compound **3** for picrate salts from water into CHCl_3

Cations	Na ⁺	K ⁺	Cs ⁺	Zn ²⁺	Cd ²⁺	Pb ²⁺	Co ²⁺	Ni ²⁺	Hg ²⁺	Ag ⁺
2	0.8	1.1	1.5	2.1	4.3	5.9	6.8	8.2	12.9	26.5
3	1.1	1.3	0.9	2.8	2.1	2.6	3.2	2.6	2.8	47.5

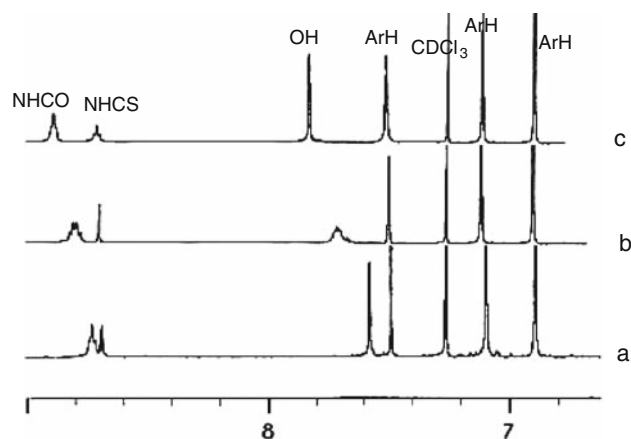


Fig. 2 Partial ^1H NMR spectra in CDCl_3 . **a** compound **3**, **b** compound **3** with 1 equiv. Ag^+ , **c** compound **3** with 2 equiv. Ag^+

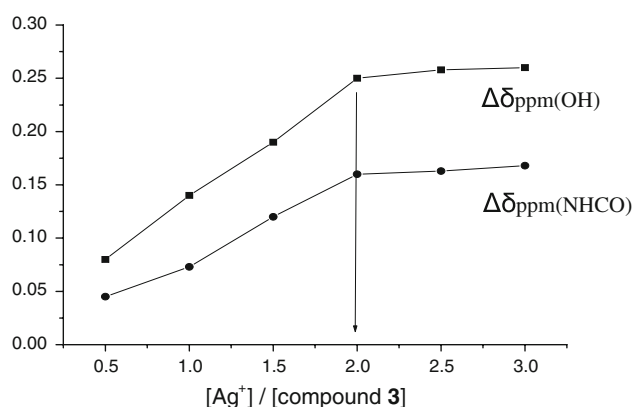


Fig. 3 The chemical shifts of NHCO and OH in the ^1H NMR titration experiments in CDCl_3

Ag^+/Na^+ and $\text{Ag}^+/\text{Hg}^{2+}$ extraction percentage of host **3** were as high as 43.2 and 16.9, respectively. On the other hand, comparing with the competitive extraction results of compound **2**, bisicalixarene **3** showed not only excellent extraction ability but also high extraction selectivity for Ag^+ . From the noncompetitive and competitive extraction results, it could be concluded that thiourea group improved both the complexation ability and complexation selectivity of bisicalixarene **3** for Ag^+ .

The complexation behaviors of compound **3** with Ag^+ were also studied by ^1H NMR spectra titrations. From the titration results as showed in Fig. 2, it can be seen that the the chemical shifts of $-\text{NH}-$ on crown ether moiety and $-\text{OH}$ moved to low magnetic field obviously in the ^1H

NMR spectra. But the chemical shifts of –NH– on thiourea bridge and other protons made little move. Moreover, from the titration curve of Fig. 3, it was found that the negligible chemical shifts were observed when excess 2 equiv. Ag^+ were added and the association constant of compound **3** with Ag^+ was calculated to be $2.6 \times 10^6 \text{ M}^{-1}$ [21]. These results indicated that 1:2 complex of compound **3** with Ag^+ was preferred to be formed in complexation system. From these titration results and above-mentioned extraction results, it might be deduced that not the –NH– but the S groups on thiourea bridge took part in the complexation and two Ag^+ cations were binded independently in two cavities of calix[4]crown units of compound **3**. Also, comparing with the complexation properties of previous reported dumbbell shaped biscalix[4]crown with soft carbochain-bridge [18], it can be concluded that soft bridge was favorable for coordinated complexation, but the rigid bridge was favorable for independent complexation of two calixarene units in dumbbell shaped biscalix[4]arene.

Conclusion

In conclusion, the novel dumbbell shaped biscalix[4]arene **3** with rigid thiourea-bridge was designed and synthesized in “1 + 2” condensation of calix[4]-1,3-aza-crown **2** and 1,4-phenyl diisothiocyanate. The yield was as high as 85% with simple separated procedure of recrystallization. The novel bicalixarene **3** adopted the high symmetric structure and cone conformation. The noncompetitive extraction experiments of biscalixarene **3** showed high extraction percentage for soft metallic cations and competitive extraction experiments exhibited high extraction selectivity for Ag^+ . The ^1H NMR titrations experiments revealed that 1:2 complex of receptor **3**- Ag^+ was formed. it was not the –NH– but the S groups on thiourea bridge taking part in the complexation. Two Ag^+ cations were binded independently in two cavities of calix[4]crown units of compound **3**.

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References

- Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J.: Calixarenes 2001. Kluwer Academic Publishers, Dordrecht, The Netherlands (2001)
- Ikeda, A., Shinkai, S.: Novel cavity design using calix[n]arene skeletons: toward molecular recognition and metal binding. Chem. Rev. **97**, 1713–1725 (1997). doi:10.1021/cr960385x
- Harrowfield, J., Vicens, J.: Calixarenes in the Nanoworld. Springer, Dordrecht, Holland (2006)
- Nabeshima, T., Saiki, T., Sumitomo, K.: Doubly bridged biscalix[4]arene for homotropic and heterotropic allosteric effects on ion recognition. Tetrahedron Lett. **45**, 4719–4722 (2004). doi:10.1016/j.tetlet.2004.04.088
- Tantrakarn, K., Ratanatawanate, C., Pinsuk, T.: Synthesis of redox-active biscalix[4]quinones and their electrochemical properties. Tetrahedron Lett. **44**, 33–36 (2003). doi:10.1016/S0040-4039(02)02520-0
- Mathieu, A., Asfari, Z., Vicens, J.: Synthesis and structure of a bis-calix[4]arene with an *o*-xylene linkage. J. Incl. Phenom. Macrocycl. Chem. **43**, 133–138 (2002). doi:10.1023/A:1020410904828
- Bhalla, V., Kumar, M., Katagiri, H., Hattori, T., Miyano, S.: Synthesis and binding studies of novel bistiactalix[4]arenes with diimide linkages. Tetrahedron Lett. **46**, 121–124 (2005). doi:10.1016/j.tetlet.2004.11.008
- Schmitt, P., Beer, P.D., Drew, M.G.B.: Uranyl binding by a novel bis-calix[4]arene receptor. Tetrahedron Lett. **39**, 6383–6386 (1998). doi:10.1016/S0040-4039(98)01315-X
- Budka, J., Lhoták, P., Stibor, I., Michlová, V., Sykora, J., Cisarová, J.: A biscalix[4]arene-based ditopic hard/soft receptor for K^+/Ag^+ complexation. Tetrahedron Lett. **43**, 2857–2860 (2002). doi:10.1016/S0040-4039(02)00343-X
- Nabeshima, T., Saiki, T., Sumitomo, K., Akine, S.: Doubly bridged biscalix[4]arene for homotropic and heterotropic allosteric effects on ion recognition. Tetrahedron Lett. **45**, 4719–4722 (2004). doi:10.1016/j.tetlet.2004.04.088
- Iglesias-Sánchez, J.C., Fragoso, A., Mendoza, J., Prados, P.: Aryl-aryl linked bi-5, 5'-p-tert-butylcalix[4]arene tweezer for fullerene complexation. Org. Lett. **8**, 2571–2577 (2006). doi:10.1021/ol0607591
- Arduini, A., Credi, A., Faimani, G., Massera, C., Pochini, A., Secchi, A., Ugozzoli, F.: Self-assembly of a double calix[6]arene pseudorotaxane in oriented channels. Chem. Eur. J. **14**, 98–106 (2008). doi:10.1002/chem.200700748
- Kerdpaiboon, N., Tomapatanaget, B., Chailapakul, O., Tuntulani, T.: Calix[4]quinones derived from double calix[4]arenes: synthesis, complexation, and electrochemical properties toward alkali metal ions. J. Org. Chem. **70**, 4797–4804 (2005). doi:10.1021/jo050324b
- Yang, F.F., Ji, Y.Q., Zheng, L.L., Guo, H.Y., Lin, J.R.: Design, syntheses and complexation properties of novel bis-calix[4]arene and tri-calix[4]arene containing two kinds of calix[4]arene derivative units. Supramol. Chem. **18**, 177–181 (2006). doi:10.1080/10610270500398706
- Yang, F.F., Zhao, X., Huang, C.Y., Guo, H.Y., Zheng, S.N., Peng, Q.: Synthesis and complexation properties of novel biscalixarene containing calix[4]arene and thiacalix[4]arene units. Chin. Chem. Lett. **17**, 1029–1033 (2006)
- Yang, F.F., Zhao, X., Guo, H.Y., Liu, C.H.: Syntheses and extraction properties of novel biscalixarene and thiacalix[4]arene polyaza derivatives. J. Incl. Phenom. Macrocycl. Chem. **61**, 139–143 (2008). doi:10.1007/s10847-007-9406-0
- Yang, F.F., Liu, L.M., Liu, C.H., Zheng, X.H., Guo, Y.: Synthesis of novel biscalixarene-tube containing two kinds of calix[4]arene derivative units. Chin. Chem. Lett. **19**, 9–11 (2008). doi:10.1016/j.ccl.2007.10.032
- Yang, F.F., Zheng, X.H., Guo, H.Y., Liu, C.H., Guo, Y.: The synthesis and anions complexation property of novel biscalixarene: dumbbell shaped biscalix[4]-1, 3-aza-crown. J. Incl.

- Phenom. Macrocycl. Chem. **62**, 371–375 (2008). doi:[10.1007/s10847-008-9480-y](https://doi.org/10.1007/s10847-008-9480-y)
19. Bitter, I., Grün, A., Tóth, G., Balázs, B.: Studies on calix(-aza)crowns. I. Synthesis, alkylation reactions and comprehensive NMR investigation of capped calix[4]arenes. *Tetrahedron* **53**, 9799–9812 (1997). doi:[10.1016/S0040-4020\(97\)00627-3](https://doi.org/10.1016/S0040-4020(97)00627-3)
 20. Oueslati, I., Thuéry, P., Nierlich, M., Asfari, Z., Harrowfield, J., Vicens, J.: Synthesis and complexing properties of methylated calix[4](aza)crown derivatives. *Tetrahedron Lett.* **41**, 8263–8266 (2000). doi:[10.1016/S0040-4039\(00\)01438-6](https://doi.org/10.1016/S0040-4039(00)01438-6)
 21. Connors, K.A.: *Binding Constants*. New York, Wiley (1987)