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SHORT COMMUNICATION

One-pot synthesis of *p-tert*-butylthiacalix[6/8]arenes

Takashi Kimuro · Manabu Yamada ·
Fumio Hamada

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Abstract Since Miyano and co-workers' facile synthesis of *p-tert*-butylthiacalix[4]arene (**1**), many studies related to **1** have been published. In contrast, because of their extremely low yields, investigation of the larger macrocycles *p-tert*-butylthiacalix[6]arene (**2**) and *p-tert*-butylthiacalix[8]arene (**3**) has been limited. An improved synthetic method for **1**–**3** by the heating of *p-tert*-butylphenol, sulfur, and catalytic NaOH in a one-pot, two-stage procedure is described. The first step (oligomer formation) proceeds optimally at 180 °C for 24 h with 2 mol % NaOH. The second step (cyclization) is conducted at 230 °C with 50 mol % NaOH. Investigations by ^{1}H NMR spectroscopy and matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS) revealed that **2** and **3** transform into **1** and oligomers at the high temperature required for the cyclization step. Moreover, even **1** transforms into oligomers at high temperature for 48 h. Heating times of 5 and 24 h were optimal for the preparation of **2** (18.1 %) and **3** (4.6 %), respectively. A comparison of the thermal stability of the *p-tert*-butylthiacalix[*n*]arenes determined their stability in the order **1**, **2**, and **3**.

Keywords Thiacalix[*n*]arenes · Cyclization · Macrocyclic compounds · Synthetic method

Introduction

p-tert-Butylthiacalix[*n*]arenes (Fig. 1) [1–3], cyclic oligomers composed of phenol units linked by sulfides, have attracted considerable attention because of their different structural and electronic properties compared to those of *p-tert*-butylcalix[*n*]arenes ($n = 4$–20) [4–6]. Possible applications that have been explored for *p-tert*-butylthiacalix[*n*]arenes include metal extraction [7–12], the adsorption of volatile organic compounds [13–16], and chemosensing [17–22]. These macrocycles show high affinities for metal ions through coordination bonds formed between the empty *d*-orbitals on the metals and the lone pairs on the sulfur atoms bridging the *tert*-butylphenol residues [1, 23]. Compared to *p-tert*-butylthiacalix[4]arene (**1**), the molecular structures of the two larger macrocycles *p-tert*-butylthiacalix[6]arene (**2**) and *p-tert*-butylthiacalix[8]arene (**3**) are more flexible due to the weaker hydrogen bonds between their phenolic hydroxyl units. This conformational flexibility, which allows accommodation of larger ionic radii, has been exploited in the recognition of a wide range of metal ions. For example, **2** formed a Cu^{2+} complex in a cone-type 1,2,3-alternate conformation, whereas a chair-type conformation was observed for the K^+ complex [16, 24]. We previously reported that two conformations could be adopted by water-soluble *p*-sulfonatothiacalix[6]arene–lanthanide complexes depending on the nature of the lanthanide anions and the flexibility of the macrocycle: (1) 1,2,3-alternate conformers without pseudo-

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T. Kimuro · F. Hamada (✉)
Department of Applied Chemistry for Environments, Graduate School of Engineering and Resource Science, Akita University,
1-1 Tegatagakuen-machi, Akita 010-8502, Japan
e-mail: hamada@gipc.akita-u.ac.jp

M. Yamada (✉)
Research Center for Engineering Science, Graduate School of Engineering and Resource Science, Akita University,
1-1 Tegatagakuen-machi, Akita 010-8502, Japan
e-mail: myamada@gipc.akita-u.ac.jp

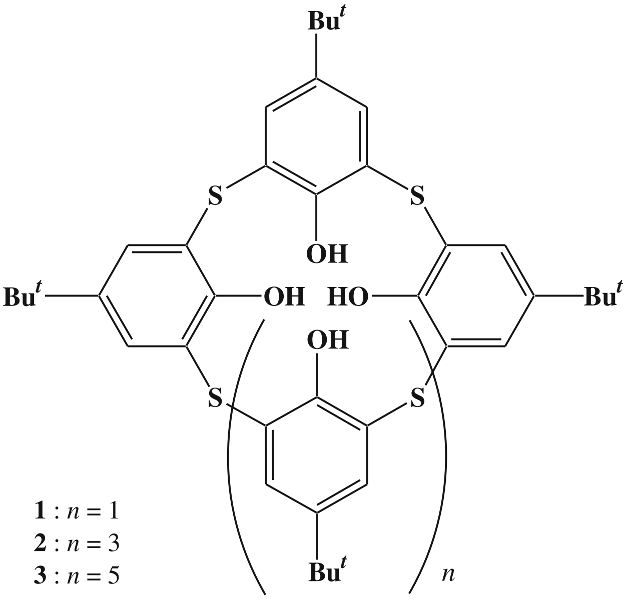

Fig. 1 General structure of thiacalix[*n*]arenes

Table 1 One-pot synthesis of *p*-*tert*-butylthiacalix[*n*]arenes: effects of reaction time and *p*-*tert*-butylphenol/NaOH molar ratio

Run	Conditions		Yield %/g[c]		
	NaOH[a,b]	T °C:time h[b]	**1**	**2**	**3**
1	0.004/0.1	180:24/230:5	10.1/3.6	18.1/6.5	0/0
2	0.004/0.1	180:24/230:12	53.4/19.3	7.5/2.7	2.7/1.0
3	0.004/0.1	180:24/230:24	77.0/27.8	0/0	4.6/1.7
4	0.004/0.1	180:24/230:48	72.8/26.3	0/0	1.5/0.5
5	0.004/none	180:24/none	1.6/0.6	0/0	0/0
6	0.002/0.102	180:24/230:5	15.0/5.4	12.6/4.6	0/0
7	0.02/0.084	180:24/230:5	29.3/10.6	7.9/2.9	0.3/0.1

[a] Molar ratio with 0.2 mol of *p*-*tert*-butylphenol

[b] For the first/second step, respectively

[c] Isolated yields of **1**, **2**, and **3**

thiacalix[3]arene cavities for lighter lanthanide complexes (La and Ce), and (2) up-down double partial-cone conformers possessing pseudo 'thiacalix[3]arene-like' cavities in heavier lanthanide complexes (Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, and Lu) [25–27]. For **3**, a few examples of crystal structures involving inclusion and metal coordination have been reported. Guest-free crystals of **3** obtained via crystallization from chloroform were constructed by the self-inclusion of its *tert*-butyl groups after adopting a pleated-loop conformation [28]. Crystals of a K^+ complex of **3** were assembled by changing the chair-type conformation of the macrocycle to accommodate the metal cations [15]. These larger thiacalixarene molecules are fascinating macrocyclic compounds for many applications, especially selective metal recognition and interesting three-dimensional supramolecular network assemblies.

Gutsche et al. [29] achieved a facile and highly efficient synthesis of *p*-*tert*-butylcalix[6/8]arenes using different alkali metals (RbOH and KOH, respectively) as template-inducing catalysts with *p*-*tert*-butylphenols in xylene. However, much higher reaction temperatures are required to synthesize *p*-*tert*-butylthiacalix[*n*]arenes, and their very low yields by conventional methods are the main problem, limiting the widespread use of **2** and **3**. For example, Miyano and co-workers reported the synthesis of thiacalix[6/8]arenes from an acyclic dimer consisting of two sulfur-bridged *p*-*tert*-butylphenol residues (yields: **2**, 5.3 %; **3**, 4.3 %) [30]. Subsequently, Hamada et al. described a synthetic method for **1** and **2** based on a terephthalate-induced cyclization of a mixture of acyclic oligomers, which were obtained by the reaction of *p*-*tert*-butylphenol with elemental sulfur over CaO in ethylene glycol/diphenyl ether. For these methods, the effects of both the reaction temperature and the base catalyst were investigated. When NaH was used as a catalyst with the mixture of acyclic oligomers and sulfur, the yields of **2** and **3** increased [28, 31], as determined by NMR analysis of the crude mixture, but the isolated yields were small. However, although both synthetic methods succeeded in the low-yield synthesis of **2** and **3**, neither approach would constitute a satisfactory synthesis. For example, both methods involved two separate reaction steps, the synthesis of the dimer or oligomer and their subsequent cyclizations. To enable practical applications of **2** and **3**, we searched for a simple synthetic strategy that would offer improved yields and step economy (one-pot synthesis).

Results and discussion

Our synthetic method consists of a one-pot reaction carried out at two different temperatures (Table 1). In the first step, acyclic oligomers are formed at 180 °C for 24 h, and in the second, they are cyclized at 230 °C for several hours to form **1**, **2**, and **3**. The resulting solids, consisting of **1**, **2**, and **3**, were separated by fractional crystallization from a small amount of chloroform. Pure octamer **3** was isolated first as a white powder, and the hexamer **2** was next recovered. Finally, the tetramer **1** crystallized from the mother liquor (see supporting information for experimental section). Our approach differs from the conventional methods in two key aspects. First, as described in the Introduction, the previous syntheses of **2** and **3** required two individual steps: epithio-bridged oligomer preparation followed by cyclization. This required the separate synthesis and purification of both the sulfur-bridged phenol oligomer intermediates and the macrocyclic targets [28,

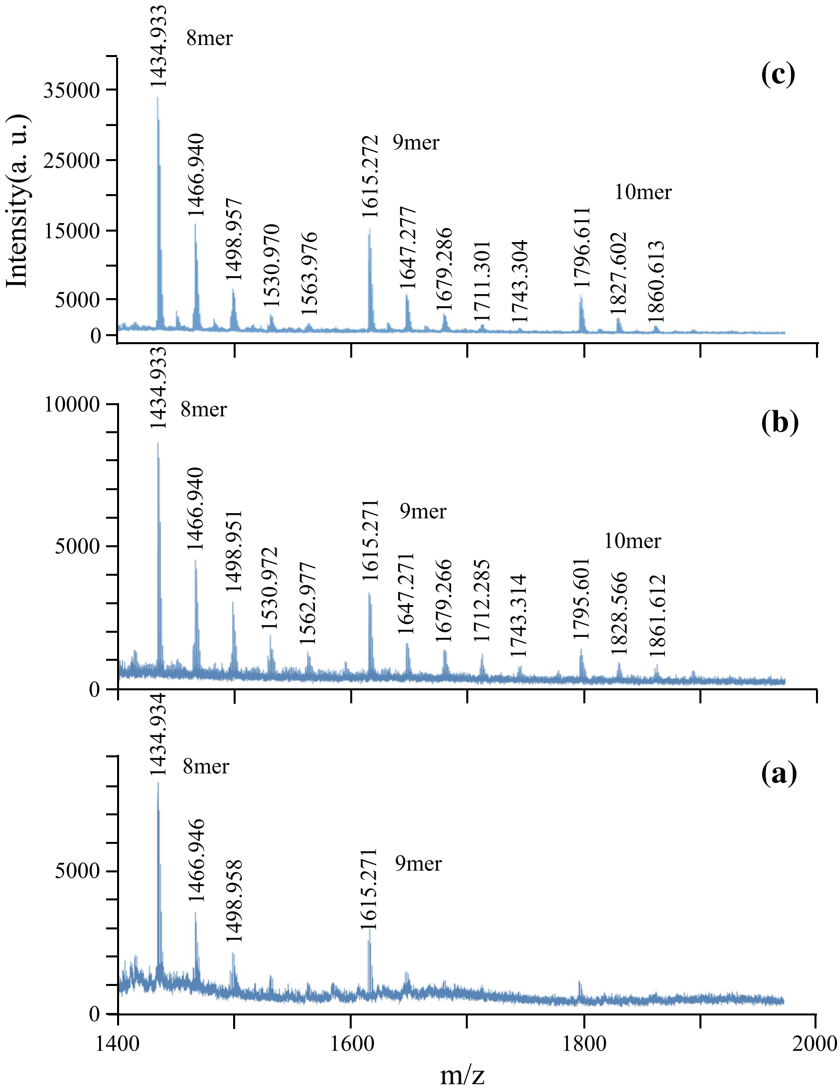

Fig. 2 MALDI-TOF MS analysis of the crude reaction mixture of the first step at **a** 8, **b** 12, and **c** 24 h, indicating the formation of the longer oligomers (octa-, nona-, and decamers) necessary for the formation of larger macrocycles

30]. In contrast, our one-pot synthetic method uses commercial *p-tert*-butylphenol as a starting material and does not require the purification of intermediates. Second, because a high concentration of NaOH results in the predominant formation of **1** via the conventional methods, the NaOH concentration was kept low (<2 mol % relative to *p-tert*-butylphenol) during the initial oligomer formation, and was raised during the cyclization (42–51 mol%).

To successfully synthesize larger *p-tert*-butylthiacalix[*n*]arenes, high molecular weight oligomers must be formed in the first step. We monitored the progress of the reaction by matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS) to observe higher-order oligomer the formation. Figure 2 shows the MALDI-TOF mass spectra at 8, 12, and 24 h. After 8 h, the presence of the nonamer ($[M+Na]^+ = 1{,}615$ *m/z*) was confirmed, but the intensity of the signal was very low. After 12 h, the formation of the decamer ($[M+Na]^+ = 1{,}795$ *m/z*) was observed. The MALDI-TOF MS results showed that the intensity of all the peaks continued to increase over the first 24 h of the reaction, even though the growth of the oligomers ceased after 12 h (Fig. 2a). Therefore, the formation of larger oligomers appears to be a slow process. In addition, oligomers larger than the decamer decompose easily during the second step upon heating at 230 °C. At reaction times longer than 12 h, other peaks differing by 32 *m/z* (in the ranges from 1,434 to 1,563 *m/z*, and from 1,615 to 1,743 *m/z*) were observed, presumably due to oligo-sulfur chains binding to the *o*-positions of the *p-tert*-butylphenol residues at the ends of the oligomers. Therefore, 24 h was chosen as the optimal time for the first step.

Next, we focused on optimizing the reaction time for the second step. The cyclization step is crucial for the formation of the macrocycles; when the reaction was terminated after the first step (at 180 °C for 24 h), the yields of **2** and **3** were 0 % and that of **1** was only 1.6 % (run 5, Table 1).

However, after cyclization at 230 °C and 5 h, the yield of the **2** was significantly improved to an isolated yield of 18.1 % (Figs. S1–S3) (run 1), almost twice the highest reported yield of **2** to date (10.6 %; calculated yield from NMR analysis) [31]. Notably, no **3** was produced. When the reaction time for the second step was increased to 12 h (run 2), the yield of **2** decreased to 7.5 % (Fig. S4), but **3** was produced in 2.7 % yield. Furthermore, when the reaction time for the second step was 24 h (run 3), **3** was obtained in a maximal yield of 4.6 % (Fig. S5). Even though this yield was low, the reaction was selective for **1** (77.0 % yield) and **3**, with no formation of **2** observed. Finally, when the reaction time was extended to 48 h (run 4), the yield decreased not only for **3** (1.5 %), but also for **1** (72.8 %) (Fig. S6). Changing the amount of NaOH in both the first and second steps (runs 6 and 7) did not improve the yields compared to runs 1 and 3. The optimal amounts of NaOH relative to *p-tert*-butylphenol were thus confirmed to be 2 mol % in the first step and 50 mol % in the second step.

The results in Table 1 demonstrate that there is a clear relationship between the generation of macrocyclic *p-tert*-butylthiacalix[*n*]arenes and reaction time in the second step. However, this relationship is not linear: even though the reaction times for runs 2 and 3 were longer than run 1, the yield of **2** decreased considerably more (reaching 0 %) than the yield of **3** increased. We found that **2** and **3** decomposed with heat to give **1** and oligomers, which is consistent with the observed reaction outcome. In the calixarene chemistry, Gutsche and coworkers reported conversion of octameric calix[8]arenes to tetrameric calix[4]arenes at high temperatures (molecular mitosis) [32]. To elucidate 'molecular mitosis' in this issue, **2** and **3** were separately heated to 230 °C in Ph_2O for either 2 or 24 h. Compound **2** was mostly unchanged during the initial 2 h. However, after 24 h, **2** decomposed by decyclization, changing almost completely to **1**. MALDI-TOF MS analysis showed the transformation of **2** into **1** and oligomers by the decrease in the relative intensity of the $[M+Na]^+$ peak for **2** ($\sim$1,102 *m/z*), and the increase in the relative intensity of that for **1** ($\sim$743 *m/z*) (Fig. S7). ^{1}H NMR analysis confirmed the conclusions from the mass spectral results: a peak ($\delta = 9.6$ ppm) attributed to the hydroxyl groups of **1** appeared, whereas the peak ($\delta = 9.2$ ppm) attributed to the hydroxyl groups of **2** disappeared (Fig. S8). In contrast, compound **3** decomposed during the initial 2 h, as indicated by the presence of only the peak for **1** at 743 *m/z* in the MALDI-TOF mass spectrum of the mixture; this peak decreased even further after 24 h (Fig. S9). The ^{1}H NMR spectrum of the colorless powder, obtained after filtration, also showed that **3** had been transformed into **1**.

Conclusion

In the first step of the one-pot synthesis of *p-tert*-butylthiacalix[*n*]arenes, the formation of epithio-bridged oligomers up to ten monomers in length was observed upon heating at 180 °C in the presence of a low concentration of NaOH. For an overall reaction on 30 g scale, we were able to isolate 6.5 g **2** (18.1 %), after second-step heating at 230 °C in the presence of highly concentrated NaOH (run 1). By varying the reaction time at 230 °C, best-case results of 1.6 g **3** (4.6 %) in addition to 27.8 g **1** (77.0 %) were obtained (run 3). This method will contribute to the development of thiacalixarene chemistry because of the facile preparation and improved yields of the higher order *p-tert*-butylthiacalix[*n*]arenes as compared to previous methods.

References

1. Morohashi, N., Narumi, F., Iki, N., Hattori, T., Miyano, S.: Thiacalixarenes. Chem. Rev. **106**, 5291–5316 (2006)
2. Iki, N., Miyano, S.: Can thiacalixarene surpass calixarene? J. Inclusion Phenom. Macrocycl. Chem. **41**, 99–105 (2001)
3. Asfari, Z., Bohmer, V., Harrowfield, J.M., Vicens, J.: Calixarenes 2001. Kluwer Academic Publishers, Dordrecht (2001)
4. Mandolini, L., Ungaro, R.: Calixarenes in action. Imperial College Press, London (2000)
5. Gutsche, C.D.: Calixarenes revisited. The Royal Society of Chemistry, Cambridge (1998)
6. Gutsche, C.D.: Calixarenes. The Royal Society of Chemistry, Cambridge (1989)
7. Torgov, V.G., Us, T.V., Korda, T.M., Kostin, G.A., Kalchenko, V.I.: Extraction of palladium with thiacalix[4]arenes from nitric acid nitrate-nitrite solutions. Russ. J. Inorg. Chem. **57**, 1621–1629 (2012)
8. Itoh, S., Li, C., Yamada, M., Akama, M., Shimakawa, Y., Kondo, Y., Hamada, F.: Selective extraction ability of thiacalix[6]arene derivatives from rare metal mixed solution. Int. J. Soc. Mater. Eng. Resour. **17**, 211–215 (2010)
9. Stoikov, I.I., Yushkova, E.A., Zhukov, A.Y., Zharov, I., Antipin, I.S., Konovalov, A.I.: The synthesis of *p-tert*-butylthiacalix[4]arenes functionalized with secondary amide groups at the lower rim and their extraction properties and self-assembly into nanoscale aggregates. Tetrahedron **64**, 7112–7121 (2008)
10. Yamada, M., Shibayama, A., Kondo, Y., Hamada, F.: Selective extraction of precious metal from automotive catalyst residue by thiacalix[6]arene derivatives. Int. J. Soc. Mater. Eng. Resour. **15**, 13–15 (2007)
11. Iki, N., Morohashi, N., Yamane, Y., Miyano, S.: Metal-ion extractability of sulfur-bridged oligomers of phenol; distinct effect of the number of sulfur bridges rather than the cyclic/acyclic form. Bull. Chem. Soc. Jpn **76**, 1763–1768 (2003)
12. Katagiri, H., Iki, N., Matsunaga, Y., Kabuto, C., Miyano, S.: Thiacalix[4]aniline as a highly specific extractant for Au(III) and Pd(II) ions. Chem. Commun. **18**, 2080–2081 (2002)
13. Yamada, M., Shimakawa, Y., Hamada, F.: Thiacalix[4]arene–alkali metal assemblies: crystal structures and guest-binding capabilities of supramolecular architectures supported by metal

coordination and cation–π interactions. Tetrahedron **67**, 7392–7399 (2011)

14. Yamada, M., Kondo, Y., Iki, N., Kabuto, C., Hamada, F.: Hydrophobic and metal coordination interacted architecture based on *p*-*tert*-butylthiacalix[4]arene–potassium complex and its vapor absorption capability. Tetrahedron Lett. **49**, 3906–3911 (2008)
15. Kondo, Y., Endo, K., Hamada, F.: Potassium–thiacalix[8]arene assembly: structure and guest sorption profiles. Chem. Commun. **6**, 711–712 (2005)
16. Endo, K., Kondo, Y., Aoyama, Y., Hamada, F.: Guest-binding properties of functionally crystal based on metal complex of *p*-*tert*-butylthiacalix[6]arene. Tetrahedron Lett. **44**, 1355–1358 (2003)
17. Evtugyn, G.A., Shamagsumova, R.V., Sitdikov, R.R., Stoikov, I.I., Antipin, I.S., Ageeva, M.V., Hianik, T.: Dopamine sensor based on a composite of silver nanoparticles implemented in the electroactive matrix of calixarenes. Electroanalysis **23**, 2281–2289 (2011)
18. Kim, J.S., Quang, D.T.: Calixarene-derived fluorescent probes. Chem. Rev. **107**, 3780–3799 (2007)
19. Ben, A.M., Bureau, C., Martelet, C., Jaffrezic-Renault, N., Lamartine, R., Ben, O.H.: Comparison of thiacalix[4]arene thin films behaviour on different transducers for copper ion detection. Mater. Sci. Eng. C **7**, 83–89 (2000)
20. Grady, T., Butler, T., MacCraith, B.D., Diamond, D., McKeyvey, M.A.: Optical sensor for gaseous ammonia with tuneable sensitivity. Analyst **122**, 803–806 (1997)
21. Aoki, I., Sakaki, T., Shinkai, S.: A new metal sensory system based on intramolecular fluorescence quenching on the ionophoric calix[4]arene ring. J. Chem. Soc. Chem. Commun. **9**, 730–732 (1992)
22. Jin, T., Ichikawa, K., Koyama, T.: A fluorescent calix[4]arene as an intramolecular excimer-forming Na^+ sensor in nonaqueous solution. J. Chem. Soc. Chem. Commun. **6**, 499–501 (1992)
23. Iki, N., Kabuto, C., Fukushima, T., Kumagai, H., Takeya, H., Miyanari, S., Miyashi, T., Miyano, S.: Synthesis of *p*-*tert*-butylthiacalix[4]arene and its inclusion property. Tetrahedron **56**, 1437–1443 (2000)
24. Kajiwara, T., Kon, N., Yokozawa, S., Ito, T., Iki, N., Miyano, S.: Synthesis, structure, and ferromagnetic behavior of decacopper(II) cluster complex supported by hexaanionic *p*-*tert*-butylthiacalix[6]arene. J. Am. Chem. Soc. **124**, 11274–11275 (2002)
25. Yamada, M., Kondo, Y., Hamada, F.: Hydrogen-bonded architecture based on *p*-sulfonatothiacalix[6]arene complex with dysprosium(III) cations and water molecules. Tetrahedron Lett. **49**, 1790–1794 (2008)
26. Yamada, M., Kondo, Y., Hamada, F.: The X-ray crystal structures of *p*-sulfonatothiacalix[6]arene inclusion complexes with lanthanide metal ions (M = Gd, Ho and Er) and water molecules. Int. J. Soc. Mater. Eng. Resour. **15**, 50–56 (2008)
27. Yamada, M., Hamada, F.: Supramolecular assemblies with water-soluble *p*-sulfonatothiacalix[6]arene lanthanide complexes: one-dimensional 'ladder-type' coordination polymers and one-dimensional hydrogen-bonded polymers. CrystEngComm **15**, 5703–5712 (2013)
28. Kondo, Y., Endo, K., Iki, N., Miyano, S., Hamada, F.: Synthesis and Crystal structure of *p*-*tert*-butylthiacalix[8]arene: a new member of thiacalixarenes. J. Inclusion Phenom. Macrocycl. Chem. **52**, 45–49 (2005)
29. Gutsche, C.D., Dhawan, B., No, K.H., Muthukrishnan, R.: Calixarenes. 4. The synthesis, characterization, and properties of the calixarenes from *p*-*tert*-butylphenol. J. Am. Chem. Soc. **103**, 3782–3792 (1981)
30. Kon, N., Iki, N., Miyano, S.: Synthesis of *p*-*tert*-butylthiacalix[*n*]arenes ($n = 4$, 6, and 8) from a sulfur-bridged a cyclic dimer of *p*-*tert*-butylphenol. Tetrahedron Lett. **43**, 2231–2234 (2002)
31. Kondo, Y., Hamada, F.: Improvement method for synthesis of *p*-*tert*-butylthiacalix[*n*]arenes: effect of using base catalyst with carboxylic acid. J. Inclusion Phenom. Macrocycl. Chem. **58**, 123–126 (2007)
32. Gutsche, C.D., Johnston, D.E., Stewart, D.R.: Pathways for the reversion of *p*-*tert*-butylcalix[8]arene to *p*-*tert*-butylcalix[4]arene. J. Org. Chem. **64**, 3747–3750 (1999)