Synthesis and Properties of Homooxa- and Homoaza-thiacalix[4]arenes

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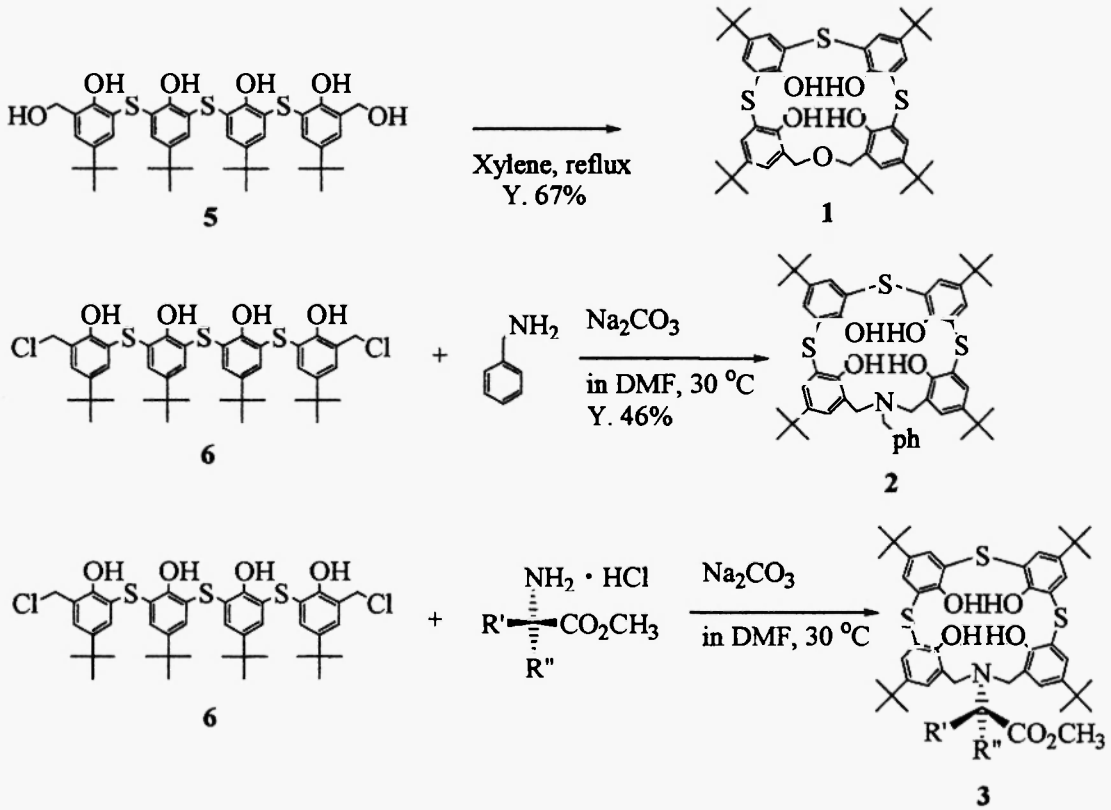
Abstract: New thiacalix[4]arene analogs incorporating a homooxa-moiety and a homoaza-moiety including amino acid residues in the macrocyclic rings were prepared and their structural properties were studied by ^{1}H NMR and CD spectra. Furthermore, their coordination ability toward metal ions was investigated by solvent extraction study.

During the last two decades, calixarenes have attracted much attention as versatile host molecules owing to their ready availability and easiness in the chemical modification.[1] Many studies of the modification of calixarenes have so far been made at the lower rim (phenolic OH groups) and/or the upper rim (the *p*-position).[1] On the contrary, there are many reports about calixarene analogs. The representative compounds are homooxa- and homoaza-calixarenes, in which CH_2 groups are partly or completely replaced by CH_2OCH_2 or CH_2NRCH_2 groups, respectively.[2] These heteroatom bridges lead to dramatic changes in dynamic and complexation properties in calixarene chemistry. So, our interest was focused on the modification of the methylene moiety by changing to another group such as carbonyl, sulfur, or amino acids.[3]

Furthermore, replacement of the original methylene bridges between the aromatic units in calixarenes by sulfur atoms has been reported, leading to thiacalix[4]arenes (TCA).[4] Since then, interest in the development of TCA has been increasing because of their unique properties.[5] This situation prompted us to combine TCA and homooxa- or homoaza-calixarene to produce novel calixarene analogs.

Herein, we report the facile synthesis of new homooxa- and homoaza-thiacalix[4]arenes, which have three bridging sulfurs and one CH_2OCH_2 group or CH_2NRCH_2 groups including amino acid residues, and their structural properties. Furthermore, their coordination ability toward metal ions was investigated by solvent extraction study.

Homooxathiacalixarene **1** was prepared in 67% yield by refluxing the bis(hydroxymethyl)phenol-sulfur tetramer **5**[6] in xylene. The homoazathiacalixarenes **2, 3a-c** were prepared by the cyclization reaction of the bis(chloromethyl)phenol-sulfur tetramer **6**[3] with benzylamine or the amino acid methyl esters in DMF at 30 °C in 21-46 % yields (Scheme 1).



3a: R'=H, R"=CH_2-C6H5 , Y. 24% **3c**: R'=H, R"=CH_2-indole , Y. 28%

3b: R'=H, R"=CH_2-C6H4-OH , Y. 21%

Scheme 1.

The structures of macrocycles (**1**, **2**, **3a-c**) were established on the basis of their FAB-MS and NMR spectra.[7] The assignment of protons was done using 2D NMR. The NOE correlations observed for **1** and **2** as

shown in Figure 1 suggested that both **1** and **2** should adopt a cone conformation.

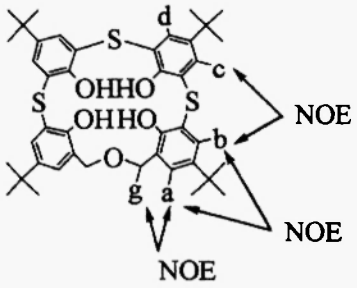


Figure 1. NOE correlation of **1**

Measurements of the ^{1}H NMR relaxation times (T_1) were made to gain deeper insight into the dynamic behavior of **1** and **2** in solution (Fig. 2). The technique has been successfully utilized for elucidating the complexation[8] and conformational mobility[9] of some calixarene derivatives. The T_1 values of the aromatic proton and the *tert*-butyl proton of **1** and **2** are smaller than those of TCA. This result shows that macrocycles **1, 2** were restrained in conformational mobility though these compounds have a larger cavity than the TCA. Furthermore, T_1 values of aromatic proton near bridging oxygen of **1** and nitrogen of **2** are smallest among aromatic protons in molecule, respectively. We postulate that these result was caused by a strong hydrogen bonding between the lone pair electron of the nitrogen or oxygen and OH of the phenol, which made a more rigid structure than that of TCA.

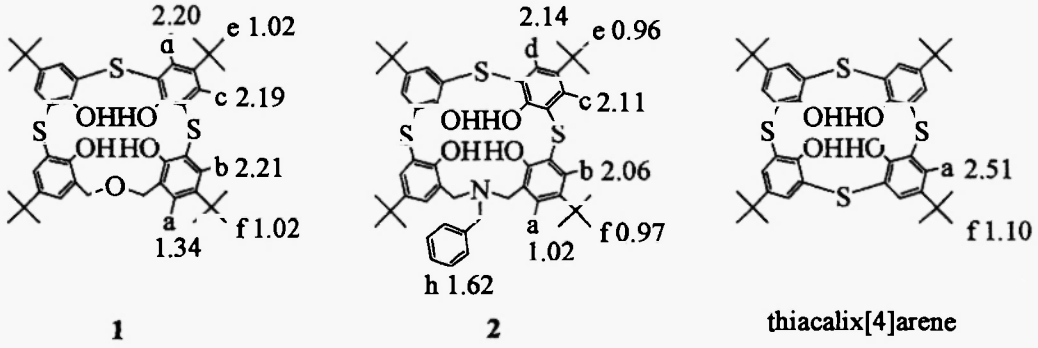


Figure 2. ^{1}H NMR relaxation times T_1[s] of macrocycles **1**,**2** and thiacalix[4]arene

The cyclophane moiety of macrocycles **3a-c** having amino acid residues should be affected by the chirality of amino acid. In order to elucidate the chirality of the sulfur-bridged tetramer unit, we measured the CD spectrum of **3a-c** in $CDCl_3$ at 20 ℃ (Fig. 3). The CD spectral absorption pattern of **3a-c** is quite similar to that of the known chiral calixarenes,[3,10] supporting the assumption that the phenol-sulfur tetramer unit is chiral. The CD spectrum of **3a-c** in 10 % MeOH-$CDCl_3$ solution decreased the signal intensities compared with those in $CDCl_3$. This result implies that the hydrogen-bonded array plays an important role in the transmission of chirality from the amino acid to the phenol-sulfur tetramer unit

It is known that TCA has the ability to coordinate with transition metals because it binds to soft metal ions *via* not only phenolic oxygen but also the bridging sulfur as a soft donor.[11] We examined the metal-binding

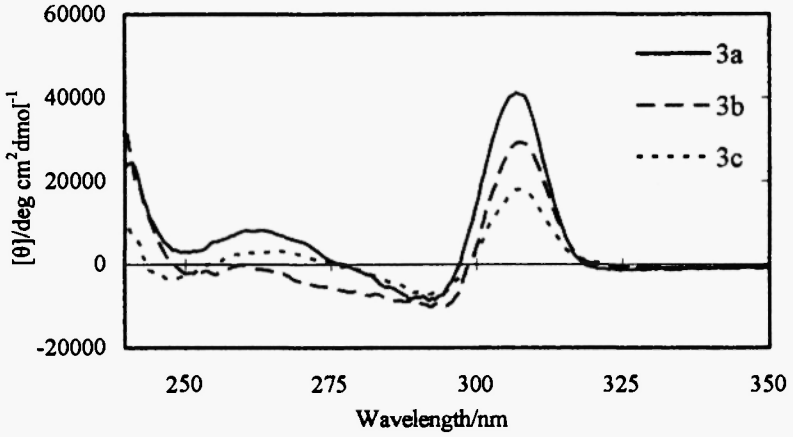


Figure 3. CD spectra of **3a-c**

ability of synthesized thiacalixarene analogs by solvent extraction toward alkali[12] and transition[13] metal ions. It can be seen from Table 1 that all of **1, 2** and **3a-c** could extract transition metal ions but not alkali metal ions, that is quite similar to the case of TCA. These results indicate that the metal binding ability of homooxa- and homoaza-thiacalixarenes depends on bridging sulfur rather than bridging oxygen and nitrogen. Neither **1** nor **2** was able to coordinate with Ni^{2+}, suggesting that slow complexation between Ni^{2+} and these macrocyles prevents extraction. Indeed, the extraction (%) reached 99% when extraction time was extended to 24 hours.

Table 1. The extraction (%) values of metal ions by macrocycles

	Alkali metal (pH 5.5)				Transition metal (pH 7.5)		
receptor	Na^+	K^+	Rb^+	Cs^+	Co^{2+}	Ni^{2+}	Zn^{2+}
1	2	2	0	0	92	0	94
2	5	7	7	4	94	0	99
3a	1	8	0	6	58	53	99
3b	3	5	3	9	99	56	99
3c	0	0	4	8	68	47	99
TCA	10	12	11	2	99	12	99

In conclusion, we have synthesized novel thiacalixarene analogs incorporating an oxygen atom or a nitrogen atom into their macrocyclic ring. ^1H NMR and CD spectroscopy of chiral calixarenes having an amino acid residue showed that a chiral cavity was constructed in the molecule *via* transmission of the

chirality from the amino acid to all the phenol moieties, in which hydrogen-bonded array plays an important role. Homooxathiacalix[4]arene and homoazathiacalix[4]arenes had the extraction ability to soft metal ions such as Co^{2+}, Ni^{2+}, and Zn^{2+} investigated by solvent extraction study.

References and Notes

1 C. D. Gutsche, "*Calixarenes Revisited*," in "Monographs in Supramolecular Chemistry," Ed. by J. F. Stoddart, The Royal Society of Chemistry, Cambridge (1998).

2 Z. Asfari, V. Böhmer, J. Harrowfield, and J. Vicens, "*Calixarenes 2001*," Kluwer Academic Publishers, Ch. 12 (2001).

3 a) K. Ito, A. Kida, Y. Ohba, and T. Sone, *Chem. Lett.*, **1998**, 1221. b) K. Ito, Y. Ohba, and T. Sone, *Nippon Kagaku Kaishi*, 217(1999).

4 a) T. Sone, Y. Ohba, K. Moriya, and K. Ito, *Tetrahedron*, **53**, 10689(1997). b) H. Kumagai, M. Hasegawa, S. Miyanari, Y. Sugawa, Y. Sato, T. Hori, S. Ueda, H. Kamiyama, and S. Miyano, *Tetrahedron Lett.*, **38**, 3971 (1997).

5 N. Morohashi, N. Iki, and S. Miyano, *Yuki Gosei Kagaku Kyokaishi*, **60**, 550 (2002).

6 Y. Ohba, K. Moriya, and T. Sone, *Bull. Chem. Soc. Jpn.*, **64**, 576 (1991).

7 The assignment of the protons was confirmed by H-H COSY. and NOESY. experiments. Spectral deta of macrocycles (**1**, **2** and **3a-c**) as follows: **1**: white crystal; mp 256-259 °C; ^{1}H NMR($CDCl_3$) δ 1.21(18H, s, *t*-Bu), 1.25(18H, s, *t*-Bu), 4.61(4H, s, CH_2OCH_2), 7.09(2H, d, J = 2.5 Hz, Ar-H), 7.59(2H, d, J = 2.5 Hz, Ar-H), 7.65(2H, d, J = 2.5 Hz, Ar-H), 7.69(2H, d, J = 2.5 Hz, Ar-H), 8.45(2H, s, OH), 9.08(2H, s, OH); FAB MS(3-NBA), m/z: 732 (M^+). **2**: white crystal; mp 178-182 °C; ^{1}H NMR($CDCl_3$) δ 1.24(18H, s, *t*-Bu), 1.25(18H, s, *t*-Bu), 3.61(2H, s, CH_2-Ar), 3.71(4H, br, CH_2NCH_2), 6.98(2H, d, J = 2.5 Hz, Ar-H), 7.28(5H, br, bezyl proton), 7.62(2H, d, J = 2.5 Hz, Ar-H), 7.65(2H, d, J = 2.5 Hz, Ar-H), 7.66(2H, d, J = 2.5 Hz, Ar-H); FAB MS(3-NBA), m/z: 823($[M+1]^+$). **3a**: white crystal; mp 168-173 °C; ^{1}H NMR($CDCl_3$) δ 1.22(18H, s, *t*-Bu), 1.25(18H, s, *t*-Bu), 3.23(1H, dd, J = 4.5, 13.5 Hz,CH*H*-Ar), 3.38(1H, dd, J = 4.5, 13.5 Hz, CH*H*-Ar), 3.48(1H, d, J = 12.5 Hz), 3.61(5H, m, CH_2NCHH, $NCHRCO_2CH_3$, $COOCH_3$), 3.88(1H, d, J = 13.5 Hz, CH_2NCHH), 4.33(1H, d, J = 12.5 Hz, CH_2NCHH), 6.96(1H, s, Ar-H), 7.08(1H, s, Ar-H), 7.21-7.31 (5H, m, benzyl proton), 7.60(1H, s, Ar-H), 7.62(2H, br, Ar-H), 7.64(1H, s, Ar-H), 7.67(1H, s, Ar-H), 7.69(1H, s, Ar-H), 9.52(4H, br, OH); FAB MS(3-NBA), m/z: 894($[M+1]^+$). **3b**: white crystal; mp 173-177 °C; ^{1}H NMR($CDCl_3$) δ 1.17(9H, s, *t*-Bu), 1.19(9H, s, *t*-Bu), 1.23(9H, s, *t*-Bu), 1.26(9H, s, *t*-Bu), 3.15(1H, dd, J = 4.5, 14 Hz, CH*H*-Ar), 3.51(2H, br, CH*H*-Ar, CH_2NCHH) 3.83(3H, s, $COOCH_3$), 3.91-3.99(4H,

m, CH_2NCHH, $NCHRCO_2CH_3$), 6.87(1H, s, Ar-H), 7.09(1H, s, Ar-H), 7.11(1H, s, Ar-H), 7.15(1H, s, Ar-H), 7.46(2H, br, Ar-H), 7.61(1H, s, Ar-H), 7.62(1H, s, Ar-H), 7.63(1H, s, Ar-H), 7.71(2H, s, Ar-H), 7.75(1H, s, Ar-H); FAB MS(3-NBA), m/z: 910($[M+1]^+$). **3c**: white crystal; mp 173-177 °C; ^1H NMR($CDCl_3$) δ 0.96(9H, s, *t*-Bu), 1.07(9H, s, *t*-Bu), 1.10(9H, s, *t*-Bu), 1.24(9H, s, *t*-Bu), 3.17(3H, s, $COOCH_3$), 3.38-3.46(4H, m), 3.63(1H, dd, J= 9.5, 10 Hz, $NCHRCO_2CH_3$), 3.86(1H, dd, J= 4.5, 10 Hz, CH*H*-indol), 4.37(1H, d, J= 12.5 Hz, CH_2NCHH), 6.61(1H, s, NH), 6.69(1H, s, Ar-H), 6.71(1H, d, indol ring proton), 6.99(1H, dd, J= 7.5, 7.5Hz, indol ring proton), 7.19(1H, m, indol ring proton), 7.30(1H, dd, J= 7.5, 7.5 Hz, indol ring proton), 7.72-7.76(3H, m, Ar-H, indol ring proton), 7.82(1H, s, Ar-H), 7.87(1H, s, Ar-H), 7.87(1H, s, Ar-H), 7.89(1H, s, Ar-H), 7.94(1H, s, Ar-H); FAB MS(3-NBA), m/z: 934($[M+1]^+$).

8 See for example: S. Ahn, S-K. Chang, T. Kim, and J. W. Lee, *Chem. Lett.*, **1995**, 297.

9 J.S. Rogers, and C. D. Gutsche, *J. Org. Chem.*, **57**, 3152 (1992).

10 K. Iwamoto, H. Smizu, K. Araki, and S. Shinkai, *J. Am. Chem. Soc.*, **115**, 3997 (1993).

11 N. Morohashi, N. Iki, A. Sugawara, and S. Miyano, *Tetrahedron*, **57**, 5557(2001).

12 To a 20-cm^3 test tube were pipetted 2.5 cm^3 of 3.5×10^{-4} M alkali metal nitrate solution, 2.5 cm^3 of 3.5×10^{-4} M picric acid and 5.0 cm^3 of receptor solution (7.0×10^{-5} M) in CH_2Cl_2, and the mixture was then shaken at 150 strokes per min for 30 min. The extraction (%) was determined by means of the differences in absorbance of picrate in the aqueous phase and calculated by the following equation:

$$\text{Extraction (\%)} = (A_0 - A) / A_0 \times 100\ \%.$$

Where A_0 and A are the absorbance (354 nm) of picrate in the absence and the presence of metal nitrate, respectively

13 Into a test tube (20 cm^3) were pipetted an aqueous solution (5.0 cm^3) containing transition metal nitrate ($[Metal]_{aq,init} = 3.0 \times 10^{-4}$ M) as well as pH buffer (pH 7.5) and a chloroform solution (5.0 cm^3, [**1**, **2**, or **3a-c**] = 1.0×10^{-3} M). The mixture was then shaken at 150 strokes per min for 30 min. The total concentration of the metal species remaining in the aqueous phase, $[Metal]_{aq}$, was measured by an atomic absorption spectrometer. The extraction (%) was calculated by the following equation:

$$\text{Extraction (\%)} = ([Metal]_{aq,init} - [Metal]_{aq})/([Metal]_{aq,init}) \times 100\ \%$$

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