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Syntheses and ion binding properties of novel cage molecules derived from homooxacalix[3]arene

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Abstract

Novel cage molecules were synthesized by capping of the homooxacalix[3]arene on the upper rim. Comparison with a reference compound established that the appropriate cavity size and rigid structure led to the very high Cs^+ selectivity. © 2000 Elsevier Science Ltd. All rights reserved.

Macrocyclic ionophores with a high binding ability and selectivity have been the focus of host−guest chemistry in the past decade. A molecular design based on the hole size selectivity is one of the simple and effective strategies used to obtain ionophores selective to alkali metal ions. In 1994, Shinkai and Yamamoto demonstrated that calix[4] crown ethers with a short oligooxyethylene crown loop on the lower rim showed a remarkably high selectivity for Na^+ among the alkali metal ions.[1] Their high recognition ability for Na^+ is ascribed to the cavity size somewhat smaller than the ion size of Na^+ and to the rigid calix[4]arene skeleton supporting the cavity as a platform. According to the concept of exclusion recognition, designing macrocycles with a smaller ring number for the selective binding to a small metal cation must reduce the conformational freedom on their structure, resulting in the enhancement of the ion selectivity. Increasing the ring size for selective binding to a large metal cation, on the other hand, will enhance the flexibility of the macrocyclic structure and consequently decrease the selectivity. Therefore, in order to develop ionophores selective for large metal cations, macrocycles possessing a cavity somewhat larger than the target metal cation and appropriately rigid structure must be designed.

Homooxacalixarenes, a family in calixarenes, are a new class of synthetic macrocycles having phenolic units linked by the CH_2OCH_2 bridges and their trimer has been widely used as a platform to generate versatile hosts.[2–12] In most cases, the functionalization of homooxacalix[3]arene has been achieved by *O*-alkylation of the OH groups on the lower rim. For example, trimethoxyhomooxacalix[3]arene shows K^+ selectivity in contrast to the fact that calix[4]arene ionophores selectively bind to Na^+ among the alkali metal ions. However, the selectivity is not very high due to the conformational flexibility. This stimulated

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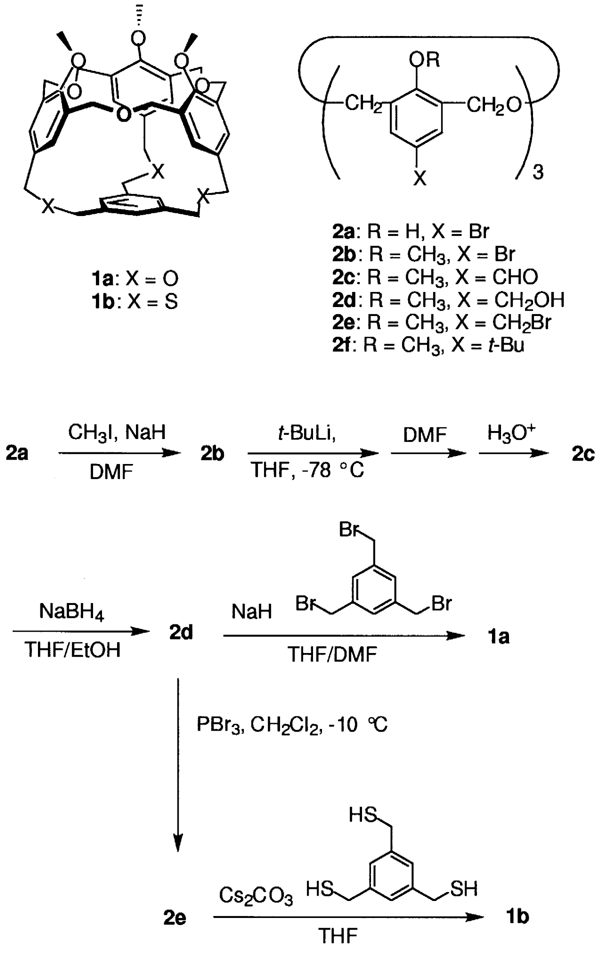
us to design ionophores based on the homooxacalix[3]arene with a rigid structure which would exhibit high selectivity for K^+ or larger alkali metal ions. We now report the synthesis and the ion selectivity of homooxacalix[3]arene **1** capped by 1,3,5-trisubstituted benzene at the upper rim.

The target upper-rim-capped homooxacalix[3]arenes **1a** and **1b** were synthesized from 7,15,23-tribromo-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene-25,26,27-triol[5] **2a** according to Scheme 1. Compound **2a** was tri-*O*-methylated with CH_3I in the presence of NaH in refluxing THF to afford **2b** in 41% yield. Compound **2b** was converted into **2c** with *t*-BuLi in THF at −78°C, followed by a reaction with DMF and subsequently treatment with aqueous HCl (65%). Compound **2c** was reduced with $NaBH_4$ in THF, yielding **2d** (85%). The synthesis of the upper-rim-capped homooxacalix[3]arene **1a** was carried out by simply adding the THF/DMF mixture solution of **2d** and 1,3,5-trisbromomethylbenzene to a boiling suspension of NaH (26%). The other target, **1b**, was synthesized by the 1:1 coupling of 1,3,5-trismercaptomethylbenzene and **2e**, which was obtained by the bromination of **2d** with PBr_3 in CH_2Cl_2 in 71% yield, in the presence of Cs_2CO_3 in THF (36%). All the products were identified by IR, ^{1}H NMR, and mass spectral evidence and elemental analysis.



Scheme 1.

The temperature-independent ^{1}H NMR peaks for the $ArCH_2OCH_2Ar$ methylene protons attached at the *ortho*-positions to the phenolic oxygen atoms in **1** showed one pair of doublets at 25°C in $CDCl_3$:

4.50 and 4.55 ppm for **1a** and 4.48 and 4.59 ppm for **1b**. The other peaks were observed as five singlets assignable to the protons in the methoxy, two ArHs in the phenols and the 1,3,5-trisubstituted benzene capping the upper rim, and two methylenes in the spacers connecting the capping benzene. This simple spectrum indicates that **1a** and **1b** possess C_{3V} symmetry. These findings reveal that the homooxacalix[3]arene skeletons are immobilized in the cone conformation. The inversion of the benzene rings in the tri-*O*-methylated homooxacalix[3]arene can take place faster than the NMR timescale, because the ring inversion proceeds along with the oxygen-through-the-annulus rotation and the methoxy group is small enough to pass the annulus.[3] The introduction of alkyl groups bulkier than propyl groups into the OH groups was the only strategy so far to inhibit the rotation and to obtain the isolatable conformers, cone and partial cone.[3] Therefore, **1a** and **1b** are the first homoxacalix[3]arenes fixed in the cone conformation by capping with covalent bonds at the upper rim.

The ion selectivity of **1a** and **1b** toward alkali metal ions was estimated by the two-phase solvent extraction experiment.[13] The percent extraction (Ex%) is illustrated in Fig. 1. Tri-*O*-methylated homooxacalix[3]arene **2f**,[3] the reference compound, extracted K^+, Rb^+ and Cs^+ with almost equal extractability. The selectivity is for K^+ but it is not very high among K^+, Rb^+ and Cs^+. The upper-rim-capped **1a**, on the other hand, preferentially extracted Cs^+ from the aqueous phase into the organic phase, compared with **2f**. This implies that **1a** is able to preferentially form a complex with Cs^+ and dissolve the Cs^+ salt in the organic phase. The high selectivity of **1a** for Cs^+ results in the fact that the Ex% of **1a** for Cs^+ increased and that for Rb^+ and K^+ decreased. This finding established that the flexible structure of the homooxacalix[3]arene was converted to a rigid one and the cone–partial cone isomerization reducing the selectively binding ability toward metal ions was fixed by capping at the upper rim. The high Cs^+ selectivity of **1a** is comparable to that of the known Cs^+ selective calixarene ionophores.[14–16] Interestingly, **1b**, which bears CH_2SCH_2 spacers connecting the capping benzene ring at the upper rim, instead of CH_2OCH_2 spacers in **1a**, did not extract any alkali metal ion at all.

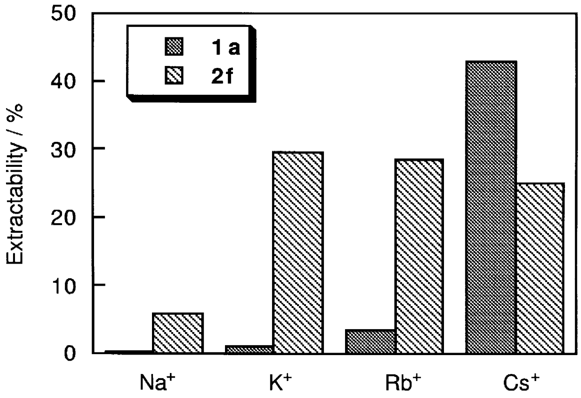


Fig. 1. Percent extraction (Ex%) of alkali metal picrate into dichloromethane at 25°C

At the present stage, the complex structure of **1a** with Cs^+ is equivocal, because the chemical shift change in the ^1H NMR of **1a** caused by the complexation with Cs^+ is explained by both the change in the structure and/or the electrostatically induced effect caused by the coordination to Cs^+. However, in the optimized structure of **1a** by using molecular mechanics and molecular orbital calculations, the trigonal cavity composed of three phenolic oxygen atoms is too small to fully include Cs^+. Therefore, it is likely that Cs^+ is surrounded by the four benzene rings of **1a** in the complex and the importance of the cation–π interaction[17] for the complex formation is strongly suggested, as seen in the known Cs^+ selective ionophores.[14,15] Added to this, the additional dipole-charge interaction between Cs^+ and oxygen atoms in the CH_2OCH_2 bridges should be taken into consideration as a contribution to the driving force for the complex formation. Indeed, the predicted cavity size of three phenolic oxygen atoms is small for Na^+. Therefore, the alkali metal ions, other than Cs^+, cannot be bound steadily in the phenolic oxygen cavity or the π-cavity.

In conclusion, an ionophoric, novel cage molecule was synthesized from the homooxacalix[3]arene. The solvent extraction experiment clarified that the cage molecule showed high Cs^+ selectivity due to the rigid structure caused by capping at the upper rim of the homooxacalix[3]arene. We are now studying the structure of the metal ion complexes.

Acknowledgements

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13. The experimental condition is as follows. Aqueous phase: 5 ml of water, [alkali metal picrate]=2.50×10^{-4} M, [MOH]=0.10 M, [MCl]=0.50 M; organic phase: 5 ml of dichloromethane, [ionophore]=1.00×10^{-3} M. The two-phase mixture was shaken for 12 h at 25°C. The extractability was determined spectrophotometrically from a decrease in the absorbance of the picrate in the aqueous phase.
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