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Synthesis and characterization of calixarene analogs locked in the cone conformation by the dimerization of *syn*-dihydroxymetacyclophanes as a building block

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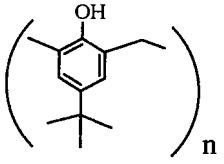
Abstract—*syn*-Dihydroxymetacyclophanes were converted to bridged calix[4]arene analogs by base-catalyzed condensation with formaldehyde. A remarkable template effect was observed on this condensation. Enlarged calix[4]arene analogs were synthesized by two different methods. All calix[4]arene analogs took the cone-type conformation and kept it even at high temperatures, according to the elucidation by ^{1}H NMR spectroscopy. The acidities (p*K*app) of calix[4]arene analogs, which partially form the hydrogen bonding, were medium values in the range of 5.1–5.5. Calix[4]arene analogs can transport Li^+ ion considerably and show the selectivity for Li^+ over Na^+ ions 15 and 30 in the weak basic and neutral solutions, respectively.

1. Introduction

Many calix[*n*]arenes **1** and their derivatives were reported as powerful host molecules in the last decade.[1–5] Rigidification is one of the most important modifications of these compounds which resulted in arranging binding sites favorably for various guests.[6] We have successfully synthesized completely cone-formed and bridged calix[4]arene analogs by the dimerization of *syn*-metacyclophanes taking face-to-face situation as a building block.[7–11] In order to make the calixarenes conformationally more rigid, oligomethylene bridges were introduced and resulted in changing hydrogen bonding nature and giving better selectivity for metal ions.[12–27] In fact, calix[4]arene analogs became selective for alkali metal ions, although parent calixarenes **1** did not work as ionophores.



	n
1a	4
b	6
c	8

Thus, calix[4]arene analogs showed many different features from the parent calix[4]arene **1** in spite of molecular similarity. Accordingly, we attempted to develop another synthetic route of calixarene analogs and characterize the nature of their hydroxy groups. We report here the synthesis and characterization of calix[4]arene analogs derived from dihydroxymetacyclophanes in detail.

2. Results and discussion

2.1. Synthesis of calix[4]arene analogs

The synthesis of calix[4]arene analogs **3** is shown in Scheme 1 and Table 1.[10] Dihydroxy[2.*n*]metacyclophanes **2** were chosen as a building block to make a series of new calix[4]-arenes, because of easy preparation and *syn*-conformation proved by NMR spectroscopic analysis.[8,28] First, we tried calixarene synthesis with alkali metal hydroxide and paraformaldehyde in xylene following the reported methods,[4] but we obtained no desired macrocycles. Therefore, we modified the reaction conditions by using ether solvent instead of xylene to increase the solubility of metacyclophanes. *syn*-Dihydroxy[2.5]metacyclophane **2b** (2.0 g, 6.5 mmol) was treated with LiOH (0.31 g, 13 mmol) and paraformaldehyde (2.0 g, 65 mmol) in 20 cm^3 of diglyme at 140–150°C for 12 h under a nitrogen atmosphere to afford a desired product **3a**. Interestingly, a remarkable template effect was observed on this condensation as shown in Fig. 1, i.e. LiOH gave **3a** in excellent 89% yield. When other larger metal ions were used, the yield was considerably decreased in the order of Na^+ (42%), K^+ (15%), and Rb^+ (5%). CsOH did not give **3a** at all under the same reaction conditions.

Keywords: calixarene; cyclophane; acidity; alkali metal; transport.

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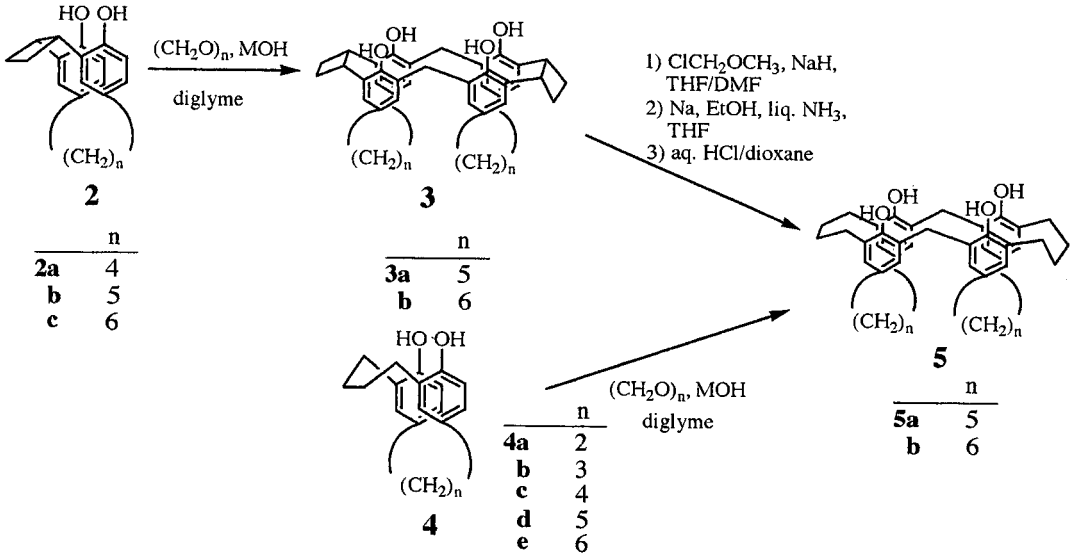


Scheme 1.

Table 1. Yields (%) of calix[4]arene analogs **3** and **5** (compounds **2a** and **4a–c** did not give any dimers)

Compd	Yield (%)				
	LiOH	NaOH	KOH	RbOH	CsOH
2b	89	42	15	5	0
2c	19	21	21	34	78
4d	<1	4	11	13	17
4e	0	0	<1	1	3

syn-Dihydroxy[2.6]metacyclophane **2c** was also converted to calix[4]arene analog **3b** by the dimerization.[14] The template effect was also observed on this reaction, i.e. CsOH gave **3b** in a good yield of 78%. When other smaller alkali metal ions were used, the yield was gradually decreased in the order of Rb^+ (34%), K^+ (21%), Na^+ (21%), and Li^+ (19%) (see Fig. 1).

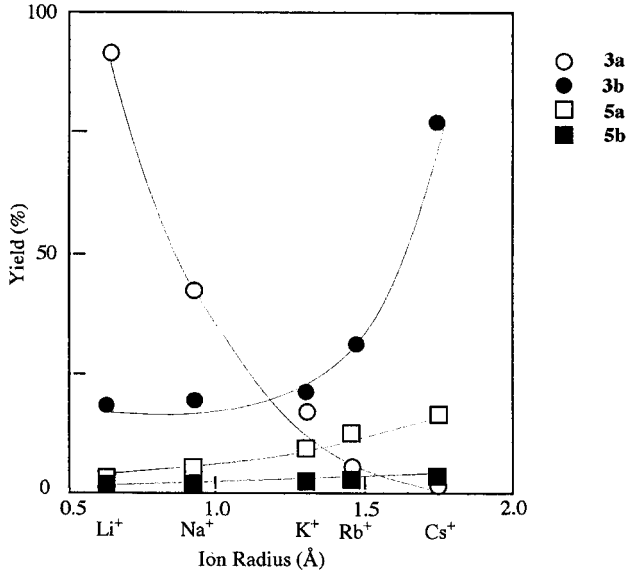
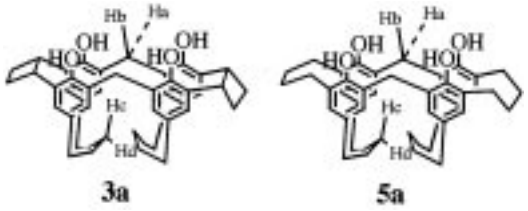


Figure 1. Template effect of alkali metal cations on the yield of calixarene analogs. Reaction conditions: metacyclophane (0.33 M), paraformaldehyde (5 equiv.), and metal hydroxide (1 equiv.) in diglyme at 140–150°C for 12 h under N_2.

VT NMR exhibits that **2b** and **c** primarily maintain *syn*-conformation, although they slightly show the conformational change at 140°C as shown in Fig. 2. Accordingly, metacyclophanes which are always maintaining *syn*-conformation were adapted to the calix[4]arene synthesis as building blocks.

Unfortunately, *syn*-dihydroxy[2.4]metacyclophane **2a** did not give any dimers. If **2a** gave a dimeric product like calix[4]arene structure, it became more strained by 10–15 kcal/mol than **3**, according to the MM2 calculation. Furthermore, **2a** showed the conformational change at 110°C and cycloreversion to 1,4-bis(*m*-vinylphenyl)butane also proceeds at about 15% for 6 h at 140°C.

Enlarged calix[4]arene analogs **5** were synthesized through introducing a protective group on phenolic OH groups as shown in Scheme 1. A methoxymethyl (MOM) group was chosen as a protective group, because its protection and deprotection are readily done under mild conditions.[17–19] The methoxymethylation was performed with **3** (31 mM), chloromethyl methyl ether (10 equiv.), and NaH (2 equiv.) in dry THF/DMF (9/1) at 40–45°C for 12 h under N_2. The desired ethers were obtained in 90–95% yields. Birch reduction was performed with the ether (4.3 mM), Na (150 equiv.), and EtOH (4 equiv.) in liq. NH_3/dry THF (1/1) at −60°C for 4 h under N_2. The deprotection was carried out with the crude product (1 mM) in THF/aq. HCl (1/1) at 50°C for 12 h. After column chromatography, pure **5** was obtained in overall 86–95% yields.



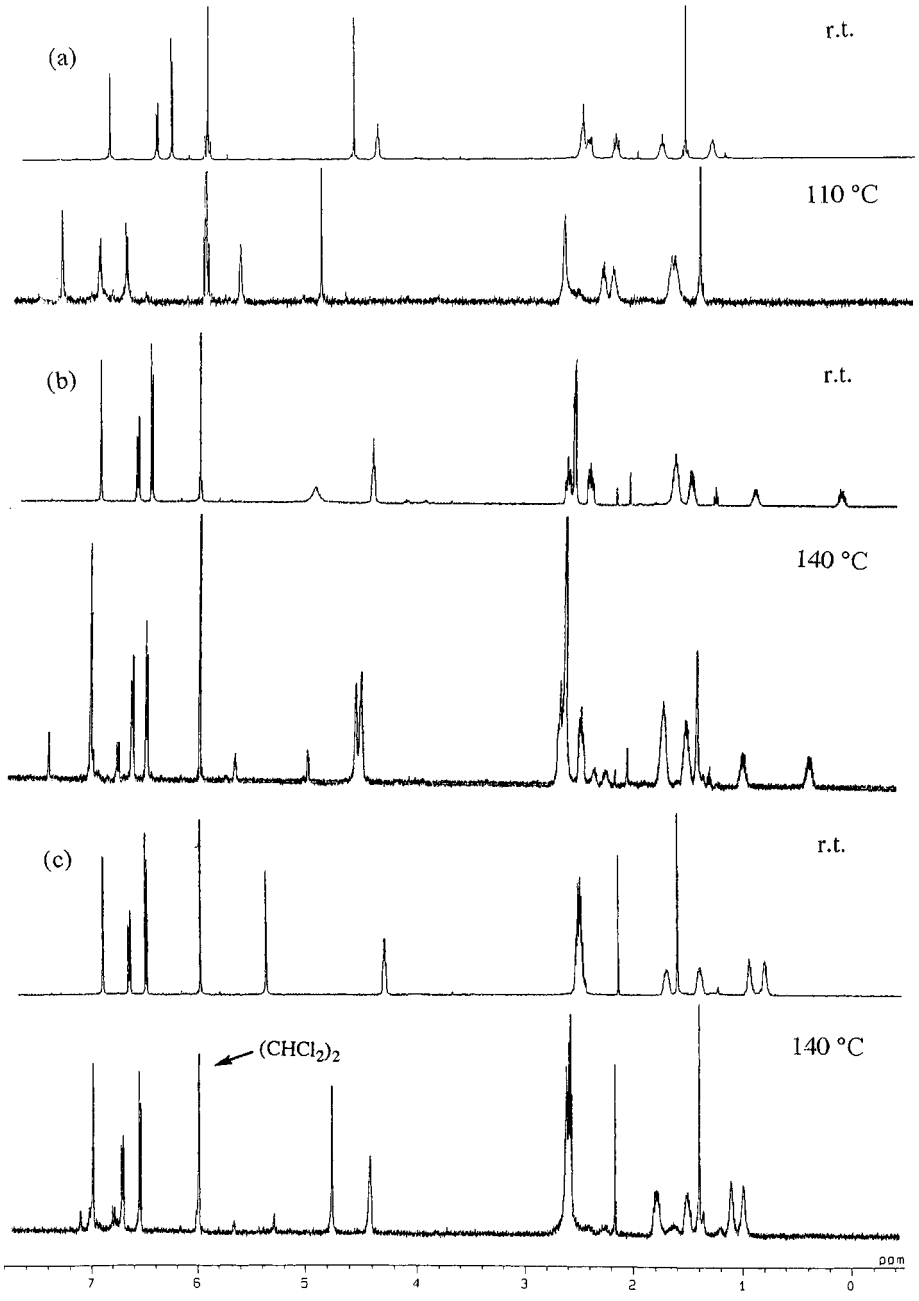


Figure 2. Temperature dependence of ^{1}H NMR spectra of **2a** (a), **2b** (b), and **2c** (c) in $CDCl_2$-$CDCl_2$.

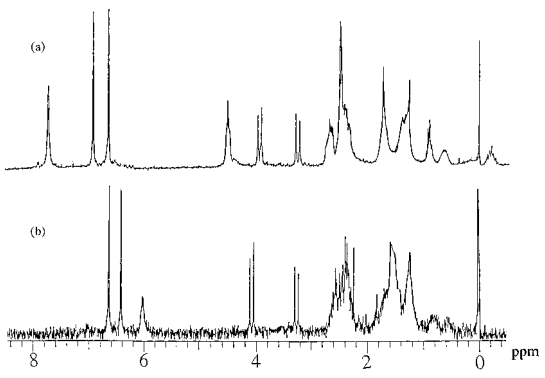


Figure 3. 500 MHz ^{1}H NMR spectra of **3a** (a) and **5a** (b) in $CDCl_3$.

Another synthetic route to enlarged calix[4]arene analogs **5** was also investigated in order to judge the applicability of this condensation method as shown in Scheme 1. The identification of products was performed by ^{1}H NMR spectroscopy. The dimerization of dihydroxy[4.*n*]metacyclophanes **4** (*n*=2–6) was carried out under the same conditions as **2**. Generally speaking, they gave **5** in low yields if they could form a dimer structure (see Table 1). In fact, their benzene rings move more freely than **2** after the reduction of cyclobutane ring from C2 to C4 bridge, although they mainly take *anti* (*n*=2–4) and *syn* (*n*=5 and 6) conformations. Accordingly, **4** would prefer polymeric structure to cyclic one **5**. When shorter alkyl chains (*n*=2–4) of [4.*n*]metacyclophanes **4a–c** were used, they did not give any dimeric products. On the other hand, when longer

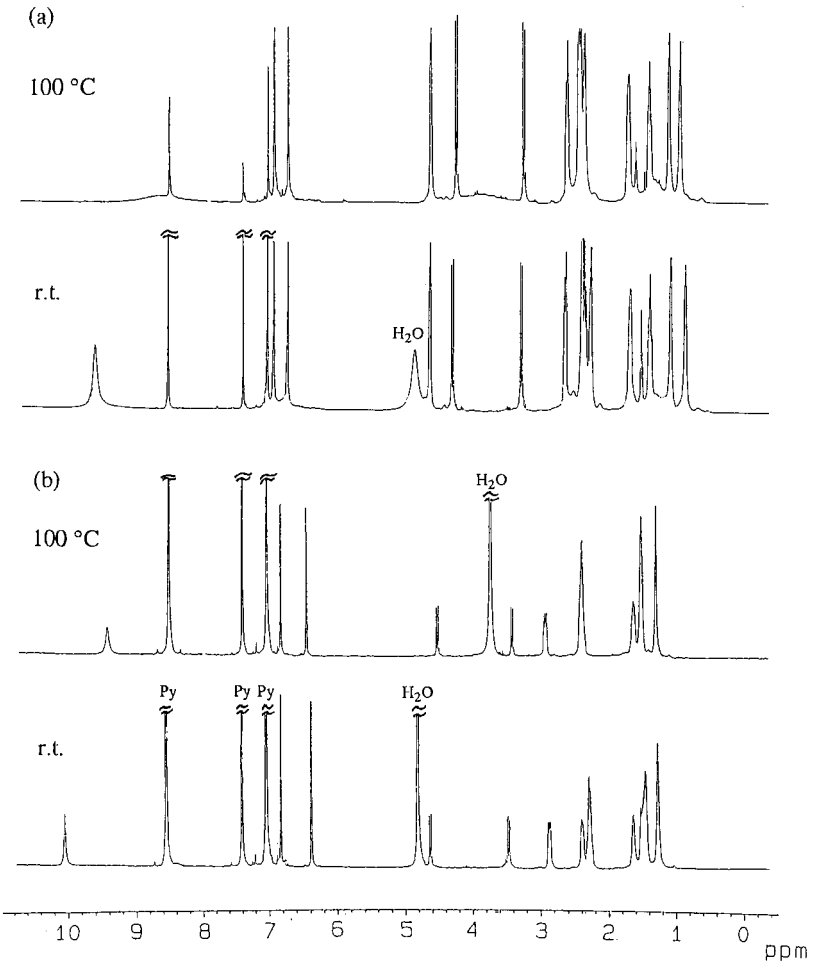


Figure 4. Temperature dependence of ^{1}H NMR spectra of **3b** (a) and **5b** (b) in pyridine-d_5.

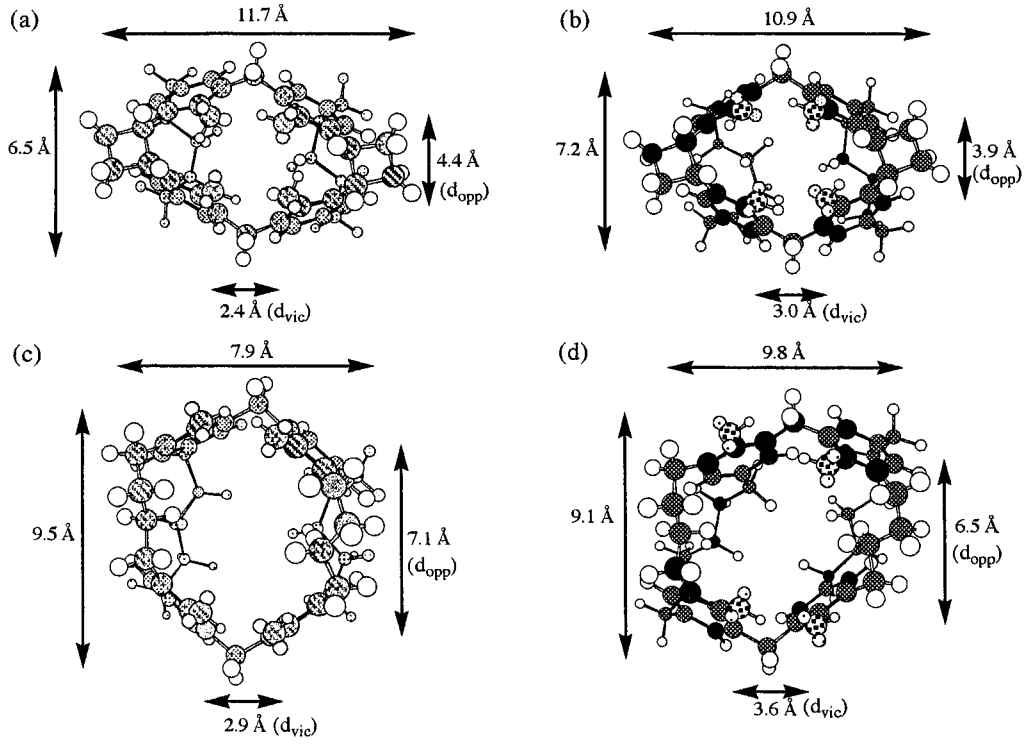


Figure 5. The molecular structure of calixarene analogs **3a** (a), **3b** (b), **5a** (c), and **5b** (d) suggested by the MM2 calculation.

Table 2. p*K*app values of metacyclophanes and calixarenes (THF, 25°C. Experimental error: $<\pm 2\%$)

Compd	p*K*app
1a	4.11[a]
1b	3.62[a]
1c	4.05[a]
2a	7.97
2b	7.79
2c	7.34
3a	5.05
3b	5.54

[a] Ref. 21.

alkyl chains (n=5 and 6) of **4d,e** were used, they gave enlarged calix[4]arene analogs **5a** and **b** in ~17% yields as a desired product. Although the addition of larger alkali metal ions gradually increased the product yield, the clear template effect could not be confirmed in this reaction as shown in Fig. 1. Other modified reaction conditions with HCl or EtMgBr and without MOH could not give any desired products.[26,27]

2.2. Structural analysis of calix[4]arene analogs

The structure of **3** and **5** was mainly elucidated by ^{1}H NMR spectroscopy as shown in Figs. 3 and 4. Since all protons could be assigned in the usual way by using several experiments like COSY and NOESY, we firstly concentrated to solve how the two metacyclophane units are arranged in **3a**. We concluded that **3a** took the head-to-head arrangement or the cone-type conformation, as depicted in Chart 1, by the following findings: the methylene bridge shows AB type coupling (Ha at δ3.28 with J=14 Hz and Hb at δ3.97 with J=14 Hz),[4] which is the same as those ascribed to the calixarene cone-form. Moreover, this same coupling constant is maintained even in pyridine-d_5 acting as a hydrogen bond acceptor solvent (Ha at δ3.39 with J=14 Hz and Hb at δ4.32 with J=14 Hz).[4] The Hc proton resonance at $\delta-0.22$ shifts to a higher field by ca. 0.4 ppm from that of the parent metacyclophane **2b**, due to the additional shielding effect (calcd 0.4 ppm)[20] from the other metacyclophane unit. The hydroxy protons of **2b**, whose OH–OH distance (d_{opp}) is estimated as 4.4 Å by the MM2 calculation as shown in Fig. 5a, resonate at δ5.04. It is the typical chemical shift value for simple monomeric phenols, suggesting the lack of intramolecular hydrogen bond. On the contrary, the hydroxy protons of **3a** resonate at much lower field, δ7.78. This large down-field shift clearly suggests the presence of intramolecular hydrogen bonding between two adjacent hydroxy groups, attaching upon each of two metacyclophane units, whose OH–OH distance (d_{vic}) is estimated to be 2.4 Å as shown in Fig. 5a.

The typical features of **3b** are as follows: the aromatic protons of **3b** were located at nearly the same position at δ6.71 and 6.85 as those of **3a** (δ6.71 and 6.99). The cyclobutane methine protons of **3b** resonate at higher field of δ4.33 more than those of **3a** at δ4.56. The AB type coupling of methylene bridge, which demonstrates the cone-form structure, shifts at higher field region from δ3.28 (Ha) and 3.97 (Hb) for **3a** to δ3.17 and 3.84 for **3b**, due to the movement of methylene protons on shielding region. According to VT NMR experiments as shown in Fig. 4a, **3b** could not undergo any intramolecular benzene ring rotation, although the total intramolecular motion of **3b** became freer than that of **3a**. Calix[4]arene analog **3b** kept the cone conformation at r.t. to 140°C (δ3.07 and 3.82, J=13 Hz) in DMSO and r.t. to 100°C (δ3.33 and 4.36, J=13 Hz) in pyridine. The hydroxyl protons of **3b** resonate at moderately higher field, δ6.71, more than those of **3a** at δ7.78, because d_{vic} of **3b** is estimated about 0.6 Å longer (3.0 Å) than that of **3a** by the MM2 calculation (see Fig. 5b). This result suggests that the hydrogen bonding of neighboring two hydroxyl groups on **3b** is weaker than that on **3a**. Moreover, d_{opp} of **3b** is estimated ca. 0.5 Å shorter (3.9 Å) than that of **3a**. The distance may be important when these hydroxyl groups make a cavity to recognize a certain guest molecule.

The structure of **5** was also judged from the following findings: after Birch reduction, cyclobutane ring methine protons (δ4.33 and 4.56) of **3** disappeared as shown in Figs. 3b and 4b. The AB type coupling of methano-bridges is shifted at lower field region from δ3.28 (Ha) and 3.97 (Hb) for **3a** to δ3.33 and 4.16 for **5a** and δ3.17 (Ha) and 3.84 (Hb) for **3b** to δ3.36 and 4.21 for **5b** as shown in Chart 1, due to the release of strain. The aromatic protons of **5b** passably shifted and largely separated from δ6.71 and 6.85 for **3b** to δ6.26 and 6.76 because of the shielding effect caused by the movement of benzene rings. These results show that **5** still sufficiently retains the cone structure at r.t. In fact, **5** did not undergo intramolecular benzene ring rotation. According to VT NMR experiments as shown in Fig. 4b, **5b** maintains the cone conformation at r.t. to 120°C (δ3.22 and 4.10, J=13 Hz) in DMSO-d_6 or r.t. to 100°C (δ3.50 and 4.68, J=13 Hz) in pyridine-d_5. Accordingly, the enlarged calix[4]arene analog **5** is rather limited in its inner movements, even if it is more flexible than **3**. The inner methine protons (Hc) of **5a** resonate at normal chemical shift δ0.59 in contrast with **3a** at $\delta-0.22$. This result suggests that the distance between benzene nuclei is spread to make the shielding effect to these protons decrease. Furthermore, Hc and Hd lie in unequal environments so that they resonate at different positions of δ0.59 and 0.84. The hydroxy proton chemical shift of **5a** (δ6.14) reveals that it has weaker hydrogen bonding than that of **3a** (δ7.78), and therefore **5a** has rather apart benzene rings by the reduction of cyclobutane ring as shown in Fig. 5c. The hydroxyl protons of **5b** resonate at remarkably higher field, δ6.05, more than those of **3b** at δ6.71, because d_{vic} of **5b** is estimated about 0.6 Å longer (3.6 Å) than that of **3b** by the MM2 calculation (see Fig. 5d). This result suggests that the neighboring two hydroxyl groups of **5b** make a very weak hydrogen bonding.

2.3. Acidity of dihydroxymetacyclophanes and calix[4]arene analogs

We determined the acidity of *syn*-dihydroxy[2.n]metacyclophanes **2** and calix[4]arene analogs **3** due to the clarity of relationship between the hydrogen bondings and their structures. Based on the reported method to measure the acidity (p*K*app) for phenol derivatives in non-aqueous solution,[21,22] we obtained every p*K*app value in THF by using the titration

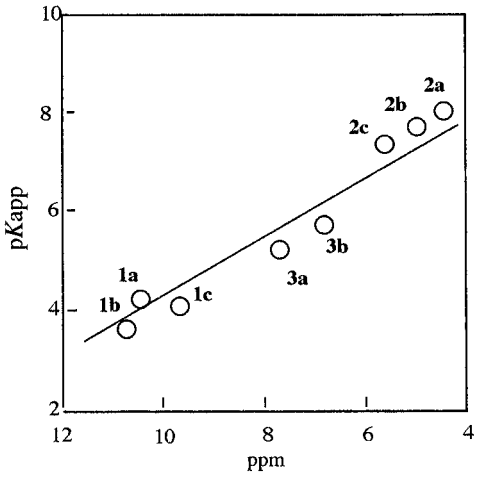


Figure 6. Plots of p*K*app vs δOH.

with phenol derivatives and tetramethylammonium salts of picrate or *p*-nitrophenolate. The results are summarized in Table 2. Unfortunately, the acidity of [4.*n*]metacyclophanes **4** and the enlarged calix[4]arene analogs **5** could not be determined because of low solubility under the conditions. The parent calix[*n*]arenes (*n*=4, 6, and 8) **1** are most strong acids among them in the p*K*app range of 3.6–4.1.[21] On the other hand, [2.*n*]metacyclophanes **2** (*n*=4–6) are most weak acids in the p*K*app range of 7.3–8.0 due to the structure similarity to monomeric phenols as mentioned above. [2.6]Metacyclophane **2c** having longest bridged chain is stronger acid than [2.4]metacyclophane **2a** having shortest one by ca. 0.7. This result suggests that the interaction between two hydroxy groups slightly increased due to the larger flexibility when the longer bridged chain is introduced to **2**.

Calix[4]arene analogs **3** exhibit medium values in the p*K*app range of 5.1–5.5. These results show that **3** partially forms the hydrogen bonding in contrast with **1** forming hydrogen bonding with all hydroxy groups. Furthermore, **3a** is moderately stronger acid than **3b** by ca. 0.5 demonstrated by NMR analysis. All observed values are in good consistency with linear relatioship by the plots of p*K*app vs δOH as shown in Fig. 6. Accordingly, when the number of hydroxy groups to make hydrogen bonding increases, the acidity becomes stronger by ca. 1.

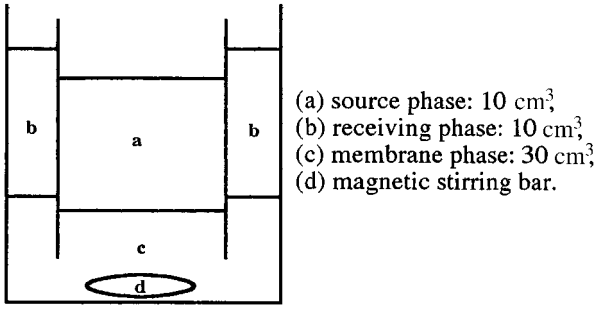


Figure 7. Liquid membrane cell.

Table 3. Cation transport rate by calixarenes **1** and **3** at 25°C (source phase: $[M^+]$=1.0 M, anion=NO_3^-/OH^-; membrane phase: 1.0×10^{-3} M of a carrier in the $CHCl_3$ solution; receiving phase: distilled water; stirring rate: 100±10 rpm; experimental error: <±10%)

Source phase		Transport rate ($\times10^{-5}$ mol/l·h)			
M^+	pH	**1a**	**1b**	**3a**	**3b**
Li^+	12.0	5.09	5.03	14.7	4.18
	10.0	1.71	3.92	12.0	4.50
	7.3	0.98	0.89	9.30	4.40
Na^+	14.0	5.40	10.5	10.2	4.89
	12.0	2.53	1.76	3.68	3.60
	10.0	0.69	0.48	0.73	0.65
	7.0	0.30	0.27	0.35	0.32
K^+	14.0	10.8	23.7	23.2	24.1
	12.0	2.00	13.2	4.39	4.39
	9.9	<0.05	0.05	0.05	<0.05
Rb^+	14.0	39.3	46.3	38.4	33.0
	12.0	5.20	17.7	8.50	7.65
	10.0	<0.05	<0.05	<0.05	<0.05
Cs^+	14.0	58.9	89.2	55.8	56.7
	12.0	14.0	27.0	12.3	11.5
	10.5	0.08	0.09	0.12	0.20
	6.9	<0.05	<0.05	<0.05	~0.0

2.4. Alkali metal ion transport of calixarenes

The alkali metal ion selectivity of calix[4]arene analogs **3** was examined in the transport experiments by using transport apparatus shown in Fig. 7 in $CHCl_3$ solution, because of their low solubility in CH_2Cl_2 or CH_2Cl_2/CCl_4.[23–25] Calix[*n*]arenes (*n*=4–6) **1** were also used as the reference compounds. The results are summarized in Table 3.

In the strong basic solution at pH 14, all calixarenes **1** and **3** selectively transported Cs^+ ion in the series of Na^+ to Cs^+. This result demonstrates again that the lower dehydration energy of Cs^+ cation governs the ion selectivity of all calixarenes under the conditions. Calix[6]arene **1b** recorded a higher transport rate (ca. 1.5 times) than **1a** and **3** for Rb^+ and Cs^+ ions. This result implies that the cooperative effect of donor moieties, which depends on the number of oxygen atoms, works more than the molecular structure. The order of Cs^+ ion transport is **1b**>**1a**≈**3a**≈**3b**. The ion selectivity of **3a** for large ions (Rb^+ and Cs^+) resembles **1a**, while that for medium size ions (Na^+ and K^+) resembles **1b**. And also, the ion selectivity of **3b** for alkali metal ions except for K^+ resembles that of **1a**. In fact, **1b** and **3** gave almost the same rate for K^+ ion. Their rates are considerably larger (2.2 times) than that for **1a**. Moreover, **1b** and **3a** showed around the same rate for Na^+ ion. Again their rates are considerably larger (ca. 2 times) than those for **1a** and **3b**. Accordingly, the molecular structure of calixarenes considerably contributed the transport for medium size ions like Na^+ and K^+. Hence, the characteristics of **3** for ion selectivity came from the preorganization of hydroxy groups by the bridging, which is adjustable by changing the oligomethylene chain length. Note that the hydrogen bonding interaction of four hydroxy groups can be tunable by changing the distance between them, using the bridged calixarene structure.

In the basic solution at pH 12, **1b** recorded the highest Cs^+ transport rate among other calixarenes. Although the transport rates at this pH region are obviously reduced more than

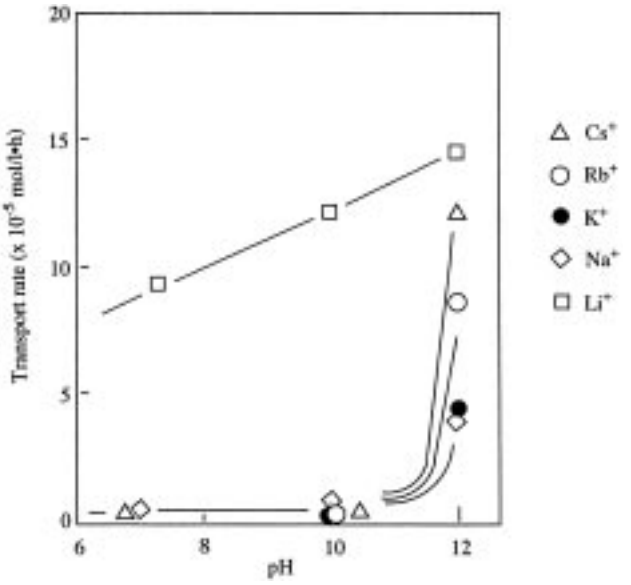


Figure 8. A plot of transport rate of calixarene **3a** as a function of source phase pH.

those at pH 14 due to the weak ion–ion interaction, the ion selectivity of **1b** from K^+ to Cs^+ ion became high compared with that of **1a** and **3**. The order of Cs^+ ion transport was **1b**>**1a**≈**3a**≈**3b**. Calix[4]arene analogs **3** can act as a carrier to have the nature of both calix[4]- and [6]arenes from Na^+ to Rb^+ ions and showed the smaller ion selectivity for Li^+ and Na^+. Especially, **3a** had higher Li^+ ion selectivity than others. It means that **3a** strongly interacts with Li^+ ion even at the high pH region. The order of Li^+ ion transport was **3a**>**1a**≈**1b**≈**3b**. The transport behavior of **3** as carriers is considerably different from that of **1**, which reflects the structural rigidity.

In the weak basic solution at pH 10, all calixarenes gave no significant ion transport of Na^+ to Cs^+ owing to the dependence on the ion–dipole interaction. Calix[4]arene analogs

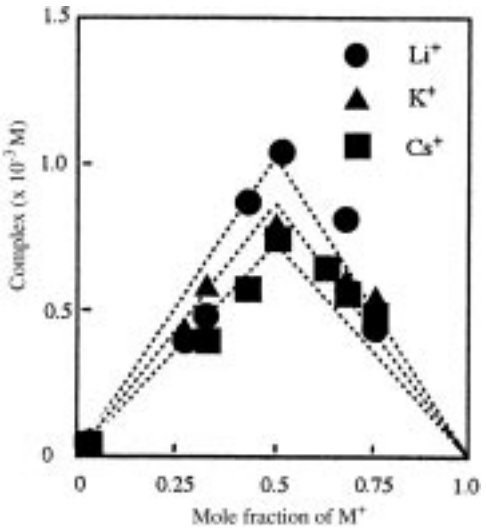


Figure 9. Job's plot of complex between **6** (3.0 mmol/l) and alkali metal thiocyanates in $CDCl_3/CD_3OD$ (7/3).

3 can transport Li^+ ion faster than **1**. The Li^+ ion transport rates of **3** were almost the same as those at pH 12. The selectivity of **3a** for Li^+ over Na^+ is about 15. Especially, **3a** showed higher rate by three to 10 times than **1**. The order of Li^+ ion transport was **3a**>**3b**>**1b**>**1a.** Hence, **1** transports only lower level of Li^+ ion due to the size incomplementary in the basic solution. Accordingly, the ion selectivity of calixarenes at pH 10 is greatly governed by the difference of their molecular structures. It is stressed that calixarene analogs **3** can act as an excellent Li^+ carrier at this pH region.

In the neutral solution at pH 7, **3** still transported Li^+ ion, although **1** hardly transported any alkali metal ions. The transport rates of Li^+ ion decreased only a little from those of pH 12 to 7. In particular, **3a** transported Li^+ ion about 10 times faster than **1**. The order of Li^+ ion transport was **3a**>**3b**>**1a**≈**1b.** These results show that the hydroxy groups of **3** are well arranged to take the ion–dipole interaction with Li^+ ion. As shown in Fig. 8, **3a** can exclusively transport Li^+ ion below pH 12. The Li^+ ion selectivity of **3a** over other alkali metal ions is more than 30. Accordingly, **3a** can be said to be the best Li^+ carrier among all calixarenes examined.

Since **3a** had the high Li^+ ion selectivity in the neutral solution, we studied the nature of their bindings to clarify the ion selectivity. Tetramethylether **6** was used in this experiment to avoid any effect of proton dissociation and to evaluate the detailed ion–dipole interaction between oxygen moieties and alkali metal ions in the neutral media.[12]

The stoichiometry of the complexation was examined by Job's plots between **6** and alkali metal thiocyanates in $CDCl_3/CD_3OD$ (7/3) (see Fig. 9). When the mole fraction of **6** was 0.5, the complex concentration reached a maximum for all alkali metal ions. This result clearly demonstrates that **6** forms a 1:1 complex with alkali metal ions. Furthermore, the binding constant for Li^+ ion with **6** recorded the largest value among the alkali metal thiocyanates in $CDCl_3/CD_3OD$ (8/2). The order is Li^+ (Ka=674)>Na^+ (512)>K^+ (343)>Rb^+ (162)>Cs^+ (87). This result suggests that smaller alkali metal ions (Li^+ and Na^+) more strongly interact with **6** than larger ones (K^+, Rb^+, and Cs^+) in the neutral media. In fact, the MM2 calculation showed that the oxygen-end cavity diameter across the methylene bridges is only ca. 1.4 Å to fit the smaller ions like Li^+ (1.36 Å) and Na^+ (1.90 Å). This is one of the most sophisticated modifications of calix[4]arene geometry, which dramatically changed the ion selectivity.

3. Conclusion

In conclusion, we synthesized calix[4]arene analogs in excellent yield firmly locked in the cone conformation. The enlarged calix[4]arene analogs could also be synthesized by the two different methods. They show different properties on the acidity of phenolic hydroxy groups and selectivities on the transport of alkali metal ions from parent calixarenes.

4. Experimental

4.1. General

Elemental analyses were performed at the Microanalytical Center of Gunma University. Melting points are not corrected. NMR spectra were recorded on a JEOL JNM-A500 spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. Mass spectra were taken on a JEOL JMS-DX302 mass spectrometer. Infrared spectra were recorded on a Hitachi 270-50 infrared spectrophotometer with KBr-disc method. UV spectra were recorded on a Shimadzu UV-160A spectrophotometer in CH_2Cl_2. The MM2 calculations were performed with Chem 3D. Thin-layer chromatographic analyses (TLC) were performed on Merck silica gel 60 F254 plates. Column chromatographic purification of reaction mixtures was performed with Merck silica gel 60 (70–230 mesh). The acidity was determined from the absorbance change of salts at 422 nm by reported method.[21] The alkali metal transport rates were determined from the analysis for cation content by atomic absorption spectrophotometry (Perkin-Elmer 603) after stirring for 24 h.[23]

4.2. Materials

Tetrahydrofuran(THF) was distilled from sodium under a nitrogen atmosphere. *N,N*-Dimethylformamide (DMF) was treated with KOH and distilled under reduced pressure. Other commercially available reagents were used without further purification.

4.3. Synthesis of calix[4]arene analogs 3 (General procedure)

A mixture of dihydroxymetacyclophane **2** or **4** (6.5 mmol), alkali metal hydroxide (2.5 N, 13 mmol), and paraformaldehyde (65 mmol) in 20 cm^3 of diglyme was treated in a Dean–Stark apparatus at 140–150°C under a nitrogen atmosphere. After stirring for 12 h, the reaction mixture was cooled and poured into cold 10% HCl solution (100 cm^3). After extraction with $CHCl_3$ and THF (200 cm^3, 9/1), the reaction mixture was dried over anhydrous Na_2SO_4 and evaporated. Pure compound **3** or **5** was obtained by column chromatography (SiO_2, benzene/ethyl acetate=9/1). Yields for each experiment were listed in Table 1. **3a:** mp >300°C. Found: C, 79.91; H, 7.59%. Calcd for $C_{44}H_{48}O_4{\cdot}H_2O$: C, 80.21; H, 7.65%. EIMS (20 eV) *m/z* 640 (M^+). IR ν 3270, 2938, 1480, 1452, and 1148 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ=−0.22 (2H, m), 0.65 (2H, m), 1.40 (4H, m), 1.72 (4H, m), 2.30–2.62 (12H, m), 2.71 (4H, m), 3.28 (2H, d, *J*=14 Hz), 3.97 (2H, d, *J*=14 Hz), 4.56 (4H, m), 6.71 (4H, d, *J*=1.9 Hz), 6.99 (4H, d, *J*=1.9 Hz), and 7.78 (4H, s). In pyridine-d_5, 0.14 (2H, m), 0.73 (2H, m), 1.44 (4H, m), 1.86 (4H, m), 2.46 (12H, m), 2.84 (4H, m), 3.39 (2H, d, *J*=14 Hz), 4.32 (2H, d, *J*=14 Hz), 4.97 (4H, m), 6.90 (4H, d, *J*=2.0 Hz), 7.28 (4H, d, *J*=2.0 Hz), and 10.17 (4H, bs). **3b:** mp>300°C. Found: C, 81.29; H, 7.78%. Calcd for $C_{46}H_{52}O_4{\cdot}0.5H_2O$: C, 81.50; H, 7.88%. EIMS (20 eV) *m/z* 668 (M^+). IR ν 3425, 2925, 1482, 1455, and 1145 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ=0.62 (4H, m), 0.90 (4H, m), 1.23 (4H, m), 1.66 (4H, m), 2.25–2.73 (16H, m), 3.17 (2H, d, *J*=14 Hz), 3.84 (2H, d, *J*=14 Hz), 4.33 (4H, m), 6.71 (4H, s), 6.71 (4H, d, *J*=1.8 Hz), and 6.85 (4H, d, *J*=1.8 Hz).

4.4. Birch reduction of calix[4]arene analogs 3 (General procedure)

A mixture of **3** (31 mM), chloromethyl methyl ether (10 equiv.), and NaH (2 equiv.) in dry THF/DMF (9/1) was reacted at 40–45°C under a nitrogen atmosphere. After stirring for 12 h, the reaction mixture was cooled and poured into cold 10% HCl solution (100 cm^3). After extraction with $CHCl_3$ (100 cm^3), the organic layer was dried over anhydrous Na_2SO_4 and evaporated. Pure ether was obtained in 90–95% yields by column chromatography (SiO_2, benzene). Liquid ammonia (20 cm^3) was condensed into a 100 cm^3 four-necked flask equipped with a magnetic stirrer and gas inlet tube at −60°C. Into the flask 150 equiv. of Na was slowly added for 15 min. Ether and 4 equiv. of EtOH in 20 cm^3 of dry THF were slowly added into the flask. After stirring at −60°C for 4 h, 20 cm^3 of H_2O was added to consume the excess Na and cease the reaction. And then the reaction mixture was allowed to stand to room temperature and extracted with 100 cm^3 of $CHCl_3$. After drying over anhydrous Na_2SO_4 and evaporation, the deprotection was carried out with the crude product (1 mM) in THF/aq. HCl (1/1) at 50°C for 12 h. After extraction with $CHCl_3$ (100 cm^3), the organic layer was dried over anhydrous Na_2SO_4 and evaporated. Pure **5** was obtained in overall 86–95% yields by column chromatography (SiO_2, benzene/ethyl acetate=9/1). **5a:** mp >300°C. Found: C, 79.45; H, 8.04%. Calcd for $C_{44}H_{52}O_4{\cdot}H_2O$: C, 79.72; H, 8.21%. EIMS (20 eV) *m/z* 644 (M^+). IR ν 3400, 2925, 1482, and 1230 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ=0.59 (2H, m), 0.84 (2H, m), 1.10–1.90 (16H, m), 2.23–2.80 (16H, m), 3.33 (2H, d, *J*=14 Hz), 4.16 (2H, d, *J*=14 Hz), 6.14 (4H, bs), 6.53 (4H, d, *J*=2.0 Hz), and 6.75 (4H, d, *J*=2.0 Hz). **5b:** mp >300°C. Found: C, 81.25; H, 8.63%. Calcd for $C_{46}H_{56}O_4{\cdot}0.5H_2O$: C, 81.01; H, 8.43%. EIMS (20 eV) *m/z* 672 (M^+). IR ν 3295, 2925, 2852, 1479, 1448, and 1225 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ=1.24 (8H, m), 1.34 (4H, m), 1.38–1.66 (12H, m), 2.15 (4H, m), 2.30 (8H, m), 2.53 (4H, m), 3.36 (2H, d, *J*=14 Hz), 4.21 (2H, d, *J*=14 Hz), 6.05 (4H, s), 6.26 (4H, d, *J*=1.8 Hz), and 6.76 (4H, d, *J*=1.8 Hz).

4.5. Tetramethoxycalix[4]arene analog 6

A mixture of **3a** (2.3 mM), CH_3I (20 equiv.), and NaH (2 equiv.) in dry THF/DMF (9/1) was reacted at 40–45°C under a nitrogen atmosphere. After stirring for 12 h, the reaction mixture was cooled and poured into cold 10% HCl solution (100 cm^3). After extraction with $CHCl_3$ (200 cm^3), the organic layer was dried over anhydrous Na_2SO_4 and evaporated. Pure **6** was obtained in 96% yield by column chromatography (SiO_2, benzene). **6:** mp 89–91°C. Found: C, 82.52; H, 8.34%. Calcd for $C_{48}H_{56}O_4$: C, 82.71; H, 8.10%. EIMS (20 eV) *m/z* 696 (M^+). IR ν 2940, 1486, 1261, 1020, and 805 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ=0.06 (2H, m), 0.83 (2H, m), 1.43 (4H, m), 1.76 (4H, m), 2.30–2.60 (12H, m), 2.66 (4H, m), 2.98 (2H, d, *J*=13 Hz), 3.49 (12H, s), 4.25 (2H, d, *J*=13 Hz), 4.42 (4H, m), 6.83 (4H, d, *J*=2.0 Hz), and 7.05 (4H, d, *J*=2.0 Hz).

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References

1. *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J.; Böhmer, V., Eds.; Kluwer: Dordrecht, 1991.
2. *Calixarenes 50th Anniversary*; Vicens, J.; Asfari, Z.; Harrowfield, J. M., Eds.; Kluwer: Dordrecht, 1994.
3. Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713.
4. Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161.
5. Shinkai, S. *J. Incl. Phenom.* **1989**, *7*, 193.
6. Chasar, D. W. *J. Org. Chem.* **1985**, *50*, 545.
7. Okada, Y.; Sugiyama, K.; Wada, Y.; Nishimura, J. *Tetrahedron Lett.* **1990**, *31*, 107.
8. Okada, Y.; Mabuchi, S.; Kurahayashi, M.; Nishimura, J. *Chem. Lett.* **1991**, 1345.
9. Okada, Y.; Sugiyama, K.; Kurahayashi, M.; Nishimura, J. *Tetrahedron Lett.* **1991**, *32*, 2367.
10. Okada, Y.; Ishii, F.; Kasai, Y.; Nishimura, J. *Chem. Lett.* **1992**, 755.
11. Okada, Y.; Kasai, Y.; Ishii, F.; Nishimura, J. *J. Chem. Soc., Chem. Commun.* **1993**, 976.
12. Okada, Y.; Ishii, F.; Kasai, Y.; Nishimura, J. *Tetrahedron Lett.* **1993**, *34*, 1971.
13. Okada, Y.; Kasai, Y.; Nishimura, J. *Tetrahedron Lett.* **1995**, *36*, 555.
14. Okada, Y.; Kasai, Y.; Nishimura, J. *Synlett* **1995**, 85.
15. Okada, Y.; Mizutani, M.; Ishii, F.; Nishimura, J. *Tetrahedron Lett.* **1997**, *38*, 9013.
16. Okada, Y.; Hagihara, M.; Mineo, M.; Nishimura, J. *Synlett* **1998**, 269.
17. Greene, T. W. In *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1981; p 92.
18. Greenberg, A.; Liebna, J. F. In *Strained Organic Molecules*; Academic Press: New York, 1978; p 58.
19. Nozaki, H.; Otani, I.; Noyori, R.; Kawanisi, M. *Tetrahedron* **1968**, *24*, 2183.
20. Bovey, F. A. In *Nuclear Magnetic Resonance Spectroscopy*; Bovey, F. A., Ed.; Academic Press: New York, 1988; p 106.
21. Araki, K.; Iwamoto, K.; Shinkai, S.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3480.
22. Schmidt, C.; Kumar, M.; Vogt, W.; Böhmer, V. *Tetrahedron* **1999**, *55*, 7813.
23. Izatt, R. M.; Lamb, J. D.; Hawkins, R. T.; Brown, P. R.; Izatt, S. R.; Christensen, J. J. *J. Am. Chem. Soc.* **1983**, *105*, 1782.
24. Izatt, S. R.; Hawkins, R. T.; Christensen, J. J.; Izatt, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 63.
25. Izatt, R. M.; Bradshaw, J. S.; Dalley, N. K. *Chem. Rev.* **1991**, *91*, 137.
26. Yamato, T.; Hideshima, C.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.,* **1991**, *56*, 2089.
27. Casiraghi, G.; Casnati, G.; Cornia, M.; Pochini, A.; Puglia, G.; Sartori, G.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 318.
28. Okada, Y.; Ishii, F.; Kasai, Y.; Nishimura, J. *Tetrahedron* **1994**, *50*, 12159.