A New Intermolecular Photochemical Approach to Calix[4]arene Synthesis

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Abstract: Calix[4]arene analogs **4a** and **b** were obtained in 15 and 13% yields, respectively, by intermolecular [2 + 2] photocycloaddition. The conformations of **4a** and **b** are assigned to be 1,2-alternate form and cone one, respectively. The calix[4]arenes **5a** and **b** having hydroxy groups were also obtained in 84 and 80% yields, respectively, by ether cleavage of **4**, whose conformations are maintained by this transformation.

Calixarenes composed of *tert*-butylphenol[1] or resorcinol[2] are well-known to act as useful receptors for metal ions and organic molecules. The sophisticated modifications of their skeletons are widely carried out to extract some new characteristics in host-guest chemistry.[3] Rigidification of calix[4]arenes was previously reported by using the dimerization of a metacyclophane unit as a building block, which was made from styrene derivatives by intramolecular [2 + 2] photocycloaddition.[4] The cyclobutane rings formed by this photocycloaddition greatly contribute to maintain the *syn*-conformation. The rigidified calix[4]arenes have introduced some dramatic change of binding property compared with parent calixarenes.

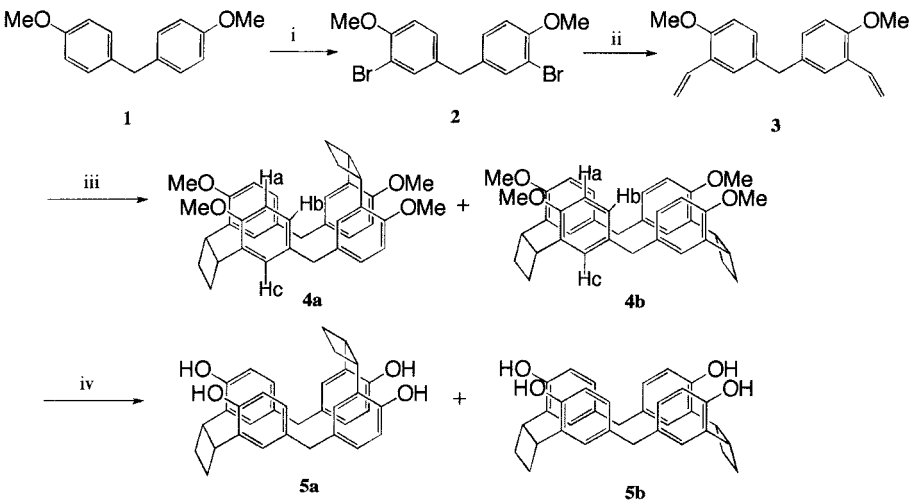
Recently, we have aimed to design a new calixarene-type molecule having *endo*-hydroxy groups instead of *exo*-ones like the structural alteration of calix[4]arene toward resorc[4]arene. A simple intermolecular [2 + 2] photocycloaddition of styrene derivatives was used for the design of new calixarenes. The transformation of functional groups was also examined to clarify whether they would change their molecular conformations. In this communication, we report the synthesis and characterization of new calix[4]arene analogs by intermolecular [2 + 2] photocycloaddition.

The synthetic route of calix[4]arene analogs **4** is shown in Scheme 1. 4-Methoxydiphenylmethane **1** was used as a starting material. Dibromide **2** was obtained in 85% yield by the treatment with bromine (1.2 equiv.) in CCl_4 at 0 °C for 12 h. Diolefin **3** was obtained in 50% yield by Kosugi-Migita-Stille reaction with vinyltributyltin (1.5 equiv.), $Pd(PPh_3)_2Cl_2$ (5 mol%), LiCl (5 equiv.), and 4-*tert*-butylcatechol in DMF at 80 - 90 °C for 3 h.[5] Intermolecular [2 + 2] photocycloaddition of **3** was carried out by the irradiation with a 400 W high-pressure Hg lamp (Pyrex filter) in benzene for 18 - 47 h under N_2. The pertinent concentration in this photoreaction was determined as summarized in Table I. In a low and high concentration (run 1 and 3), **4a-b** were produced in moderate yields. On the other hand, in a medium concentration (run 2, 31 mM), those yields were remarkably improved in 15 and 13%, respectively. Therefore, the further [2 + 2] photocycloaddition of **3** was performed in 30 mM of benzene solution. After irradiation and evaporation, **4a** and **b** were isolated in 6.9 - 15 and 7.6 - 13% yields, respectively, by column chromatography (SiO_2, benzene/ethyl acetate = 9/1 as an eluent).[6]

Table I. Product distribution of intermolecular [2 + 2] photocycloaddition

	3	Yield (%)	
Run	Conc. (mM)	**4a**	**4b**
1	10	6.9	8.7
2	31	15	13
3	60	8.9	7.6

Structural determination of calix[4]arenes **4** was carried out by NMR spectroscopy in $CDCl_3$, including COSY, NOESY, and ^{13}C NMR experiments. The cyclobutane ring of **4a-b** was assigned to be of *cis* configuration by ^1H NMR chemical shifts at δ 4.32 of its methine protons.[7] The direction of the cyclobutane ring to the methoxy group of **4a - b** was easily confirmed by NOESY experiments. That is, the methylene protons of the cyclobutane ring clearly show an NOE interaction with Hc aromatic protons. Accordingly, the cyclobutane ring of **4** is concluded to face to the opposite direction (*exo* configuration) of the methoxy groups as shown in Scheme 1.



(i) Br_2, CCl_4; (ii) LiCl, $Pd(PPh_3)_2Cl_2$, $(n\text{-Bu})_3SnCH{=}CH_2$, 4-*t*-Butylcatechol, DMF; (iii) hv (Pyrex), benzene; (iv) BBr_3, CH_2Cl_2

Scheme 1

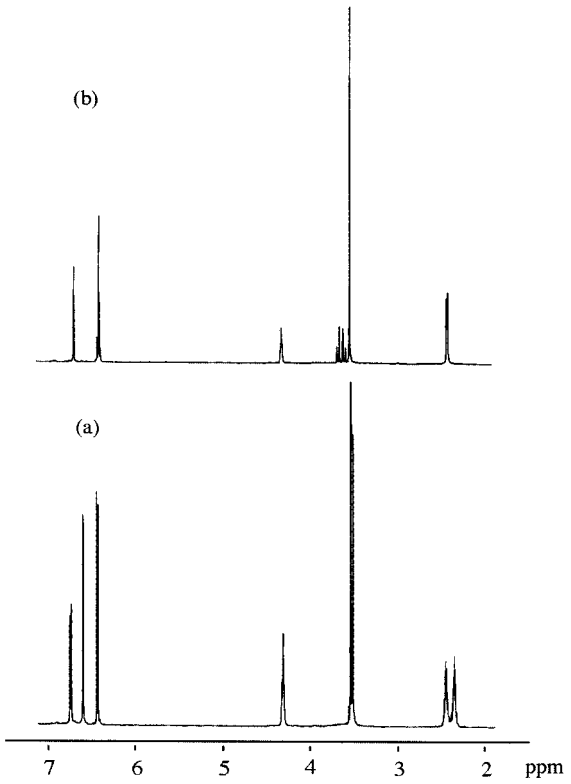


Figure 1. ^{1}H NMR spectra of **4a** (a) and **b** (b) in $CDCl_3$

The methylene bridges of **4b** show AB type coupling (δ 3.55 with *J*=15 Hz and δ 3.64 with *J*=15 Hz), which is the same as those ascribed to the cone form of calixarenes.[8] The same coupling constant is maintained from r.t. to 110 °C in $CDCl_2$-$CDCl_2$ (δ 3.56 with *J*=15 Hz and δ 3.64 with *J*=15 Hz) by VT NMR experiments. Moreover, those protons clearly show only an NOE interaction with Hc aromatic protons. Accordingly, its aromatic rings are perfectly fixed to take the cone conformation. On the other hand, those protons of **4a** show a sharp singlet at δ 3.47, which takes an alternate conformation.[8] Furthermore, they clearly show an NOE interaction with both Hb and Hc aromatic protons. These results obviously suggest that the conformation of aromatic ring connecting the methylene bridges is completely opposite (1,2-alternate form). The singlet peak of methylene bridges do not change at all from r.t. to 110 °C in $CDCl_2$-$CDCl_2$. Accordingly, VT NMR experiments demonstrate that the interconversion between **4a** and **b** cannot take place in NMR time scale even at 110 °C after the cyclobutane ring formation.

The methoxy groups of **4a** and **b** show the same *syn* conformation, judging from their NOE interactions with Ha aromatic protons and their chemical shift of singlet at δ 3.52 and 3.50, respectively. Based on these observations, it is concluded that **4a** takes 1,2-alternate form and **4b** takes cone form as shown in Scheme 1.

MM2 calculations showed that the steric energies (SE) for **4a**-**b** were nearly the same (SE=76.5 kcal/mol for **4a** and 77.0 kcal/mol for **4b**).[9] Accordingly, the product distribution by photocycloaddition is expected *ca.*1:1 ratio. In fact, the product ratio of **4a**-**b** was *ca.* 1:1 through all experiments (*see* Table I).

The synthetic route to hydroxycalix[4]arenes **5a-b** is shown in Scheme 1. Thus, **4a** and **b** were treated individually with excess of boron tribromide in dry CH_2Cl_2 at r.t. for 12 h. After evaporation, **5a** and **b** were isolated in 84 and 80% yields, respectively, by column chromatography (SiO_2, benzene/ethyl acetate = 9/1 as an eluent).

Structures of calix[4]arenes **5** were determined by ^{1}H NMR spectroscopy in DMSO-d_6. The configuration of cyclobutane ring for calix[4]arenes was assigned to be *cis* by chemical shift of its methine protons at δ 4.16 (**5a**) and 4.11 (**5b**).[7] The methylene bridges of **5b** show AB type coupling (δ 3.06 with *J*=14 Hz and δ 3.37 with *J*=14 Hz), which means the same cone conformation of **4b**. Furthermore, **5b** held the cone form from r.t. to 110 °C in same solvent. Accordingly, its structure is fixed to take the cone conformation even after the transformation to hydroxy groups from methoxy ones. On the other hand, those of **5a** show a sharp singlet at δ 3.16 to take an alternate conformation and do not change from r.t. to 110 °C as the same results for **4a**. Based on these observations, calix[4]arenes **4** and **5** rigidified and maintained their conformation even at a high temperature because of cyclobutane rings.

In conclusion, we have successfully obtained new calix[4]arene analogs **4** and **5** by intermolecular [2 + 2] photocycloaddition. They were isolated as both cone and 1,2-alternate isomers. Further investigation including a synthesis of resorcinol-based calixarenes is now in progress and will be reported elsewhere.

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6) Compd.; Anal. Calcd (found); MS (M^+); ^{1}H NMR δ (intensity, multiplicity, *J* in Hz). **4a** $C_{38}H_{40}O_4$**.**0.5H_2O, C, 80.11 (79.95), H, 7.25 (7.42); 560; 2.26 (4H, m), 2.38 (4H, m), 3.47 (4H, s), 3.52 (12H, s), 4.32 (4H, m), 6.49 (4H, d, 8.3), 6.66 (4H, d, 2.2), 6.82 (4H, dd, 2.2 & 8.3) in $CDCl_3$. **4b** $C_{38}H_{40}O_4$**.**0.5H_2O, C, 80.11 (80.19), H, 7.25 (7.28); 560; 2.36 (8H, m), 3.50 (12H, s), 3.55 (2H, d, 15), 3.64 (2H, d, 15), 4.32 (4H, m), 6.46 (4H, dd, 1.9 & 8.2), 6.48 (4H, d, 8.2), 6.76 (4H, d, 1.9) in $CDCl_3$. **5a** $C_{34}H_{32}O_4$**.**H_2O, C, 78.14 (78.41), H, 6.56 (6.62); 504; 2.12 (4H, m), 2.26 (4H, m), 3.00 (4H, m), 3.16 (4H, s), 4.16 (4H, m), 6.43 (4H, d, 8.0), 6.62 (4H, d, 2.0), 6.71 (4H, dd, 2.0 & 8.0) in DMSO-d_6. **5b** $C_{34}H_{32}O_4$**.**H_2O, C, 78.14 (78.30), H, 6.56 (6.82); 504; 2.17 (4H, m), 2.25 (4H, m), 3.00 (4H, m), 3.06 (2H, d, 14), 3.37 (2H, d, 14), 4.11 (4H, m), 6.39 (4H, d, 8.0), 6.66 (4H, dd, 2.0 & 8.0), 6.76 (4H, d, 2.0) in DMSO-d_6.

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