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# Conformational properties of $C_{2v}$-symmetrical resorcin[4]arene tetraethers

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ABSTRACT: Resorcin[4]arene tetraether derivatives, in which a resorcinol unit and a 1,3-dialkoxybenzene unit are incorporated in an alternating order, were synthesized by the $Sc(OTf)_3$ catalyzed '2 + 2' fragment condensation. The conformational properties were studied using variable temperature $^1$H-NMR spectroscopy, indicating that the resorcinarenes are flexible at room temperature but frozen in the cone formation at −90 °C in $CD_2Cl_2$, and they interconvert between two equivalent cone conformations with an energy barrier of $\Delta Gc^{\ddagger} = 10.2$–$10.5\,kcal\,mol^{-1}$. These values are slightly lower than that for the resorcin[4]arene containing four 2-hexylresorcinol units. The cone conformation is stabilized by intramolecular hydrogen bonds between the OH hydrogen and ether oxygen, which is evidenced by the low frequencies ($3423$–$3434\,cm^{-1}$) of the OH-stretching vibrations in $CDCl_3$ solution. Copyright © 2006 John Wiley & Sons, Ltd.

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KEYWORDS: conformation analysis; hydrogen bonding; resorcinarenes; calixarenes; variable temperature NMR

## INTRODUCTION

Polyhydroxy[$1_4$]metacyclophanes, such as calix[4]arenes (**A**) and resorcin[4]arenes (**B**), are readily available macrocycles, and are widely used in the fields of supramolecular chemistry.[1–6] Extensive studies on their conformational properties have been conducted for many years.[7–10] The hydrocarbon framework of [$1_4$]metacyclophane is very conformationally flexible, and there are six extreme conformations, designated 'cone (crown),' 'flattened cone (boat),' 'partial cone,' '1,3-alternate,' '1,2-alternate,' and 'chair.'[11–13] The relative stabilities of the conformational isomers and the energy barrier for the interconversion between them are largely dependent upon the substituents at the intra-annular and extra-annular positions of the macrocycles. Especially, the intramolecular hydrogen bondings between the phenolic hydroxyl groups on the neighboring aromatic rings play an important role in determining the conformational properties (Scheme 1).

Calix[4]arene (**A**; R = *tert*-Bu) possessing four OH groups at the intra-annular positions adopts a cone conformation stabilized by a circular array of hydrogen bonds, which undergoes a cone-to-cone inversion process (Scheme 2) with a barrier of $15.7\,kcal\,mol^{-1}$ in $CDCl_3$.[7] Also, resorcin[4]arene (**B**; R = *n*-hexyl) possessing eight OH groups at the extra-annular positions exists in the cone conformation, which is stabilized by four intramolecular hydrogen bonds between adjacent OH groups. For this compound, the barrier of the conformational inversion is $12.0\,kcal\,mol^{-1}$ in $CDCl_3$.[14] The circular array of hydrogen bonds is responsible for the greater conformational stability for **A**. Therefore, since the partial replacement of OH groups by $OCH_3$ groups leads to a decrease in the number of hydrogen bonds and the breakdown of the hydrogen bonding array, this structural change significantly influences both the static and dynamic stereochemistries of the resulting systems.[15–19] We are interested in the conformational properties of the resorcin[4]arene tetraethers (**C**), in which a resorcinol unit and a 1,3-dialkoxybenzene unit are incorporated in an alternating order. In this case, the number of the hydrogen bondings is the same as for (**B**), and the functionalization of the OH groups at the extra-annular positions does not sterically hinder the inversion of the macrocycles. We now describe the first '2 + 2' fragment synthesis of ABAB-type resorcin[4]arenes and their conformational properties in solution.

## RESULTS AND DISCUSSION

### Synthesis

We have previously demonstrated that the $Sc(OTf)_3$ catalyzed cyclocondensation of 2,4-dialkoxybenzyl alcohols produced resorcinarene octaethers in good yields.[20,21] Based on this study, the ABAB-type

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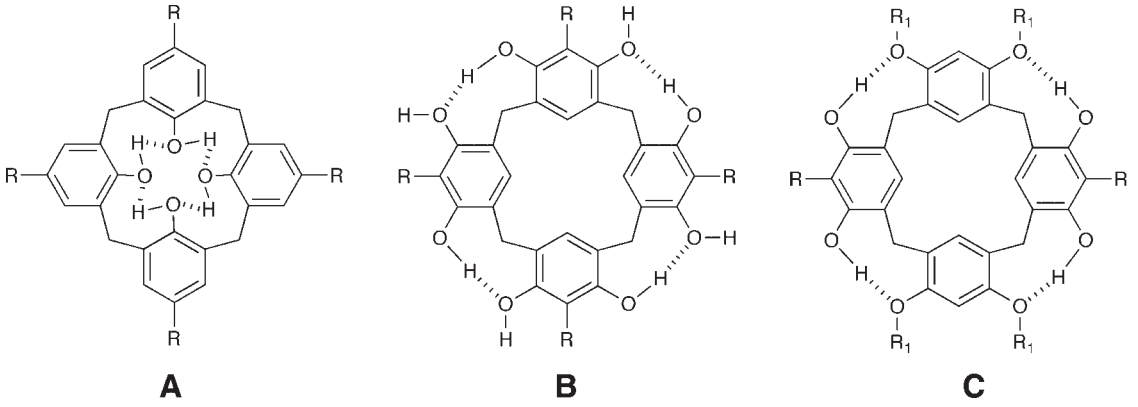
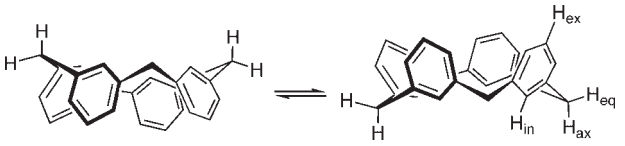
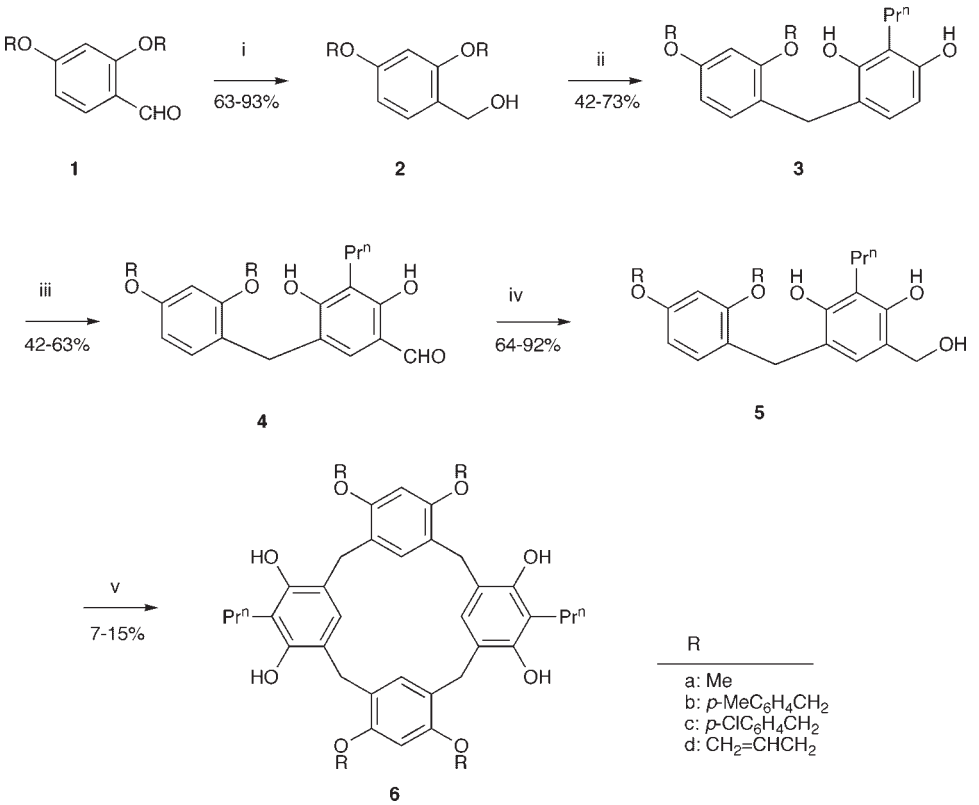


**Scheme 1.** Calix[4]arene (A) and ABAB-type resorcine[4]arene tetraether (C)



**Scheme 2.** Cone-to-cone interconversion in[$1_4$]metacyclophane system, and intraannular ($H_{in}$), extraannular ($H_{ex}$), axial ($H_{ax}$), and equatorial ($H_{eq}$) protons in the cone conformer

resorcin[4]arenes were prepared in a '2 + 2' fragment synthesis as shown in Scheme 3. Although a variety of regioselectively substituted calixarenes with well-defined structures have been prepared by fragment synthesis,[22] this methodology has been scarcely used for the construction of resorcinarenes. For example, resorcin[4]arenes bearing alternating substituents at their bridging positions were synthesized.[23] However, the direct synthesis of ABAB type resorcin[4]arenes consisting of different resorcinol units has not been reported.



**Scheme 3.** '2 + 2' Fragment synthesis of resorcin[4]arene tetraethers. Reagents and solvents: (i) $NaBH_4$, EtOH; (ii) 2-propylresorcinol, $Sc(OTf)_3$, MeCN; (iii) $POCl_3$, DMF; (iv) $NaBH_4$, EtOH; (v) $Sc(OTf)_3$, MeCN

The condensation of 2-propylresorcinol with 2,4-dialkoxybenzyl alcohols **2** in $CH_3CN$ was catalyzed by $Sc(OTf)_3$ to give diphenylmethanes **3** in 42–73% yields. The Vilsmeier formylation of **3** produced the benzaldehydes **4** in 42–63% yields. The aldehydes were then reduced with $NaBH_4$ to give the dimeric components **5** in 64–82% yields. Finally, the cyclocondensation was conducted in $CH_3CN$ in the presence of $Sc(OTf)_3$ that resulted in the formation of the ABAB-type cyclic tetramers **6**. Although the yields in the last step were in the range of 7–15%, the cyclic tetramers **6a**, **6b**, and **6c** precipitated during the reaction and were easily obtained as pure materials. On the other hand, compound **6d** was soluble in the reaction solvent and isolated by preparative gel permeation chromatography (GPC). The structure and composition of the ABAB resorcinarenes **6** were confirmed by $^1$H and $^{13}$C NMR spectroscopies, FAB-mass spectrometry, and elemental analysis.

To clarify the low yields of the fragment synthesis, we analyzed the soluble fraction of the reaction mixture obtained from the synthesis of **6a**. The GPC separation of the soluble fraction gave various types of low linear oligomers such as dimers and trimers. Interestingly, it was also shown that most of these isolated oligomers had no terminal hydroxymethyl groups. These products probably resulted from the fragmentation of the initially formed linear oligomers *via* an *ipso*-attack of the benzyl cations[24–26] and the dimerization of the activated benzyl alcohols *via* dehydroxymethylation.[27] Thus, we conclude that the fragmentation and recombination of linear oligomers are responsible for the low yields of the '2 + 2' fragment synthesis.

## Conformational properties

The $^1$H-NMR spectra of **6** recorded at 30 °C showed three singlets for the aromatic protons of the metacyclophane core and one singlet for the bridge methylene protons, indicating that these compounds are conformationally flexible systems. To confirm the preferred conformation of the cyclic tetramers, we measured their low-temperature $^1$H-NMR spectra. Since compounds **6a**, **6b**, and **6d** have good solubilities in $CD_2Cl_2$, their conformational properties could be analyzed by variable-temperature NMR spectroscopy. The $^1$H-NMR spectrum

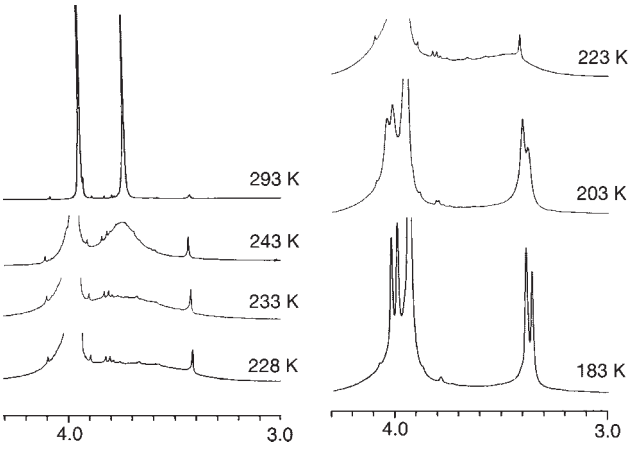



**Figure 1.** $^1$H-NMR spectrum of the methylene region of 6a in $CD_2Cl_2$ at different temperatures

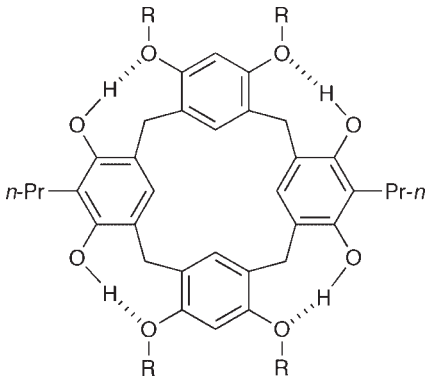
of **6a** at different temperatures is shown in Fig. 1 and the results are summarized in Table 1. At −90 °C in this solvent, compound **6a** showed one AB quartet (3.38 and 4.01 ppm, $J = 14.2$ Hz) arising from the four equivalent bridging methylene groups, indicating conformational freezing on the NMR time scale. The large chemical shift difference between the two methylene protons ($\Delta\delta = 0.63$ ppm) suggests that the adjacent two aromatic rings adopt *syn* arrangements. That is, the freezing conformation should be a cone or flattened cone. These conformations can be discriminated by examination of the chemical shifts of the intra-annular aromatic protons ($H_{in}$), since they significantly depend upon the orientation of the adjacent aromatic rings. Two $H_{in}$ signals in **6a**, which were assigned by two-dimensional NMR spectroscopy (NOESY), appeared as singlets at 6.99 and 7.25 ppm, respectively. On the other hand, the dimer **3a** showed their corresponding aromatic protons at 6.90 and 7.12 ppm ($\Delta\delta = 0.22$ ppm), respectively. Therefore, the difference in the chemical shifts that observed for **6a** ($\Delta\delta = 0.26$ ppm) can be primarily accounted for the difference in the substituents at the *meta*-positions. Namely, it is reasonably concluded that both $H_{in}$ protons are under the same anisotropy influence of the aromatic rings, and that the metacyclophane framework adopts a cone conformation with nearly $C_{4v}$ symmetry.

The bridging methylene signal that appeared at a higher field (3.38 ppm) showed an NOE correlation with two $H_{in}$ signals. Hence, the higher field signal is assigned

**Table 1.** Chemical shifts of the intra-annular aromatic protons ($H_{in}$) and methylene protons ($H_{ax}$ and $H_{eq}$) at −90 °C in $CD_2Cl_2$ and the activation energies for the conformational change at the coalescence temperature ($T_c$)

| Compound | $H_{in}$ | $H_{ax}$ | $H_{eq}$ | $J$/Hz | $\Delta G^{\ddagger}$/kcal mol$^{-1}$ | $T_c$/K |
|---|---|---|---|---|---|---|
| 6a | 7.25/6.99 | 3.38 | 4.01 | 14.2 | 10.2 | 228 |
| 6b | 7.02/6.89 | 3.27 | 3.91 | 13.7 | 10.5 | 233 |
| 6d | 7.02/6.90 | 3.29 | 3.93 | 14.0 | 10.5 | 233 |
| B (R = *n*-Hexyl)[a] | 7.19 | 3.51 | 4.08 | 13.0 | 11.7 | 251 |

[a] Reference [14]. Determined at −50 °C in $CDCl_3$.




**Scheme 4.** Intramolecular hydrogen bondings in a resorcin[4]arene tetraether

to the axial protons ($H_{ax}$) and the lower field signal is assigned to the equatorial protons ($H_{eq}$) (Scheme 2). In contrast, in the calix[4]arene systems, the equatorial methylene proton resonates at a higher field than the axial ones.[28,29] This is because the $H_{eq}$ protons of **6** is in close proximity to the oxygen functions (OH, OR), and are in an environment similar to the $H_{ax}$ of calix[4]arenes.

Upon raising the temperature, the AB quartet of the methylene groups coalesced into a broad singlet. Based on the coalescence temperature of this signal,[30] a barrier of $Gc^{\ddagger} = 10.2\,kcal\,mol^{-1}$ was calculated for the conformational exchange (cone to cone inversion). Compounds **6b** and **6d** showed temperature-dependent NMR spectra similar to **6a**. The data in Table 1 show that the barriers to inversion vary only slightly as the alkyl groups change from methyl to allyl to *p*-methylbenzyl. The inversion barriers for these resorcin[4]arene tetraethers **6** in $CD_2Cl_2$ are slightly lower than that of resorcin[4]arene **B** (R = *n*-hexyl) in $CDCl_3$ ($\Delta Gc^{\ddagger} = 11.7\,kcal\,mol^{-1}$).

In the $^1$H-NMR spectrum of **6a** in $CDCl_3$, the OH signal appears at 7.09 ppm; the downfield shift compared with 2-hexylresorcinol (4.7 ppm) is attributed to the hydrogen bonding. Moreover, the hydrogen bonding is evidenced by IR spectroscopy. In $CDCl_3$ solution, the 2,4-dialkoxybenzyl resorcinol **4d** shows two OH stretching vibrations at 3604 and 3416 $cm^{-1}$. The latter one is assigned to the intramolecular hydrogen-bonded OH stretching. On the other hand, the resorcin[4]arene **6a** displays one hydrogen-bonding OH stretching vibration at 3423 $cm^{-1}$. The presence of only one OH stretching vibration in the IR spectrum indicates the formation of four intramolecular hydrogen bondings between the OH and alkoxy groups as shown in Scheme 4. The value of 3423 $cm^{-1}$ is close to the values of 3420 $cm^{-1}$ for the hydrogen bonded OH groups in the resorcin[4]arene **B** (R = *n*-hexyl). These spectral features are commensurate with a cone conformation that is stabilized by intramolecular hydrogen bonding.

## CONCLUSION

Resorcin[4]arene tetraether derivatives, in which a resorcinol unit and a 1,3-dialkoxybenzene unit are incorporated in alternating order, were synthesized by the $Sc(OTf)_3$ catalyzed '2 + 2' fragment condensation. The conformational properties were studied by variable temperature $^1$H-NMR and IR spectroscopy. The preferred conformation is a cone with nearly $C_{4v}$ symmetry, which is stabilized by intramolecular hydrogen bonds between the OH hydrogen and ether oxygen. On the NMR time scale, the resorcinarenes are flexible at room temperature, but frozen in the cone formation at $-90\,^{\circ}C$ in $CD_2Cl_2$. Their activation energies for the interconversion between two equivalent cone conformations are slightly lower than that for the resorcin[4]arene containing four 2-hexylresorcinol units.

Experimental procedures and spectral data for all new compounds are available *via* the Internet at EPOC website.

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