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$Sc(OTf)_3$-catalyzed Cyclooligomerization of 2,4-Dialkoxybenzyl Alcohols. Formation of Resorcin[n]arene Peralkyl Ethers

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Summary

The cyclooligomerization of 2,4-dialkoxybenzyl alcohols **3** catalyzed by $Sc(OTf)_3$ in CH_3CN under high dilution conditions produced a series of resorcin[n]arene peralkyl ethers containing four to nine resorcinol units. When the reactions were conducted at 50°C, the cyclic tetramers **4**, which are thermodynamically favored products, are selectively formed in good yields. It is noteworthy that the reaction of 2,4-dimethoxybenzyl alcohol **3d** at 0°C produced the corresponding cyclic octamer **8d** as the major product. In other cases, such as the selective formation of a cyclic octamer could not be observed. This selective formation of **8d** is due to a combination of the reversibility of the oligomerization in the presence of **3d** and the insolubility of the octamer in the reaction medium. The conformational analysis of these cyclic oligomers was done by variable temperature ^1H NMR spectroscopy.

Introduction

Resorcin[n]arenes are [1.$_n$]metacyclophane compounds in which resorcinol units are linked *via* methylene bridges at their 4,6-positions [1]. It is well known that the cyclic tetramers bearing substituents at the bridging positions are almost exclusively formed by the condensation of resorcinols with aliphatic or aromatic aldehydes [2-6]. On the other hand, only one example of the formation of resorcin[6]arene as a minor product has been described in the literature [7].

The HCl catalyzed condensation of 2-alkylresorcinols with formaldehydes or its equivalent produced a mixture of resorcin[n]arenes (n=4, 5, 6, 7) with unsubstituted methylene bridges [8-10]. Since the cyclic pentamer and higher homologues are readily converted to the cyclic tetramer *via* a fragmentation/recombination mechanism under the given reaction conditions for their formation, the product distribution is largely dependent upon the reaction conditions such as temperature, time, and acid concentration. Recently, we have observed that the condensation was also catalyzed by $Sc(OTf)_3$ to produce a mixture of the cyclic oligomers with a kinetically controlled

product distribution, *i.e.*, the higher homologues are stable in the presence of the catalyst [11].

The acid-catalyzed condensation of resorcinol dialkyl ethers with aldehydes afforded resorcin[4]arene octaalkyl ethers [12-14]. Furthermore, the cyclooligomerization of 2,4-dialkoxybenzyl alcohols [15-17] and 2,4-dimethoxycinnamate [18] produced the corresponding resorcin[4]arene derivatives. Again, the selective formation of cyclic tetramers was described. We speculate that the formation of cyclic compounds is a reversible process under these experimental conditions and the cyclic tetramers are the thermodynamically favored products. Based on this speculation, we anticipated that a series of resorcin[n]arene peralkyl ethers with a kinetically controlled distribution would be obtained if $Sc(OTf)_3$ was used as a catalyst for the synthesis of the peralkyl ether derivatives.

We have previously reported that the $Sc(OTf)_3$ catalyzed condensation of 2,4-dialkoxybenzyl alcohols produced the resorcin[4]arene octaalkyl ethers in moderate yields. In these syntheses, we observed that a large fraction of the by-products were higher linear oligomers. Therefore, we carried out the condensation under high-dilution conditions in order to improve the yields of the cyclic oligomers. We now describe the results of the $Sc(OTf)_3$-catalyzed reaction and unprecedented selective formation of a cyclic tetramer, resorcin[8]arene hexadecamethyl ether **8d**.

Experimental

General methods

Melting points were taken on a MEL-Temp apparatus (Laboratory Devices) and are uncorrected. Recycling preparative gel permeation chromatography (GPC) was performed using a JAICO LC-918 equipped with JAIGEL 1H and 2H columns (eluent: $CHCl_3$). The ^1H and ^{13}C NMR spectra were recorded with a JEOL GX-270 or a JEOL ECP-500 spectrometer, and the chemical shifts are reported as δ values. The infrared spectra were taken using a Perkin-Elmer 1610 spectrophotometer. Fast atom bombardment mass spectra were recorded using xenon ionization techniques with *m*-nitrobenzyl alcohol (MNBA) as the matrix on a JEOL AX-505 spectrometer at the Faculty of Agriculture, Tottori University. The elemental analyses were performed at the Center for Organic Elemental Microanalysis, Kyoto University or at the Division of Instrumental Analysis, Research Center for Bioscience and Technology, Tottori University

*Synthesis of 2,4-Dialkoxybenzyl alcohol (**3**): General procedure*

A mixture of 2,4-dihydroxybenzaldehyde **1** (10 mmol), alkyl bromide (25 mmol) and K_2CO_3 (25 mmol) in acetone (50 ml) was heated to reflux for 8 h under an argon atmosphere. After removal of the insoluble material by suction, the filtrate was concentrated on a rotary evaporator. The residue was dissolved in diethyl ether and washed with 5% aq. NaOH. Removal of the solvent gave the crude 2,4-dialkoxybenzaldehyde **2**, which was used for the preparation of the alcohol without

further purification. A mixture of the crude aldehyde (6 mmol) and $NaBH_4$ (3 mmol) in ethanol (50 ml) was stirred for 45 min at ambient temperature. Most of the solvent was removed in *vacuo*. The residue was dissolved in diethyl ether and washed with water. The organic layer was concentrated on a rotary evaporator to give the corresponding benzyl alcohol **3**.

*2,4-Diethoxybenzyl alcohol (**3a**):* white solid, mp. 70°C. Calcd for $C_{11}H_{16}O_3$: H, 8.22; C, 67.32. Found: H, 8.32; C, 67.30. 270 MHz ^{1}H NMR ($CDCl_3$, 30°C) δ 1.404 (t, CH_3, J = 6.9 Hz, 3H), 1.430 (t, CH_3, J = 6.9 Hz, 3H), 2.229 (t, OH, J = 6.6 Hz, 1H), 4.017 (q, CH_2, J = 6.9 Hz, 2H), 4.056 (q, CH_2, J = 6.9 Hz, 2H), 4.611 (d, CH_2OH, J = 6.6 Hz, 2H), 6.40-6.46 (m, ArH, 2H), 7.11-7.15 (m, ArH, 1H). IR (KBr, cm^{-1}) 3287, 2978, 1617, 1587.

*2,4-Dipropyloxybenzyl alcohol (**3b**):* light yellow oil (190°C/6 Pa). Calcd for $C_{13}H_{20}O_3$: H, 8.99; C, 69.61. Found: H, 9.18; C, 69.37. 270MHz ^{1}H NMR ($CDCl_3$, 30°C) δ 1.033 (t, CH_3, J = 7.4 Hz, 3H), 1.050 (t, CH_3, J = 7.4 Hz, 3H), 1.73-1.90 (m, $CH_3CH_2CH_2$, 4H), 2.20 (bs, OH, 1H), 3.906 (t, $CH_3CH_2CH_2$, J = 6.6 Hz, 2H), 3.954 (t, $CH_3CH_2CH_2$, J = 6.6 Hz, 2H), 4.615 (s, CH_2OH, 2H), 6.40-6.46 (m, ArH, 2H), 7.11-7.15 (m, ArH, 1H). IR (KBr, cm^{-1}) 3411, 2964, 1614, 1588.

*2,4-Diallyloxybenzyl alcohol (**3c**):* white solid, mp. 32-33°C. Calcd for $C_{13}H_{16}O_3$: H, 7.32; C, 70.89. Found: H, 7.40; C, 70.95. 270 MHz ^{1}H NMR ($CDCl_3$, 30°C) δ 2.143 (t, OH, J = 6.1 Hz, 1H), 4.50-4.62 (m, CH_2=CHCH_2, 4H), 4.636 (d, CH_2OH, J = 6.1 Hz, 2H), 5.25-5.45 (m, CH_2=CHCH_2, 4H), 5.97-6.12 (m, CH_2=CHCH_2, 2H), 6.43-6.50 (m, ArH, 2H), 7.14-7.18 (m, ArH, 1H). IR (neat, cm^{-1}) 3384, 2872, 1613, 1505.

*Sc(OTf)$_3$ catalyzed cyclooligomerization of **3a**. A Typical Procedure.*

A solution of **3a** (193 mg, 1.00 mmol) in acetonitrile (20 ml) was added by a syringe pump over 2.0 h to a solution of $Sc(OTf)_3$ (10 mg) in acetonitrile (40 ml) at 50°C. After a further 3 h of stirring, most of the solvent was removed under vacuum. The residue was dissolved in chloroform, washed with water, and dried over Na_2SO_4. The solution was evaporated to dryness to give white solid (178 mg), which was subjected to GPC separation.

*Resorcin[4]arene octaethyl ether (**4a**):* recrystallization from chloroform/hexane, white solid, mp 198°C. Calcd for $C_{44}H_{56}O_8$•0.5H_2O: H, 7.96; C, 73.20. Found: H, 7.94; C, 72.89. FAB-MS (MNBA, m/z) Calcd: 712.5. Found: 712.4. ^{1}H NMR ($CDCl_3$, 30°C) δ 1.311 (t, CH_3, J = 6.8 Hz, 24H), 3.705 (s, ArCH_2Ar, 8H), 3.934 (q, CH_2, J = 6.8 Hz, 16H), 6.245 (s, H_{in}, 4H), 6.376 (s, H_{ex}, 4H). ^{13}C NMR ($CDCl_3$, 30°C) δ 15.2 (q), 28.2 (t, ArCH$_2$Ar), 64.4 (t), 98.3 (d, ArC-H_{ex}), 121.8 (s), 130.9 (d, ArC-H_{in}), 155.5 (s). IR (KBr, cm^{-1}) 2977, 2901, 1614, 1586.

*Resorcin[5]arene decaethyl ether (**5a**):* FAB-MS (MNBA, m/z) Calcd: 890.5. Found: 890.4. ^{1}H NMR ($CDCl_3$, 30°C) δ 1.258 (t, CH_3, J = 6.9 Hz, 30H), 3.663 (s, ArCH_2Ar, 10H), 3.838 (q, CH_2, J = 6.9 Hz, 20H), 6.326 (s, H_{ex}, 5H), 6.521 (s, H_{in}, 5H).

*Resorcin[6]arene dodecaethyl ether (**6a**):* mp 245°C. Calcd for $C_{66}H_{84}O_{12}$: H 7.92; C 74.13. Found: H 7.80; C 73.84. FAB-MS (MNBA, m/z) Calcd: 1068.6. Found: 1068.5. ^{1}H NMR ($CDCl_3$, 30°C) δ 1.250 (t, CH_3, J = 6.9 Hz, 36H), 3.605 (s, ArCH_2Ar, 12H), 3.837 (q, CH_2, J = 6.9 Hz, 24H), 6.262 (s, H_{ex}, 6H), 6.421 (s, H_{in}, 6H).

*Resorcin[7]arene tetradecaethyl ether (**7a**):* FAB-MS (MNBA, m/z) Calcd: 1246.7. Found: 1246.5. ^{1}H NMR ($CDCl_3$, 30°C) δ 1.238 (t, CH_3, J = 6.9 Hz, 42H), 3.638 (s, ArCH_2Ar, 14H), 3.847 (q, CH_2, J = 6.9 Hz, 28H), 6.281 (s, H_{ex}, 7H), 6.659 (s, H_{in}, 7H).

*Resorcin[8]arene hexadecaethyl ether (**8a**):* FAB-MS (MNBA, m/z) Calcd: 1424.8. Found: 1424.8. ^{1}H NMR ($CDCl_3$, 30°C) δ 1.179 (t, CH_3, J = 6.9 Hz, 48H), 3.646 (s, ArCH_2Ar, 16H), 3.788 (q, CH_2, J = 6.9 Hz, 32H), 6.250 (s, H_{ex}, 8H), 6.797 (s, H_{in}, 8H).

*Resorcin[9]arene octadecaethyl ether (**9a**):* FAB-MS (MNBA, m/z) Calcd: 1602.9. Found: 1603.1. ^{1}H NMR ($CDCl_3$, 30°C) δ 1.181 (t, CH_3, J = 6.9 Hz, 54H), 3.648 (s, ArCH_2Ar, 18H), 3.788 (q, CH_2, J = 7.0 Hz, 36H), 6.242 (s, H_{ex}, 9H), 6.757 (s, H_{in}, 9H).

*Resorcin[4]arene octapropyl ether (**4b**):* recrystallization from chloroform/hexane, colorless crystal, mp 204°C. Calcd for $C_{52}H_{72}O_8$: H, 8.80, C, 75.69. Found: H, 8.55; C, 75.47. FAB-MS (MNBA, m/z) Calcd 824.5. Found 824.6. ^{1}H NMR ($CDCl_3$, 30°C) δ 0.957 (t, CH_3CH$_2$CH$_2$, J = 7.6 Hz, 24H), 1.713 (sext, CH$_3$CH_2CH$_2$, J = 7.3 Hz, 16H), 3.718 (s, ArCH_2Ar, 8H), 3.824 (t, CH$_3$CH$_2$CH_2, 16H), 6.259 (s, H_{in}, 4H), 6.360 (s, H_{ex}, 4H). ^{13}C NMR ($CDCl_3$, 30°C) δ 10.7 (q), 23.0 (t), 28.1 (t, Ar*C*H$_2$Ar), 70.4 (t), 98.0 (d, Ar*C*-H_{ex}), 121.7 (s), 130.9 (d, Ar*C*-H_{in}), 155.6 (s). IR (KBr, cm^{-1}) 2965, 2875, 1613, 1586.

*Resorcin[5]arene decapropyl ether (**5b**):* FAB-MS (MNBA, m/z) Calcd: 1030.7. Found: 1030.6. ^{1}H NMR ($CDCl_3$, 30°C) δ 0.928 (t, CH_3CH$_2$CH$_2$, J = 7.6 Hz, 30H), 1.677 (sext, CH$_3$CH_2CH$_2$, J = 7.6 Hz, 20H), 3.676 (s, ArCH_2Ar, 10H), 3.737 (t, CH$_3$CH$_2$CH_2, J = 7.6 Hz, 20H), 6.306 (s, H_{ex}, 5H), 6.517 (s, H_{in}, 5H).

*Resorcin[6]arene dodecapropyl ether (**6b**):* FAB-MS (MNBA, m/z) Calcd: 1236.8. Found: 1236.8. ^{1}H NMR ($CDCl_3$, 30°C) δ 0.914 (t, CH_3CH$_2$CH$_2$, J = 7.6 Hz, 36H), 1.649 (sext, CH$_3$CH_2CH$_2$, J = 7.6 Hz, 24H), 3.613 (s, ArCH_2Ar, 12H), 3.731 (t, CH$_3$CH$_2$CH_2, J = 7.6 Hz, 24H), 6.254 (s, H_{ex}, 6H), 6.416 (s, H_{in}, 6H).

*Resorcin[7]arene tetradecapropyl ether (**7b**):* FAB-MS (MNBA, m/z) Calcd: 1442.9. Found: 1442.9. ^{1}H NMR ($CDCl_3$, 30°C) δ 0.918 (t, CH_3CH$_2$CH$_2$, J = 7.3 Hz, 42H), 1.657 (sext, CH$_3$CH_2CH$_2$, J = 7.3 Hz, 28H), 3.654 (s, ArCH_2Ar, 14H), 3.747 (t, CH$_3$CH$_2$CH_2, J = 7.3 Hz, 28H), 6.271 (s, H_{ex}, 7H), 6.600 (s, H_{in}, 7H).

*Resorcin[4]arene octaallyl ether(**4c**):* recrystallization from chloroform/hexane, microcrystals, mp 158-160°C. Calcd for $C_{52}H_{56}O_8$: H, 6.98; C, 77.20. Found: H, 7.02; C, 76.80. FAB-MS (MNBA, m/z) Calcd; 808.4. Found; 808.4. ^{1}H NMR ($CDCl_3$,

30°C) δ 3.769 (s, ArC*H*$_2$Ar, 8H), 4.423 (d, CH_2=CHC*H*$_2$O, *J* = 5.1 Hz, 16H), 5.183 (dd, CH_2CH=CH*H*, *J* = 10.5, 1.6 Hz, 8H), 5.329 (dd, CH_2CH=CH*H*, *J* = 17.3, 1.6 Hz, 8H), 5.978 (m, CH_2C*H*=CH_2, 8H), 6.302 (s, H_{in}, 4H), 6.399 (s, H_{ex}, 4H). ^{13}C NMR ($CDCl_3$, 30°C) δ 28.2 (t, Ar*C*H$_2$Ar), 69.7 (t), 98.8 (d, Ar*C*-H_{ex}), 116.6 (t), 122.1 (s), 131.1 (d, Ar*C*-H_{in}), 133.9 (s), 155.3 (s). IR (KBr, cm^{-1}) 3014, 2853, 1651,1611.

*Resorcin[5]arene decaallyl ether (**5c**):* light yellow oil. FAB-MS (MNBA, m/z) Calcd; 1010.5. Found; 1010.5. 270 MHz ^{1}H NMR ($CDCl_3$, 30°C) δ 3.720 (s, ArC*H*$_2$Ar, 10H), 4.347 (d, CH_2=CHC*H*$_2$O, *J* = 5.1 Hz, 20H), 5.149 (dd, CH_2CH=CH*H*, *J* = 10.5, 1.6 Hz, 10H), 5.295 (dd, CH_2CH=CH*H*, *J* = 17.4, 1.6 Hz, 10H), 5.927 (m, CH_2C*H*=CH_2, 10H), 6.342 (s, H_{ex}, 5H), 6.549 (s, H_{in}, 5H). ^{13}C NMR ($CDCl_3$, 30°C) δ 28.9 (t, Ar*C*H$_2$Ar), 69.6 (t), 98.9 (d, Ar*C*-H_{ex}), 116.5 (t), 122.4 (s), 131.9 (d, Ar*C*-H_{in}), 134.0 (s), 154.9 (s). IR (neat, cm^{-1}) 2857, 1614,1505.

*Resorcin[6]arene dodecaallyl ether (**6c**):* recrystallization from hexane/chloroform to give off-white solid, mp 138°C. Calcd for $C_{78}H_{84}O_{12}$: H, 6.98; C, 77.20. Found; H, 6.98; C, 77.04. FAB-MS (MNBA, m/z) Calcd: 1212.6. Found: 1212.6. ^{1}H NMR ($CDCl_3$, 30°C) δ 3.570 (s, ArC*H*$_2$Ar, 12H), 4.338 (d, CH_2=CHC*H*$_2$O, *J* = 5.1 Hz, 24H), 5.137 (dd, CH_2CH=CH*H*, *J* = 10.4, 1.6 Hz, 12H), 5.291 (dd, CH_2CH=CH*H*, *J* = 17.3, 1.6 Hz, 12H), 5.921 (m, CH_2C*H*=CH_2, 12H) 6.289 (s, H_{ex}, 6H), 6.399 (s, H_{in}, 6H). ^{13}C NMR ($CDCl_3$, 30°C) δ 28.6 (t, Ar*C*H$_2$Ar), 69.5 (t), 98.6 (d, Ar*C*-H_{ex}), 116.5 (t), 121.8 (s), 131.7 (d, Ar*C*-H_{in}), 134.1 (s), 155.1 (s). IR (neat, cm^{-1}) 2854, 1614, 1505.

*Sc(OTf)$_3$-catalyzed cyclooligomerization of **3d***

The reaction of **3d** was analogously performed as described as a typical procedure. In this case, most of the products precipitated during the reaction. The crude products were treated several times with hot chloroform, and the pure cyclic tetramer **4d** was obtained as an insoluble solid. The chloroform solution was evaporated, and residual material was triturated with toluene to leave a white powder, which was recrystallized from DMF to produce cyclic octamer **8d**. The cyclic pentamer **5d** and cyclic hexamer **6d** were obtained from the toluene soluble fraction by GPC separation.

*Resorcin[4]arene octamethyl ether (**4d**):* white solid, mp 300°C. FAB-MS (MNBA, m/z) Calcd: 600.2. Found: 600.3. ^{1}H NMR ($CDCl_3$, 30°C) δ 3.691 (s, ArC*H*$_2$Ar, 8H), 3.774 (s, CH_3, 24H), 6.189 (s, H_{in}, 4H), 6.441 (s, H_{ex}, 4H). ^{13}C NMR ($CDCl_3$, 30°C) δ 28.3 (t, Ar*C*H$_2$Ar), 55.8 (q), 95.1 (d, Ar*C*-H_{ex}), 120.6 (s), 130.7 (d, Ar*C*-H_{in}), 156.5 (s). IR (KBr, cm^{-1}) 2931, 2833, 1612, 1587.

*Resorcin[5]arene decamethyl ether (**5d**):* FAB-MS (MNBA, m/z) Calcd: 750.3. Found: 750.4. ^{1}H NMR ($CDCl_3$, 30°C) δ 3.650 (s, ArC*H*$_2$Ar, 10H), 3.716 (s, CH_3, 30H), 6.386 (s, H_{ex}, 5H), 6.441 (s, H_{in}, 5H). ^{13}C NMR ($CDCl_3$, 30°C) δ 28.0 (t, Ar*C*H$_2$ Ar), 56.0 (q), 96.1 (d, Ar*C*-H_{ex}), 121.2 (s), 131.4 (d, Ar*C*-H_{in}), 156.0 (s). IR (KBr, cm^{-1}) 2932, 2833, 1612, 1587.

*Resorcin[6]arene dodecamethyl ether (**6d**):* FAB-MS (MNBA, m/z) Calcd: 900.4. Found: 900.4. ^{1}H NMR ($CDCl_3$, 30°C) δ 3.596 (s, ArC*H*$_2$Ar, 12H), 3.694 (s, CH_3,

30H), 6.281 (s, H_{in}, 6H), 6.314 (s, H_{ex}, 6H). ^{13}C NMR ($CDCl_3$, 30°C) δ 28.4 (t, ArCH_2Ar), 55.8 (q), 95.6 (d, Ar*C*-H_{ex}), 120.8 (s), 131.2 (d, Ar*C*-H_{in}), 156.2 (s). IR (KBr, cm^{-1}) 2938, 2834, 1613, 1587.

*Resorcin[8]arene hexadecamethyl ether (**8d**):* white solid, mp 320°C. Calcd for $C_{72}H_{80}O_{16}$•C_3H_7NO: H 6.88; C 70.68. Found: H 6.81; C 70.54. FAB-MS (MNBA, m/z) Calcd: 1200.6. Found: 1200.7. ^1H NMR ($CDCl_3$, 30°C) δ 3.481 (s, ArCH_2Ar, 16H), 3.558 (s, CH_3, 48H), 6.201 (s, H_{ex}, 8H), 6.556 (s, H_{in}, 8H). ^{13}C NMR ($CDCl_3$, 30°C) δ 28.9 (t, Ar*C*H_2Ar), 55.5 (q), 95.2 (d, Ar*C*-H_{ex}), 120.6 (s), 131.4 (d, Ar*C*-H_{in}), 156.1 (s). IR (KBr, cm^{-1}) 2938, 2832, 1611, 1587.

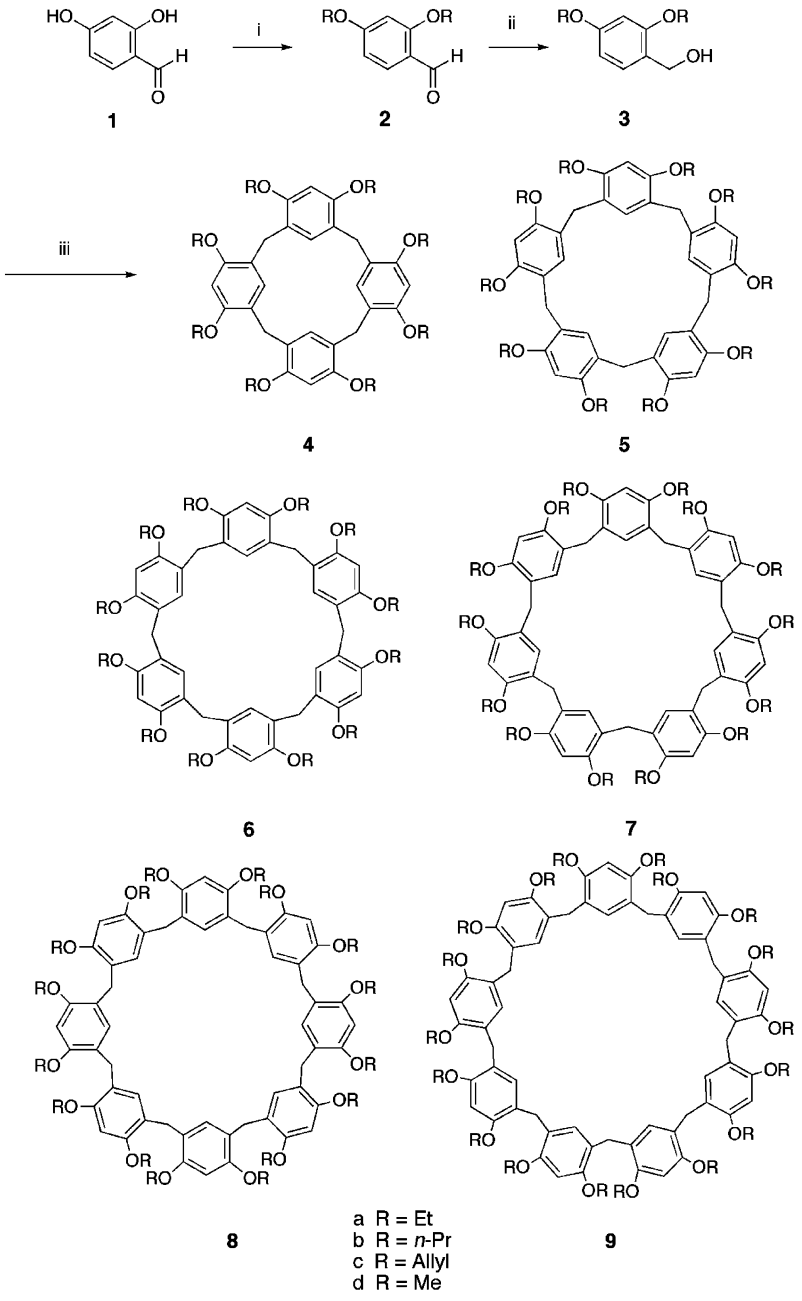
Results and discussion

Cyclooligomerization of 2,4-Dialkoxybenzyl Alcohols

Four 2,4-dialkoxybenzyl alcohols **3** were used as substrates (Scheme 1). The cyclooligomerization was conducted in CH_3CN and the high-dilution conditions were achieved by syringe pump addition of the substrate to the catalyst solution. The reactions were carried out at 50°C or 0°C, the initial concentration of catalyst was 2.0 mmol/l or 0.50 mmol/l, and the final substrate/catalyst ratio was 50:1 (mol/mol). These results are summarized in Table 1. The cyclic oligomers, except for **4d** and **8d**, were isolated by gel permeation chromatography (GPC). On the other hand, **4d** and **8d** were precipitated during the reaction and isolated, based on their different solubilities (see experimental). The yields shown in Table 1 are based on the amount of the isolated products. These cyclic compounds were characterized by ^1H NMR and FAB-MS.

The syringe pump addition of 2,4-diethoxybenzyl alcohol **3a** to 2.0 mmol/l $Sc(OTf)_3$ in CH_3CN over 4 h at 50°C produced the cyclic tetramer **4a** in 89% yield (entry 1). Moreover, small amount of the pentamer **5a** and hexamer **6a** were isolated. When the reaction was conducted at 0°C (entry 2), six cyclic oligomers **4a**, **5a**, **6a**, **7a**, **8a** and **9a** were isolated from the reaction mixture. The total yields of the cyclic oligomers and the selectivity of the cyclic tetramer were decreased either by lowering the temperature (entry 2, 4) or by decreasing the catalyst concentration (entry 3, 4). The cyclooligomerization of 2,4-dipropoxybenzyl alcohol **3b** (entry 5, 6) or 2,4-diallyloxybenzyl alcohol **3c** (entry 7, 8) gave analogous results.

In the case of 2,4-dimethoxybenzyl alcohol **3d**, most of the products precipitated during the reaction. When the reaction was conducted at 50°C (entry 9), the formation of **4d** was predominant (87%), and only a small amount of the cyclic pentamer **5d** and hexamer **6d** were isolated from the reaction mixture by GPC separation. This product selectivity is similar to that of **3a** at the same temperature (entry 1). Most interestingly, the reaction of **3d** at 0°C (entry 10) produced **4d** and **8d** in 27% and 54% yields, respectively. In contrast to **3d**, it is noteworthy that **3a** produced only a small amount of the octamer **8a** under analogous conditions. Furthermore, the formation of the octamers from **3b** or **3c** could not be confirmed by GPC separation. Therefore, the predominant formation of the octamer at 0°C may be considered to be specific for **3d**.



Scheme 1. $Sc(OTf)_3$-catalyzed cyclooligomerization of 2,4-dialkoxybenzyl alcohols. Reagents (i) alkyl bromide, K_2CO_3, acetone; (ii) $NaBH_4$, ethanol; (iii) $Sc(OTf)_3$, MeCN.

Table 1. The $Sc(OTf)_3$-catalyzed cyclooligomerization of 2,4-dialkoxybenzyl alcohols.

Entry	R	Reaction conditions			Yield /%[c]						Total yield of cyclic oligomers/%
		Catalyst /M[a]	Temp /°C	Time /h[b]	**4**	**5**	**6**	**7**	**8**	**9**	
1	Et	2.0	50	4	89	3	1	-	-	-	93
2	Et	2.0	0	4	61	5	6	2	1	1	76
3	Et	0.5	50	2	80	7	4	1	-	-	92
4	Et	0.5	0	2	57	9	10	6	-	-	82
5	*n*-Pr	0.5	50	2	76	7	4	1	-	-	88
6	*n*-Pr	0.5	0	2	63	5	6	4	-	-	78
7	Allyl	0.5	50	2	60	11	8	-	-	-	79
8	Allyl	0.5	0	2	47	10	14	-	-	-	71
9[d]	Me	2.0	50	4	87	4	1	-	-	-	92
10[d]	Me	2.0	0	4	27	-	-	-	54	-	81
11[d]	Me	0.5	50	2	76	-	-	-	-	-	76
12[d]	Me	0.5	0	2	35	-	-	-	10	-	45

a The initial concentration of $Sc(OTf)_3$. The final **3**:$Sc(OTf)_3$ ratio is 50:1. b Time of addition of **3** to catalyst solution. c Isolated yields by GPC separation. d **4d** and **8d** were isolated by recrystallization

The reaction temperature significantly affects the product distribution as shown in Table 1. The results may be explained as follows. At 50°C, the condensation of the benzyl alcohol rapidly occurs. Therefore, the concentration of the reactant maintains at very low level in the reaction mixture. Accordingly, the experiments at 50°C favor the intramolecular oligomerization, resulting in the selective formation of the smallest cyclic oligomers, *i. e.* the resorcin[4]arenes. On the other hand, it is expected that the consumption of the benzyl alcohol is much slower at 0°C, then its concentration in the reaction media much increase. Consequently, the intermolecular condensation significantly occurs, producing a series of cyclic oligomers with larger ring sizes although the total yield of the cyclic oligomers decreases and higher linear oligomeric products comprise the material balance.

To further explore the factor for the product distribution, a reconstruction experiment was evaluated by the reaction of a mixture of **4a**, **5a**, and **6a** with **3a** in the presence of $Sc(OTf)_3$. At 50°C, the syringe pump addition of **3a** to the mixture produced **4a** in good yield. The important points of this experiment are that the oligomerization is a reversible process and the cyclic tetramer is the thermodynamically favored product at 50°C. It has been reported that the C-C bond of calixarenes and resorcinarenes were cleaved by the *ipso*-attack of benzyl cations [11,19,20]. Since benzyl cations are generated from benzyl alcohols in the presence of $Sc(OTf)_3$ [21], it is reasonably assumed that the larger cyclic oligomers convert to the cyclic tetramer during the addition of a benzyl alcohol to the reaction mixture. Namely, the selective formation of the cyclic tetramer can be attributed to both the kinetically and thermodynamically controlled reaction under the high dilution conditions at 50°C.

The oligomerization of **3d** at 0°C should produce a series of resorcin[n]arene permethyl ethers. However, only two types of products, **4d** and **8d**, were isolated in reasonable yields. Very interestingly, the favored formation of an octamer is specific for **3d** as described above. Because **4d** and **8d** have very low solubilities in the reaction medium, the cyclic oligomers immediately precipitate out of solution as they form. Since the oligomerization is reversible, the cyclic oligomers with different ring sizes, that are soluble in solution, are converted to insoluble products, **4d**, **8d** and higher linear oligomers. In other cases, since all of the cyclic oligomers are soluble in the reaction medium, an analogous phenomenon could not be observed.

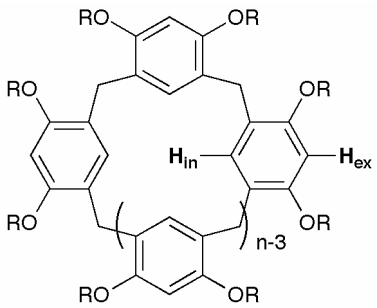


Figure 1. Intraannular aromatic proton (H_{in}) and extraannular aromatic proton (H_{ex}).

Table 2. The chemical shifts of the intraannular aromatic protons (H_{in}) and the extraannular aromatic protons (H_{ex}) for resorcin[n]arene perethyl ethers[a].

	4a	**5a**	**6a**	**7a**	**8a**	**9a**
H_{in}	6.25	6.52	6.42	6.66	6.80	6.76
H_{ex}	6.38	6.33	6.26	6.28	6.25	6.24

a Determined in $CDCl_3$ at 30°C

Conformational properties

The ^1H NMR spectrum ($CDCl_3$) of the cyclic oligomers that are described here showed three singlets for the extraannular aromatic protons (H_{ex}), intraannular

aromatic protons (H_{in}), and bridge methylene protons (Figure 1), indicating highly symmetrical structures on the NMR time scale. The assignment of H_{in} and H_{ex} were based on the selective decoupling experiments of the ^{13}C signals of the corresponding aromatic carbons. Table 2 lists the chemical shifts of H_{in} and H_{ex} in the series of ethyl ether derivatives **4a**-**9a**. The H_{ex} protons resonate in the range of 6.24 to 6.38 ppm, and the chemical shifts may be explained by the substitution effect of two alkoxy groups at the *ortho*-positions. On the other hand, the chemical shifts of the H_{in} protons shifted to a high field region by 0.6-1.0 ppm as compared with the proton at the 6-position of 2,4-diethoxybenzene. This upfield shift can be accounted for by the ring current effect of adjacent aromatic nuclei. The most remarkable feature of the spectra was observed for the cyclic tetramers. The signals of H_{in} for **4a**, **4b**, **4c**, **4d** appeared at 6.25, 6.26, 6.30, and 6.19 ppm, respectively. Only small chemical shift changes were detected when measured at -50°C, and these values strongly suggest that the preferred conformation of the cyclic tetramers is '1,3-alternate' (Figure 2). Indeed, 1,3-alternate conformer of resorcin[4]arene octa(isopropyl) ether was observed in the solid state [17]. The [1.4]metacyclophanes bearing no substituents at the intraannular positions have very flexible hydrocarbon framework [22]. In the present system, the preference of the 1,3-alternate conformation is presumably due to steric repulsion of the eight alkoxy groups at the extraannular positions.

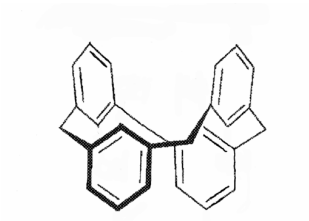


Figure 2. 1,3-Alternate conformation of [1.4]metacyclophane.

In the case of the cyclic oligomers containing five or more resorcinol nuclei, their macrocyclic frameworks should be a regular polygonal in order to show the magnetically equivalent methylene protons. However, this situation could not be feasible due to the internal-angle strains of the macrocycles. The ^1H NMR spectra of these cyclic oligomers at -50°C were similar to those determined at 30°C, indicating that their conformational freezing could not be attained at -50°C. Hence, we concluded that the larger cyclic oligomers exist as a fast equilibrium among the conformationally flexible species.

Conclusion

We have found that the cyclooligomerization of 2,4-dialkoxybenzyl alcohols **3** catalyzed by $Sc(OTf)_3$ in CH_3CN under high dilution conditions produced a series of resorcin[n]arene peralkyl ethers containing four to nine resorcinol units. The reactions conducted at 50°C produced cyclic tetramers **4** as the major products, which are the thermodynamically favored products. When the reaction of 2,4-dimethoxybenzyl alcohol **3d** was conducted at 0°C, the corresponding cyclic octamer **8d** was obtained as the major product. In other cases, such as the selective formation of a cyclic octamer was not observed. This selective formation of **8d** is due to a combination of

the reversibility of the oligomerization in the presence of **3d** and the insolubility of the octamer in the reaction medium. The cyclic tetramers possess a 1,3-alternate conformation on the ^{1}H NMR time scale, and the larger cyclic oligomers exist as a mixture of the conformationally mobile species.

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