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# $Sc(OTf)_3$-catalyzed cyclocondensation of 2-propylresorcinol with diethoxymethane. Formation and fragmentation of resorcin[*n*]arenes

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**Abstract**—The cyclocondensation of an equimolar amount of 2-propylresorcinol with diethoxymethane in the presence of $Sc(OTf)_3$ in acetonitrile produced a mixture of resorcin[*n*]arenes ($n = 4$–7) with a kinetically controlled product distribution. However, the reaction with an excess amount of diethoxymethane produced the thermodynamically favored resorcin[4]arene as the major product. The fragmentation/recombination mechanism of the resorcin[*n*]arenes was discussed.
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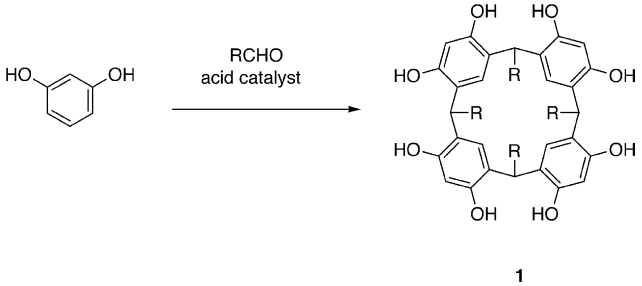
The HCl-catalyzed condensation of resorcinol with an aliphatic or aromatic aldehyde produces a mixture of two or three diasteroisomeric cyclic tetramers, resorcin[4]arenes **1** (Scheme 1).[1–4] Interestingly, in most cases, only one stereoisomer can be selectively obtained by increasing the reaction time. The main factors for the determination of the final product are the conversion of the kinetically favored isomers to the thermodynamically stable isomer and its selective precipitation.[5]




**1**

**Scheme 1.**

The resorcin[4]arenes with unsubstituted methylene bridges have been prepared by the HCl-catalyzed condensation of 2-alkylresorcinols with formaldehyde or its equivalents.[6–8] This reaction initially yields a mixture of cyclic oligomers, resorcin[*n*]arenes.[9–11] Under the conditions of their formation, the cyclic pentamer and higher homologues readily convert to the cyclic tetramer via fragmentation/recombination.[11] Moreover, except for 2-methylresorcinol, the reaction of 2-alkylresorcinols with formaldehyde proceeds in a homogeneous solution. Evidently, the cyclic tetramer is the thermodynamically most stable product.

A few examples of Lewis acid-catalyzed condensations of resorcinol with aromatic aldehydes have been reported.[12–15] In sharp contrast to the HCl catalyzed reactions, a mixture of stereoisomers of the resorcin[4]arenes was produced. Furthermore, in most cases, their product distributions were not time dependent, that is, the Lewis acids are not effective catalysts for the isomerization of the resorcin[4]arenes.[15] Accordingly, it is expected that the resorcinarenes containing five or more resorcinol units should be stable during the Lewis acid-catalyzed reaction. Recently we reported that $Sc(OTf)_3$ could be used as a catalyst for the synthesis of resorcinarene derivatives.[16,17] This finding prompted us to investigate the $Sc(OTf)_3$ catalyzed condensation of 2-alkylresorcinols with formaldehyde with the objective of obtaining resorcin[*n*]arenes with larger ring sizes. The cyclic

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pentamer and higher homologues are useful molecular blocks for the construction of sophisticated molecules in supramolecular chemistry.[10,18] Herein, we describe the formation of resorcin[*n*]arenes from 2-propylresorcinol (**2**) and diethoxymethane (**3**) in the presence of $Sc(OTf)_3$ and their ring contraction mechanism.

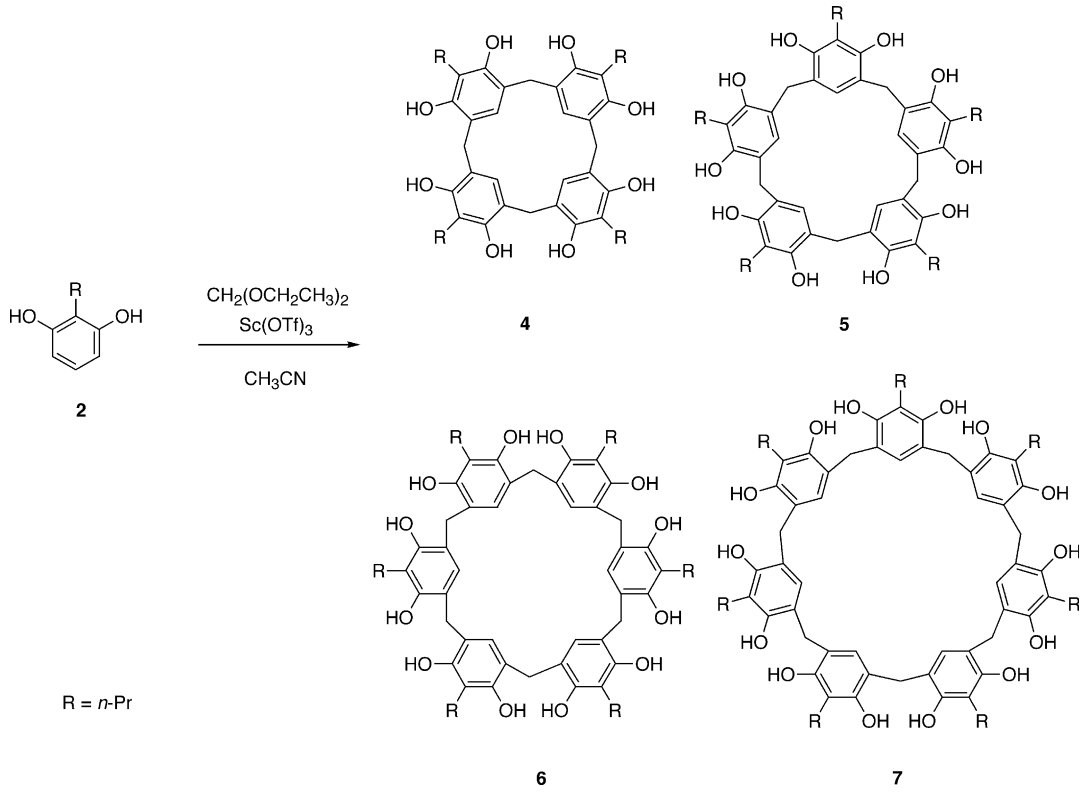
Equimolar amounts of **2** and **3** in acetonitrile (each 0.1 mol $L^{-1}$) were allowed to react in the presence of 1 mol% of $Sc(OTf)_3$[†]. The crude products were acetylated and separated by gel permeation chromatography (GPC) to give four major fractions, which were identified as the cyclic tetramer **4**, pentamer **5**, hexamer **6**, and heptamer **7**[‡] (Scheme 2). The GPC trace indicated the formation of small amounts of the larger resorcin[*n*]arenes ($n \geqslant 8$). However, we could not isolate these products in their pure form, since the higher molecular fractions were a complex mixture containing linear oligomers. Table 1 shows the product distribution, which is based on the isolated yields of the acetylated resorcin[*n*]arenes. The reaction at 60 °C for 3 h gave four resorcin[*n*]arenes in total yields of 56% (entry 1). Prolonged heating did not affect the total yield and the product distribution (entry 2). Upon decreasing or increasing the reaction temperature, the total yield of the cyclic oligomers decreased. At 30 °C (entry 3), the GPC and $^1$H NMR analysis of the reaction mixture showed the presence of lower linear oligomers in much larger quantities, indicating that the condensation was not complete within 24 h. On the other hand, at 80 °C (entry 4), the reaction mixture contained a considerable amount of the higher linear oligomers. In any event, in all cases, the yields of the cyclic oligomers are in the order of **6** $\geqslant$ **4** > **5** $\geqslant$ **7**, and the product distribution is similar to each other. Next, we considered the influence of the amount of the condensation agent **3**. When the 1:2 ratio of **2** and **3** was used, the reaction at 30 °C for 24 h (entry 5) gave **4** (51%) and **6** (15%), and at 80 °C for 1 h (entry 6) selectively yielded **4** (84%). These results strongly suggested that the contraction of the larger resorcinarenes took place in the presence of **3**. This assumption, in fact, was experimentally supported. Thus the addition of **3** to a mixture of cyclic oligomers resulted in the selective formation of **4** (entry 7). In addition, it was found that the formation of resorcinarenes was much faster than the ring contraction. Therefore, we concluded that the relative amounts of the four resorcin[*n*]arenes formed in the reaction containing an equimolar amount of **2** and **3** reflect a kinetically controlled process.

The cleavage of the aromatic alkyl C–C bonds involves the *ipso*-attack of electrophiles. In calixarene systems, benzyl cations are more effective electrophiles for the fragmentation than proton or protonated formaldehyde.[19,20] In the present system, the fact that resorcin[*n*]arenes are readily reconstructed into resorcin[4]arene in the presence of a protic acid indicated that the activated species derived from **3** and $Sc(OTf)_3$ may act as an electrophile for the cleavage of the C–C bond. This reconstruction mechanism was confirmed by the following experiments. Thus, the reaction of the $CD_2$ bridged cyclic hexamer **6**-$d_{12}$[§] with formaldehyde in the presence of $Sc(OTf)_3$ conducted in acetonitrile, and the reaction mixture was analyzed by $^1$H NMR spectroscopy in DMSO-$d_6$. Its spectrum showed the bridge methylene signal as a singlet at 3.568 ppm, which confirmed the selective formation of the cyclic tetramer. Based on the integral ratio of the methylene protons, the average number of $CH_2$ groups incorporated in the tetramer was 1.4 (Scheme 3). These data clearly demonstrate the *ipso*-attack of the activated formaldehyde and the reconstruction via a fragmentation/recombination mechanism. Furthermore, the analogous reaction of the $CD_2$ bridged cyclic tetramer **4**-$d_8^3$ did not show a $CD_2$–$CH_2$ exchange, indicating the thermodynamic stability of the cyclic tetramer.

[†] $Sc(OTf)_3$-catalyzed cyclocondensation of **2** with **3**; General procedure: A solution of **2** (152 mg, 1 mmol), **3** (104 mg, 1 mmol), and $Sc(OTf)_3$ (5 mg, 0.01 mmol) in $CH_3CN$ (10 mL) was stirred at 60 °C for 3 h. After cooling, diethyl ether and water were added. The organic layer was separated and washed with water. The solution was dried over $Na_2SO_4$ and concentrated to dryness. The residue was dissolved in acetic anhydride (5.5 mL) and pyridine (0.5 mL). This solution was stirred at 70 °C for 24 h. Most of the solvent was removed by Kugel–Rohr distillation and the residue was subjected to GPC separation (JAI LC-918, column: JAIgel 1H and 2H, eluent: chloroform). The isolated samples were weighed and characterized by FAB-MS (*m*-nitrobenzyl alcohol matrix) and 270 MHz $^1$H NMR spectroscopy. **4-Octaacetate**: $^1$H NMR ($CDCl_3$, 30 °C) $\delta$ 0.906 (t, $CH_3$, 12H, $J = 7.4$ Hz), 1.446 (sext, $CH_2$, 8H), 2.235 (s, $COCH_3$, 24H), 2.301 (m, $ArCH_2$, 8H), 3.497 (s, bridge $CH_2$, 8H), 6.412 (s, ArH, 4H). FAB-MS *m*/*z* calcd: 992.4, found: 993.4. **5-Decaacetate**: $^1$H NMR ($CDCl_3$, 30 °C) $\delta$ 0.910 (t, $CH_3$, 15H, $J = 7.2$ Hz), 1.427 (sext, $CH_2$, 10H), 2.204 (s, $COCH_3$, 30H), 2.257 (m, $ArCH_2$, 10H), 3.506 (s, bridge $CH_2$, 10H), 6.488 (s, ArH, 5H). FAB-MS *m*/*z* calcd: 1240.5, found: 1241.4. **6-Dodecaacetate**: $^1$H NMR ($CDCl_3$, 30 °C) $\delta$ 0.884 (t, $CH_3$, 18H, $J = 7.3$ Hz), 1.449 (sext, $CH_2$, 12H), 2.135 (s, $COCH_3$, 36H), 2.301 (m, $ArCH_2$, 12H), 3.530 (s, bridge $CH_2$, 12H), 6.488 (s, ArH, 6H). FAB-MS *m*/*z* calcd: 1488.6, found: 1489.7. **7-Tetradecaacetate**: $^1$H NMR ($CDCl_3$, 30 °C) $\delta$ 0.869 (t, $CH_3$, 21H, $J = 7.3$ Hz), 1.319 (sext, $CH_2$, 14H), 2.109 (s, $COCH_3$, 42H), 2.233 (m, $ArCH_2$, 14H), 3.516 (s, bridge $CH_2$, 14H), 6.677 (s, ArH, 7H). FAB-MS *m*/*z* calcd: 1736.7, found: 1737.8.

[‡] Resorcin[7]arene **7**: A mixture of cyclic oligomers was prepared according to the general procedure. The crude product was dissolved in chloroform, and the chloroform soluble fraction was subjected to GPC separation. Recrystallization from chloroform gave **7**: mp 189–192 °C (dec). Anal. Calcd for $C_{70}H_{84}O_{14}\cdot CHCl_3\cdot H_2O$: C, 66.27; H, 6.81. Found: C, 65.95; H, 6.81. (dried at 80 °C, 8 h). FAB-MS *m*/*z* calcd: 1148.6, found: 1148.6. $^1$H NMR (DMSO-$d_6$ 50 °C) $\delta$ 0.875 (t, $CH_3$, 21H, $J = 7.4$ Hz), 1.418 (sext, $CH_2$, 14H), 2.560 (m, $ArCH_2$, 14H), 3.592 (s, bridge $CH_2$, 14H), 6.754 (s, ArH, 7H), 8.303 (s, OH, 14H). $^{13}$C NMR (125.6 MHz, DMSO-$d_6$, 50 °C) $\delta$ 14.0 ($CH_3$), 22.2 ($CH_2$), 25.8 ($ArCH_2$), 30.6 (bridge C), 117.5 (ArC), 120.3 (ArC), 128.4 (ArC), 150.4 (ArC–OH).

[§] $CD_2$-bridged resorcin[*n*]arenes: A mixture of $CD_2$-bridged resorcin[*n*]arenes was prepared according to the general procedure using paraformaldehyde-$d_2$ (30 mg, 1 mmol, 99 atom% D, Aldrich Co.) instead of **3**. The mixture was separated by GPC as described for the separation of **7**. **4**-$d_8$: $^1$H NMR ($CDCl_3$, 30 °C) $\delta$ 0.947 (t, $CH_3$, 12H, $J = 7.4$ Hz), 1.509 (m, $CH_2$, 8H), 2.497 (m, $ArCH_2$, 8H), 7.137 (s, ArH, 4H). **6**-$d_{12}$: $^1$H NMR ($CDCl_3$, 30 °C) $\delta$ 0.958 (t, $CH_3$, 18H, $J = 7.6$ Hz), 1.509 (m, $CH_2$, 12H), 2.528 (t, $ArCH_2$, 12H, $J = 7.6$ Hz), 7.257 (s, ArH, 6H).

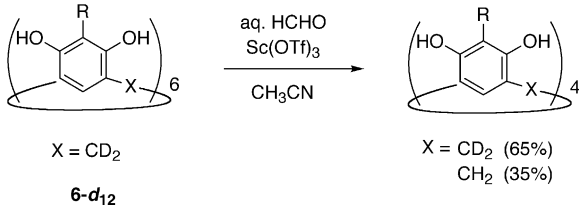



**Scheme 2.**

**Table 1.** $Sc(OTf)_3$-catalyzed cyclocondensation of 2-propylresorcinol **2** with diethoxymethane **3** in acetonitrile[a]

| Entries | Molar ratio **2**:**3** | Temp/°C | Time/h | Yield %[b] | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | **4** | **5** | **6** | **7** | Total of **4**–**7** |
| 1 | 1:1 | 60 | 3 | 18 | 10 | 22 | 6 | 56 |
| 2 | 1:1 | 60 | 24 | 20 | 11 | 24 | 5 | 60 |
| 3 | 1:1 | 30 | 24 | 11 | 9 | 18 | 9 | 47 |
| 4 | 1:1 | 80 | 24 | 17 | 8 | 17 | 3 | 45 |
| 5 | 1:2 | 30 | 24 | 51 | <1 | 15 | <1 | 66 |
| 6 | 1:2 | 80 | 1 | 84[c] | — | — | — | 84 |
| 7 | 1:(1+1[d]) | 60 | 24 | 82[c] | — | — | — | 82 |

[a] [**2**] = [**3**] = 0.1 mol $L^{-1}$. $Sc(OTf)_3$, 1 mol %.
[b] Isolated yield after acetylation.
[c] Isolated yield of octol **4**.
[d] After a 3 h reaction, 1 molar equivalent of **3** was added to the reaction mixture.




**Scheme 3.**

In conclusion, the $Sc(OTf)_3$-catalyzed reaction of an equimolar amount of 2-propylresorcinol with diethoxymethane produced resorcin[*n*]arenes ($n = 4$–7) with a kinetically controlled product distribution, **6** ⩾ **4** > **5** ⩾ **7**. The C–C bond scission is conducted by the formaldehyde activated with $Sc(OTf)_3$, and the thermodynamically most stable cyclic tetramer is formed via a fragmentation/recombination mechanism.

## References and notes

1. Högberg, A. G. S. *J. Org. Chem.* **1980**, *45*, 4498–4500.
2. Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046–6050.
3. Abis, L.; Dalcanale, E.; Du-vosel, A.; Spera, S. *J. Org. Chem.* **1988**, *53*, 5475–5479.
4. Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305–1312.

5. Weinelt, F.; Schneider, H.-J. *J. Org. Chem.* **1991**, *56*, 5527–5535.
6. Konishi, H.; Iwasaki, Y.; Okano, T.; Kiji, J. *Chem. Lett.* **1989**, 1815–1816.
7. Konishi, H.; Iwasaki, Y.; Morikawa, O.; Okano, T.; Kiji, J. *Chem. Express* **1990**, 869–871.
8. Konishi, H.; Morikawa, O. *J. Chem. Soc., Chem. Commun.* **1993**, 34–35.
9. Konishi, H.; Ohata, K.; Morikawa, O.; Kobayashi, K. *J. Chem. Soc., Chem. Commun.* **1995**, 309–310.
10. Naumann, C.; Román, E.; Peinador, C.; Ren, T.; Patrick, B. O.; Kaifer, A. E.; Sherman, J. C. *Chem. Eur. J.* **2001**, *7*, 1645–1673.
11. Konishi, H.; Nakamura, T.; Ohata, T.; Kobayashi, K.; Morikawa, O. *Tetrahedron Lett.* **1996**, *37*, 7383–7386.
12. Pieroni, O. I.; Rodriguez, N. M.; Vuano, B. M.; Cabaleiro, M. C. *J. Chem. Res. (S)* **1994**, 188–189.
13. Curtis, A. D. M. *Tetrahedron Lett.* **1997**, *38*, 4295–4296.
14. Peterson, K. E.; Smith, R. C.; Mohan, R. S. *Tetrahedron Lett.* **2003**, *44*, 7723–7725.
15. Baarrett, A. D. M.; Braddock, D. C.; Henschake, J. P.; Walker, E. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 873–878.
16. Konishi, H.; Sakakibara, H.; Kobayashi, K.; Morikawa, O. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2583–2584.
17. Konishi, H.; Morikawa, O.; Kobayashi, K.; Abe, K.; Ohkubo, A. *Tetrahedron Lett.* **2003**, 7425–7427.
18. Naumann, C.; Place, S.; Sherman, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 16–17.
19. Stewart, D. R.; Gutsche, C. D. *J. Am. Chem. Soc.* **1999**, *121*, 4136–4146.
20. Tsue, H.; Enyo, K.; Hirao, K. *Org. Lett.* **2000**, *2*, 3071–3074.