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# The Synthesis of Octamethoxyresorc[4]arenes Catalysed by Lewis Acids

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**Abstract:**

Lewis acids catalyse the condensation of isovaleraldehyde with 1,3-dimethoxybenzene. All conformers formed in this reaction were isolated and analysed spectroscopically. $SnCl_4$, when used in this reaction, catalysed selective formation of the *rccc* conformer in high yield. Its selectivity was compared to other aliphatic aldehydes. © 1998 Elsevier Science Ltd. All rights reserved.

*Keywords*: *Lewis acids, 1,3-dimethoxybenzene, calixresorcarene, condensation.*

## INTRODUCTION

Among macrocyclic compounds, calixarenes take a particular place. The most frequently studied compounds of this type are calixresorc[4]arenes [1]. These compounds can be modified in various ways at the phenol hydroxy groups as well as by electrophilic substitution in the phenol ring [2]. Because of that, they are useful platforms for construction of novel molecular receptors for ions and neutral compounds [3]. Their synthesis from aldehydes and resorcinol is catalysed by mineral acids as well as Lewis acids [4]. The presence of an alkyl or aryl substituent coming from the aldehyde results in formation of four conformers labeled *rccc* (all-*cis*, the crown conformer), *rcct* (the diamond conformer), *rctt*, and *rtct* [5].

Extensive studies on the application of Lewis acids in organic synthesis have been conducted for many years. They have found application in the synthesis of calixarenes as well [6]. This paper concerns the Lewis acid-catalysed synthesis of the octamethoxyresorcarenes **1** from aliphatic aldehydes and 1,3-dimethoxybenzene. The crown conformers of calixresorc[4]arenes are particularly often used as receptors in complexation studies [7]. Therefore, special attention was paid to the selective synthesis of the crown conformer of octamethoxyresorcarene.

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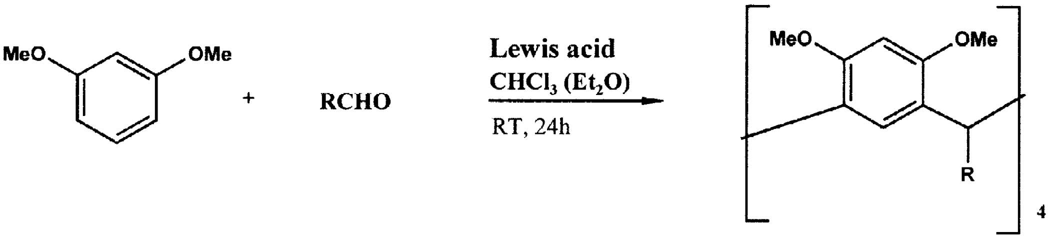
## RESULTS AND DISCUSSION

The preparation of octametoxyresorc[4]arenes was based on a one-step cyclisation reaction according to Scheme 1. The catalytic properties of typical Lewis acids were checked using isovaleraldehyde and 1,3-dimethoxybenzene as an example (Table 1). Among them, only $SnCl_4$ catalyses this reaction selectively and promotes formation of the *rccc* conformer in high yield. This finding is very important from the synthetic viewpoint, because it greatly simplifies the preparative procedure [8] of compound **1**. The crown conformer (*rccc*) of the octamethoxyresorc[4]arene can be the starting compound for subsequent functionalisation.



**1**

Scheme 1

Table 1. Type of Lewis acid used, resulting conformers, and total yield of the reaction between isovaleraldehyde and 1,3-dimethoxybenzene.

| | Conformers of **1d*** | | | |
|---|---|---|---|---|
| Lewis acid | *rccc* | *rctt* | *rcct* | Total yield [%] |
| $SOCl_2$ | + | + | + | 80 |
| $POCl_3$ | + | + | + | 70 |
| $AlCl_3$ | + | + | + | 20 |
| $SiCl_2Me_2$ | + | + | + | 75 |
| $SiClMe_3$ | + | + | + | 77 |
| $SnCl_4$ | + | - | - | 85 |

* notation according to Table 2.

Except for the $SnCl_4$-catalysed reaction, three conformers were obtained. However, the formation of crown (*rccc*) and diamond (*rcct*) conformers predominates in all cases. Because of different solubilities in a mixture of chloroform and methanol, these two conformers can be readily separated. Only the diamond conformer has been obtained in a crystalline form useful for crystallographic investigation (Figure 1). The diamond conformer (*rcct*) of **1d** crystallises from the mixture of chloroform and methanol along with one chloroform molecule within its structure.

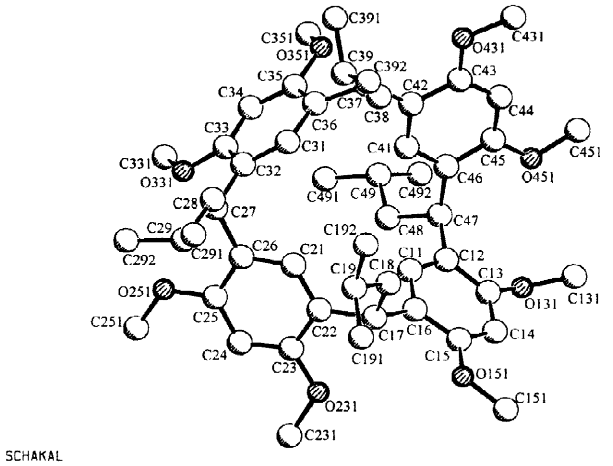


Fig. 1. X-ray structure of the diamond conformer of **1d** [9] (the molecule of chloroform is omitted for clarity).

Because of the high selectivity of $SnCl_4$ in the reaction of isovaleraldehyde, subsequent studies addressed whether if this Lewis acid is a selective catalyst for the reactions of other aliphatic aldehydes with 1,3-dimethoxybenzene. Only the branched-chain alkyl aldehydes undergo the reaction with chloroform as solvent according to Scheme 1. The reaction yield is the highest for isovaleraldehyde (85%, Table 2). In the case of isobutyraldehyde, the yield is only up to 40%. The other aldehydes tested afford a number of unidentified products. Replacement of the solvent by diethyl ether results in reaction of straight-chain aldehydes with 1,3-dimethoxybenzene leading to formation of the crown conformer of octamethoxyresorc[4]arene. In this case, minute amounts of other conformers of octamethoxyresorc[4]arene are also formed. The crown conformers of **1** were obtained in pure form after column chromatography on silica gel using chloroform or dichloromethane as eluents.

Table 2. Yields of formation of the crown conformers **1** in chloroform and diethyl ether.

| Alkyl moiety **R** of the aldehyde substrate | **1** | Yield of **1**, in $CHCl_3$ [%] | Yield of **1**, in $Et_2O$ [%] |
|---|---|---|---|
| $CH_2CH_2CH_3$ | **1a** | - | 30 |
| $CH(CH_3)_2$ | **1b** | 40 | |
| $CH_2CH_2CH_2CH_3$ | **1c** | - | 45 |
| $CH_2CH(CH_3)_2$ | **1d** | 85 | |
| $CH_2CH_2CH_2CH_2CH_3$ | **1e** | - | 55 |

The individual conformers of **1d** can easily be identified by analysis of $^1$H NMR and $^{13}$C NMR spectra. The analysis of $^1$H NMR spectra shows that the *rccc* conformer is characterised by one triplet for the -CH- group. For the *rctt* conformer, the signal of the -CH- group appears as a multiplet. In turn, the *rcct* conformer has two characteristic signals (triplet and multiplet) for the -CH- group. The *rcct* conformer can be identified especially easily on the basis of $^{13}$C NMR DEPT spectrum, which shows 3 negative signals for the -CH$_2$- group of the aldehyde alkyl moiety.

High symmetry of all crown conformers of octamethoxyresorc[4]arene **1** was observed in the NMR spectra. $^1$H NMR spectra show characteristic signals for -OMe and -CH- groups attached to the aromatic rings, as well as for aromatic protons ArH. The single signals for -OMe and -CH- groups and two signals of ArH protons are typical for the crown conformers of octamethoxyresorc[4]arene.

In summary, Lewis acids catalyse the condensation of aldehydes with 1,3-dimethoxybenzene. In this reaction, SnCl$_4$ is a selective catalyst which, in the case of isovaleraldehyde, results in formation of the crown conformer in high yield.

## EXPERIMENTAL

### General:

Melting points were measured on a Boetius apparatus and are not corrected. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra were recorded with a Bruker AM-300 spectrometer for solution in CDCl$_3$ (internal standard: Me$_4$Si). EI-and LSI-mass spectra were taken on an AMD-604 mass spectrometer.

### Typical Experimental Procedure:

*Preparation of octamethoxyresorc[4]arenes (1d):* 1,3-Dimethoxybenzene (1 ml) and isovaleraldehyde (7.63 mmol) were added to the Lewis acid (7.63 mmol) in chloroform (10 ml). The solution was stirred at room temperature for 24 h. Subsequently, methanol (20 ml) was added, and the mixture was stirred for 1 h. The resulting precipitate was collected by filtration and crystallised from a mixture of chloroform and methanol to give the crown conformer (*rccc*). During slow evaporation of the mother liquor, the diamond conformer (*rcct*) crystallised out. The resulting crystalline precipitate was recrystallised from a mixture of chloroform and methanol. The *rctt* conformer was obtained after chromatography on silica gel using dichloromethane as eluent.

**1d (*rccc*):** mp 288-289°C; $^1$H NMR δ: 0.91 (d, J = 6.3 Hz, 24H, Me), 1.55 (m, 4H, CH), 1.69 (dd, J = 7.2 Hz, 8H, CH$_2$), 3.60 (s, 12H, OMe), 4.60 (t, J = 7.4 Hz, 4H, CH), 6.32 (s, 4H, H-Ar), 6.60 (s, 4H, H-Ar); $^{13}$C NMR δ: 22.89, 25.90, 33.17, 44.11, 56.21, 97.27, 126.22, 126.27, 155.85; MS (EI, 70 eV) m/z: 824 (M$^+$-H).

**1d (*rcct*):** mp 162-163°C; $^1$H NMR δ: 0.55 (d, J = 6.3 Hz, 6H, Me), 0.79 (m, 2H, CH), 0.89 (m, 18H, Me), 1.33 (m, 2H, CH), 1.55 (m, 4H, CH$_2$), 1.82 (m, 4H, CH$_2$), 3.58 (s, 6H, OMe), 3.76 (s, 6H, OMe), 3.83 (s, 6H, OMe), 3.86 (s, 6H, OMe), 4.76 (m, 3H, CH), 5.23 (t, J = 8.2 Hz, 1H, CH), 6.36 (s, H-Ar), 6.43 (s, H-Ar), 6.52 (s, H-Ar), 7.66 (s, H-Ar); $^{13}$C NMR δ: 21.78, 22.57, 22.71, 23.90, 25.60, 26.13, 26.15, 28.68, 29.21, 32.90, 44.325, 46.01, 47.63, 55.87, 56.07, 56.59, 56.97, 96.50, 97.49, 124.52, 126.00, 126.26, 127.41, 127.47, 155.08, 155.22, 155.97, 156.38; MS (EI, 70 eV) m/z: 824 ($M^+$-H).

**1d (*rctt*):** mp 60-160°C (conformational transition); $^1$H NMR δ: 0.82 (d, J = 5.8 Hz, 24H, Me), 1.42 (m, 4H, CH), 1.60 (m, 8H, $CH_2$), 3.62 (s, 12H, OMe), 3.88 (s, 12H, OMe), 4.66 (m, 4H, CH), 6.25 (s, H-Ar), 6.40 (s, H-Ar), 6.59 (s, H-Ar) 6.93 (s, H-Ar); $^{13}$C NMR δ: 22.04, 23.54, 25.84, 33.36, 44.21, 56.13, 56.29, 96.34, 97.49, 125.91, 126.83, 127.52; MS (EI, 70 eV) m/z: 824 ($M^+$-H).

*Preparation of crown conformers of octamethoxyresorc[4]arenes (1):* 1,3-Dimethoxybenzene (1 ml) and aliphatic aldehyde (7.63 mmol) were added to $SnCl_4$ (7.63 mmol) in either chloroform (10 ml) or diethyl ether (20 ml). The solution was stirred at room temperature for 24 h. Subsequently, methanol (20 ml) was added and the mixture was stirred for 1 h. The precipitate was collected by filtration. The solvent was evaporated and the crown conformer was obtained after chromatography on silica gel using chloroform or dichloromethane as eluent.

**1a**: mp 283-284°C; $^1$H NMR δ: 0.92 (t, J = 7.2 Hz, 12H, Me), 1.37 (m, 8H, $CH_2$), 1.82 (m, 12H, $CH_2$), 3.60 (s, 24H, OMe), 4.48 (t, J = 7.4 Hz, 4H, CH), 6.32 (s, 4H, ArH), 6.64 (s, 4H, ArH); $^{13}$C NMR δ: 14.31, 21.23, 35.08, 37.15, 56.21, 97.16, 125.85, 126.08, 126.33, 155.83; MS (EI, 70 eV) m/z: 768.8 ($M^+$-H); HR-MS: found 768.4601, calcd. 768.46012.

**1b**: mp 277-278°C; $^1$H NMR δ: 0.83 (d, J = 6.3 Hz, 24H, Me), 2.33 (m, 4H, CH), 3.68 (s, 24H, OMe), 4.39 (d, J = 11.4 Hz, 4H, CH), 6.33 (s, 4H, ArH), 7.08 (s, 4H, ArH); MS (EI, 70 eV) m/z: 769 ($M^+$-H)

**1c**: mp 306-307°C; $^1$H NMR δ: 0.80 (t, J = 7.4, 12H, Me), 1.25 (m, 8H, $CH_2$), 1,32 (m., 8H, $CH_2$), 1.65 (m., 8H, $CH_2$), 3.60 (s, 24H, OMe), 4.47 (t, J = 7.2, 4H, CH), 6.32 (s, 4H, ArH), 6.61 (s, 4H, ArH); MS (LSIMS (+), NBA, 70 eV) m/z: 825 ($M^+$-H); HR-MS: found 824.5305, calcd. 824.52272.

**1d = 1d (*rccc*)**

**1e**: mp 211-212°C; $^1$H NMR δ: 0.84 (t, J = 6.3 Hz, 12H, Me), 1.29 (m, 24H, $CH_2$), 1.81 (m, 8H, $CH_2$), 3.60 (s, 24H, OMe), 4.45 (t, J = 7.5 Hz, 4H, CH), 6.31 (s, 4H, ArH), 6.62 (s, 4H, ArH); $^{13}$C NMR δ: 14.15, 22.64, 27.85, 32.15, 34.68, 35.34, 56.15, 97.11, 126.07, 126.30, 155.80; MS (EI, 70 eV) m/z: 880 ($M^+$-H).

**X-ray crystallographic data:** Single crystals of **1d (rcct)** were obtained from chloroform/methanol, $C_{52}H_{72}O_8 \cdot CHCl_3$, $M_r$ = 944.46, triclinic, space group P.-1 No. 2, a = 12.322(1), b = 12.742(1), and c = 20.633(2) Å, V = 2709.8(4) Å$^3$, Z = 2, $D_x$ = 1.157, λ (Cu Kα) = 1.54178 Å, F(000) = 1012 e, T = 223 K. Data collection with Enraf-Nonius CAD4 diffractometer. The structure was solved by direct methods and refined on $F^2$ using SHELXL-93 [10]. Refinement led to R = 0.062, wR = 0.176 and S = 1.028.

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## REFERENCES

[1] a) Timmerman P., Verboom W., Reinhoudt D.N., *Tetrahedron*, **1996**, 52, 2663; b) Böhmer V. *Angew. Chem. Int. Ed. Engl.*, **1995**, 34, 713.

[2] a) Iwanek W., Mattay J. *Liebigs Ann.*, **1995**, 1463; b) Arnecke R., Böhmer V., Friebe S., Gebauer S., Krauss G.J., Thondorf I., Vogt W. *Tetrahedron Lett.*, **1995**, 36, 6221; c) Schneider U., Schneider H.J. *Chem. Ber.*, **1994**, 127, 2455; d) Iwanek W., Wolff C., Mattay J. *Tetrahedron Lett.*, **1995**, 36, 8969; e) Matsushita Y., Matsui T. *Tetrahedron Lett.*, **1993**, 34, 7433; f) Yanagihara R., Tominaga A.M., Aoyama Y.J. *J. Org. Chem.*, **1994**, 59, 6865; g) Fransen J., Dutton P.J. *Can. J. Chem.*, **1995**, 73, 2217; h) Inouye M., Hashimoto K., Isagawa K. *J. Am. Chem. Soc.*, **1994**, 116, 5517; i) Hayatt J. *J. Org. Chem.*, **1978**, 43, 1808; j) Xu W., Rourke J.P., Vittal J.J., Puddephatt R.J. *Inorg. Chem.*, **1995**, 34, 323; k) Kalchenko W., Rudkevich D., Schivanyuk A., Cymbal I., Pirozhenko V.V., Markovsky L. *Zh. Obschch. Khim.*, **1994**, 64, 731; l) Pellet-Rostaing S., Regnof de Vains J.-B., Lamartine R. *Tetrahedron Lett.*, **1995**, 36, 5745; m) Lukin O.V., Pirozhenko V.V., Schivanyuk A.N. *Tetrahedron Lett.*, **1995**, 36, 7725.

[3] a) Tanaka Y., Aoyama Y., *Bull. Chem. Soc. Jpn*, **1990**, 63, 3343; b) Kikuchi Y., Kato Y., Tanaka Y., Toi H., Aoyama Y., *J. Am. Chem. Soc.*, **1991**, 113, 1349; c) Tanaka Y., Ubukata Y., Aoyama Y., *Chem. Lett.*, **1989**, 1905; d) Kobayashi K., Asakawa Y., Kikuchi Y., Toi H., Aoyama Y., *J. Am. Chem. Soc.*, **1993**, 115, 2648; e) Kobayashi K., Tominaga M., Asakawa Y., Aoyama Y., *Tetrahedron Lett.*, **1993**, 34, 5121; f) Kikuchi Y., Kobayashi K., Aoyama Y., *J. Am. Chem. Soc.*, **1992**, 114, 1351; g) Schneider H.J., Güttes D., Schneider U., *Angew. Chem.*, **1986**, 98, 635; h) Schneider H.J., Güttes D., Schneider U., *J. Am. Chem. Soc.*, **1988**, 110, 6449; i) Kipmann T., Wilde H., Pink M., Schäter A., Hesse M., Mann G., *Angew. Chem.*, **1993**, 105, 1258; j) Schneider U., Schneider H.J., *Chem. Ber.*, **1994**, 2455.

[4] a) Högberg A.G.S., *J. Am. Chem. Soc.*, **1980**, 102, 6046; b) 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; c) Weinelt F., Schneider H.J., *J. Org. Chem.*, **1991**, 56, 5527; d) Mann G., Weinelt F., Hauptmann S., *J. Phys. Org. Chem.*, **1989**, 2, 531; e) Pieroni O.I., Rodriguez N.M., Vuano B.M., Cabaleiro M.C., *J. Chem. Research (S)*, **1994**, 188; f) Botta B., Iacomacci P., Di Giovanni C., Delle Monache G., Gacs-Baitz E., Botta M., Tafi A., Corelli F., Misiti D., *J. Org. Chem.*, **1992**, 57, 3259; g) Botta B., Di Giovanni M.C., Delle Monache G., De Rosa M.C., Gacs-Baitz E., Botta M., Corelli F., Tafi A., Santini A., Benedetti E., Pedrone C., Misiti D., *J. Org. Chem.*, **1994**, 59, 1532; h) Botta B., Delle Monache G., De Rosa M., Carbonetti A., Gacs-Baitz E.M., Botta B., Corelli F., Misiti D., *J. Org. Chem.*, **1995**, 60, 3657.

[5] Abis L., Dalcanale E., Du vosel A., Spera S., *J. Org. Chem.*, **1988**, 53, 5475.

[6] a) Wu T.T., Spesa J.R., *J. Org. Chem.*, **1987**, 52, 2330; b) Dahan E., Biali E., *J. Org. Chem.*, **1989**, 54, 6003; c) Jaume C., de Mendoza J., Prados P., Nieto P.M., Sanchez C., *J. Org. Chem.*, **1991**, 56, 3372; d) Sartori G., Bigi F., Porta C., Maggi R., Mora R., *Tetrahedron Lett.*, **1995**, 36, 2311; e) Sartori G., Porta C., Bigi F., Maggi R., Peri F., Marzi E., Lanfranchi M., Pellinghelli M.A., *Tetrahedron*, **1997**, 53, 3287.

[7] a) Gutsche C.D., *Calixarenes*, The Royal Society of Chemistry, Cambrige, UK, 1989; b) *Calixarenes, a Versatile Class of Macrocyclic Compounds*, Eds. Vicens J. and Böhmer V., Kluwer, Dordrecht, The Nederlands, 1991; c) Roundhill D.M., ***Progress*** *in Inorganic Chemistry*, **1995**, 43, 533.

[8] Mann G., Hennig L., Weinelt F., Müller K., Meusinger R., Zahn G., Lipmann T., *Supramol. Chem.*, **1994**,3, 101.

[9] Fröhlich R., personal communication, to be published.

[10] Sheldrick G. M., University of Göttingen, Germany.