Högberg Compounds with a Functionalized Box-Like Cavity[#]

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Abstract. Preparations of the Högberg compounds (**Ia-e**) with functionalized box-like cavities, designed for complexation of soft cations like silver and copper(II), are described. The structure of **Ia** was determined by X-ray analysis.

1. Introduction

After the first reports on the cyclic tetramers, obtained from the condensation of resorcinol and aldehydes were published [1, 2], a number of possible applications for these interesting 'Högberg compounds' has been recognized. Although several geometrical isomers can in principle be formed in this condensation, only two (Figure 1) have been isolated, generally in high yields. The all-*cis* (ccc) isomer of the macrocycle has a bowl-shaped cavity (Figure 1, face view) with eight oxygen atoms, that can be used for the complexation of neutral molecules like sugars and of quaternary ammonium ions [3, 4]. Cram *et al.* have synthesized the so-called cavitands by means of a four-fold ring closure with $BrCH_2Cl$, together with the carcerands, by coupling of two modified cavitands. These compounds are also capable of complexing neutral molecules [5, 6].

In most cases aliphatic aldehydes were preferred over arylaldehydes, probably because of the better solubility properties of the products formed. Although several arylaldehydes have been used in the condensation reaction [7], the only application of a modified arylaldehyde was reported by Beer *et al.* [8] who described the condensation of resorcinol with 4-formylbenzo-15-crown-5. These derivatives are able to bind bipyridinium ions in the crown ether moiety of the molecule.

However, the four aryl groups, which form a concave box-like cavity, in principle offer another possibility to complex cations, as we concluded from CPK model

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[#] This paper is dedicated to the memory of the late Dr C. J. Pedersen.
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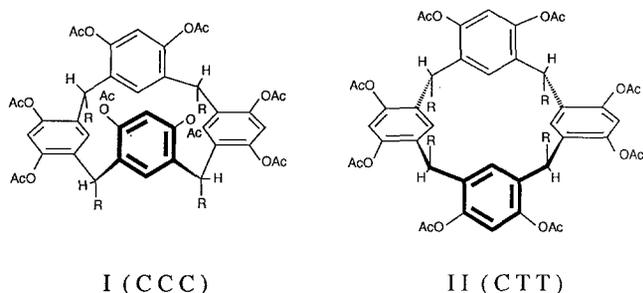
I (CCC)   II (CTT)

R =
a   2 - thienyl
b   3 - (methylthio)phenyl
c   3 - methoxyphenyl
d   4 - (benzyloxy)phenyl
e   4 - hydroxyphenyl
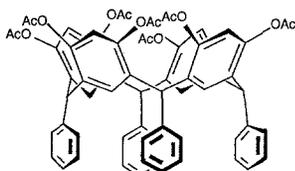
I (face view)

Fig. 1. Structures of the Högberg compounds.

studies. Suitable substituted (benz)aldehydes could, after condensation, yield Högberg compounds with a second set of donor atoms arranged in a more or less square planar fashion. Introduction of sulfur atoms as donor sites might offer a cavity which is able to complex the softer b and ab type cations, such as silver and copper(II). Furthermore, by choosing different substituted aldehydes, and modification of functional groups present in the aldehyde, the size of the box-like cavity can be varied in a simple way.

In this paper we report the synthesis of a number of such 'Högberg compounds' with differently functionalized box-like cavities.

2. Experimental

A small sample of **Ia** was recrystallized from $CHCl_3$ and its crystal structure was determined by X-ray diffraction. Crystal data: $C_{60}H_{48}O_{16}S_4 \cdot 3CHCl_3$, monoclinic, space group $C2/c$; $a = 23.242(2)$Å, $b = 15.864(4)$ Å, $c = 20.435(8)$ Å, $b = 110.86(1)°$; $V = 7041(6)$ Å^3; $T = 193(5)$K; $Z = 4$; $d = 1.43$ g cm^{-3}, $\mu = 5.35$ cm^{-1}. Reflections were measured in the $\omega/2\theta$ scan mode, using graphite monochromated Mo$K\alpha$ radiation [scan width (ω) $1.50 + 0.34 \tan \theta$]. The structure was solved by

direct methods (MULTAN [9]) and refined with full-matrix least-squares methods. A total of 2591 reflections with $F_0^2 > 3\sigma(F_0^2)$ was used in the refinement. The molecule has a crystallographic two-fold axis. The C-atom of one of the chloroform molecules is on a two-fold axis implying disorder in the positions of the chlorine atoms. The five-membered rings occupy two positions related by a 180° rotation around the C—C bond, which connects them to the macrocycle. Hydrogen atoms were included in the refinement, except for the hydrogens of the disordered S/C atoms and the disordered chloroform molecule. The number of parameters refined was 522 (scale factor, positional parameters and thermal parameters (anisotropic for the non-hydrogen atoms, isotropic for H-atoms)). The final R factors were $R = 5.8\%$, $R_w = 7.0\%$. All calculations were performed with SDP [10].

All reactions were carried out under an argon atmosphere. FAB mass spectra were recorded using 3-nitrobenzyl alcohol as matrix. Silica gel (230–400 mesh ASTM) was obtained from Merck. Resorcinol was purchased from Merck–Schuchardt, and 2-thiophenecarboxaldehyde, 3-anisaldehyde and 4-(benzyloxy)benzaldehyde were obtained from Janssen Chimica. 3-(Methylthio)benzaldehyde was synthesized starting from 3-bromobenzaldehyde (Janssen Chimica), which was converted into its ethylene acetal. Lithiation and quenching with dimethyl disulfide, followed by deprotection with 2N HCl and distillation under reduced pressure, afforded the pure product. The method is similar to the one described by Euerby [11], who used the Grignard route to obtain the same compound. All newly synthesized compounds showed satisfactory elemental analyses.

2,8,14,20-*Tetra-2-thienyl-pentacyclo*[19.3.1.1$^{3, 7}$.1$^{9, 13}$.1$^{15, 19}$]*octacosa*-1(25),3,5,7(28), 9,11,13(27),15,17,19(26),21,23-*dodecaene*-4,6,10,12,16,18,22,24-*octol octaacetate* (*Stereoisomers*, **Ia** *and* **IIa**).

To a solution of resorcinol (11.01 g, 0.10 mol) in a mixture of ethyl alcohol (100 mL) and concentrated HCl (25 mL) was added 2-thiophenecarboxaldehyde (11.22 g, 0.10 mol) at room temperature over a period of 15 min. The color changed from orange to purple and after a few minutes a purple precipitate was formed. After stirring at room temperature for 3 h, water (200 mL) was added and the resulting suspension was centrifuged. The liquid was decanted and the residue was washed with water (100 mL) and centrifuged again. The residue was mixed with diethyl ether (100 mL), stirred and filtered. The crude product was dried *in vacuo*, and dissolved in acetic anhydride (75 mL). Pyridine (5 mL) was added and the mixture was stirred at 100°C (oil bath temperature) for 1 h. After cooling to room temperature the solvent was removed under reduced pressure. The residue was stirred with methanol (75 mL) and filtered to remove the last traces of acetic anhydride. Column chromatography (SiO$_2$, CH$_2$Cl$_2$:EtOAc 9:1) afforded the pure isomers **Ia** and **IIa** in yields of 12 and 22%, respectively.

    Ia. mp > 300°C(CH$_2$Cl$_2$–MeOH). Mass spectrum (EI): (M$^+$) 1152 (*calc.* 1152). ^{1}H NMR: δ 7.11 and 6.96 (*s*, 4H, H$_c$), 7.1–7.0 (*m*, 4H, S—CH), 6.8–6.7 (*m*, 4H, S—CH=C*H*), 6.37 (*d*, 4H, S—C=CH), 6.31 and 6.17 (*s*, 4H, H$_b$), 5.68 (*s*, 4H, H$_a$), 2.12 and 2.02 (*s*, 24H, C[O]CH$_3$). ^{13}C NMR: δ 168.2 and 167.9 (*s*, C=O), 147.0, 146.9, 143.5, 132.6, 130.1 (*s*, aryl-C and thiophene-C), 130.7, 127.1, 127.0, 126.5, 126.4, 124.5, 117.4, 116.3 (*d*, aryl-CH, thiophene-CH and CH$_a$), 20.6 (*q*, C[O]CH$_3$).

IIa. mp > 300°C (CH$_2$Cl$_2$–MeOH). Mass spectrum (EI): (M$^+$) 1152 (*calc.* 1152). ^{1}H NMR: δ 7.14 and 6.98 (*s*, 4H, H$_c$), 7.00 (*dd*, 4H, J = 5.2 and 1.2 Hz, S—CH), 6.71 (*dd*, 4H, J = 3.5 and 5.2 Hz, S—CH=CH), 6.31 (*d*, 4H, J = 2.7 Hz, S—C=CH), 6.27 (*s*, 4H, H$_b$), 5.73 (*s*, 4H, H$_a$), 2.12 and 2.03 (*s*, 24H, CH$_3$). ^{13}C NMR: δ 168.3 and 168.1 (*s*, C=O), 146.9, 146.7, 142.2, 131.1, 130.9 (*s*, aryl-C and thiophene-C), 132.4, 128.0, 127.2, 126.8, 124.3, 117.2, 116.6 (*d*, aryl-CH, thiophene-CH, and CH$_a$), 20.6 (*q*, C[O]CH$_3$).

Synthesis of the Högberg compounds with 3-(methylthio)phenyl substituents (**Ib** *and* **IIb**)

To a solution of resorcinol (4.07 g, 0.037 mol) in a mixture of ethanol (30 mL), water (30 mL) and concentrated HCl (15 mL) was added 3-(methylthio)benzaldehyde (5.62 g, 0.037 mol) at room temperature over a period of 15 min. The reaction mixture was refluxed for 20 h. After cooling down to room temperature, the precipitate was collected by centrifugation and decanting of the liquid. The solid was washed with water and centrifuged again. The almost dry solid was mixed with diethyl ether (100 mL) and stirred. Filtration and successive drying *in vacuo* afforded the crude octol mixture which was acylated as described in the synthesis of **Ia/IIa**. After purification by column chromatography (SiO$_2$, CH$_2$Cl$_2$:EtOAc 4:1) **Ib** and **IIb** were isolated in yields of 26 and 51%, respectively.

Ib. mp 277–280°C (CH$_2$Cl$_2$–MeOH). Mass spectrum (FAB): m/z ([M + 2H]$^+$) 1314 (*Calc.* 1314). ^{1}H NMR: δ 7.15 and 6.87 (*s*, 4H, H$_c$), 7.05–6.9 (*m*, 8H, aryl-H), 6.7–6.3 (*m*, 8H, aryl-H), 6.06 and 5.80 (*s*, 4H, H$_b$), 5.36 (*s*, 4H, H$_a$), 2.32 (*s*, 12H, SCH$_3$), 2.06 and 1.99 (*s*, 24H, C[O]CH$_3$). ^{13}C NMR: δ 168.1 (*s*, C=O), 44.9 (*d*, CH$_a$), 20.7 (*q*, C[O]CH$_3$), 15.7 (*q*, SCH$_3$).

IIb. mp 289–292°C (dec) (CH$_2$Cl$_2$–MeOH). Mass spectrum (FAB): m/z ([M + 2H]$^+$) 1314 (*Calc.* 1314). ^{1}H NMR: δ 7.08 and 6.93 (*s*, 4H, H$_c$), 7.05–6.9 (*m*, 8H, aryl-H), 6.7–6.3 (*m*, 8H, aryl-H), 6.18 and 5.78 (*s*, 4H, H$_b$), 5.43 (*s*, 4H, H$_a$), 2.33 (*s*, 12H, SCH$_3$), 2.06 (*s*, 24H, C[O]CH$_3$). ^{13}C NMR: δ 168.5 and 168.1 (*s*, C=O), 44.6 (*d*, CH$_a$), 20.6 (*q*, C[O]CH$_3$), 15.7 (*q*, SCH$_3$).

Synthesis of the Högberg compounds with 3-methoxyphenyl substituents (**Ic** *and* **IIc**)

Starting from resorcinol (5.51 g, 0.05 mol) and 3-anisaldehyde (6.81 g, 0.05 mol) compounds **Ic** and **IIc** were prepared analogously to the synthesis of **Ib** and **IIb**. The crude mixture was purified by chromatography (SiO$_2$, CH$_2$Cl$_2$:EtOAc 9:1) to give **Ic** (25%) and **IIc** (49%).

Ic. mp > 300°C (dec) (CH$_2$Cl$_2$–MeOH). Mass spectrum (FAB): m/z ([M + 2H]$^+$) 1250 (*Calc.* 1250). ^{1}H NMR: δ 7.13 and 6.87 (*s*, 4H, H$_c$), 7.0–6.9 (*m*, 4H, aryl-H), 6.58 (*dd*, 4H, J = 8.1 and 2.2 Hz, aryl-H), 6.4–6.05 (*m*, 8H, aryl-H), 6.08 and 5.85 (*s*, 4H, H$_b$), 5.37 (*s*, 4H, H$_a$), 3.62 (*s*, 12H, OCH$_3$), 2.05 and 2.00 (*s*, 24H, C[O]CH$_3$). ^{13}C NMR: δ 168.2 (*s*, C=O), 55.7 (*q*, OCH$_3$), 44.9 (*d*, CH$_a$), 20.7 and 20.5 (*q*, C[O]CH$_3$).

IIc. mp 286–289°C (dec) (CH$_2$Cl$_2$–MeOH). Mass spectrum (FAB): m/z ([M + 2H]$^+$) 1250 (*Calc.* 1250). ^{1}H NMR: δ 7.0–6.9 (*m*, 8H, H$_c$ and aryl-H), 6.65–6.55 (*m*, 4H, aryl-H), 6.35–6.15 (*m*, 4H, aryl-H), 6.22 and 5.87 (*s*, 4H, H$_b$),

5.44 (s, 4H, H$_a$), 3.62 (s, 12H, OCH$_3$), 2.05 (s, 24H, C[O]CH$_3$). ^{13}C NMR: δ 168.5 and 168.1 (s, C=O), 54.8 (q, OCH$_3$), 44.6 (d, CH$_a$), 20.6 (q, C[O]CH$_3$).

Synthesis of the Högberg compounds with 4-(benzyloxy)phenyl substituents (**Id** *and* **IId**)

Starting from resorcinol (5.51 g, 0.05 mol) and 4-(benzyloxy)benzaldehyde (10.62 g, 0.05 mol) compounds **Id** and **IId** were prepared analogously to the preparation of **Ib** and **IIb**. Chromatography (SiO$_2$, CH$_2$Cl$_2$:EtOAc 4:1) afforded **Id** (26%) and **IId** (50%).

   Id. mp 232–235°C (dec) (CH$_2$Cl$_2$–MeOH). Mass spectrum (EI): (M$^+$) 1552 (*Calc.* 1552). ^{1}H NMR: δ 7.4–7.2 (*m*, 20H, aryl-H), 7.10 and 6.85 (s, 4H, H$_c$), 6.8–6.6 (*m*, 8H, aryl-H), 6.11 and 6.04 (s, 4H, H$_b$), 5.34 (s, 4H, H$_a$), 4.97 (s, 8H, OCH$_2$Ar), 2.05 and 2.00 (s, 24H, C[O]CH$_3$). ^{13}C NMR: δ 168.2 (s, C=O), 70.0 (t, OCH$_2$Ar), 44.2 (d, CH$_a$), 20.6 and 20.5 (q, C[O]CH$_3$).

   IId. mp > 300°C (CH$_2$Cl$_2$–MeOH). Mass spectrum (EI): (M$^+$) 1552 (*Calc.* 1552). ^{1}H NMR: δ 7.35–7.2 (*m*, 20H, aryl-H), 7.14 and 6.90 (s, 4H, H$_c$), 6.8–6.6 (*m*, 8H, aryl-H), 6.29 and 6.14 (s, 4H, H$_b$), 5.45 (s, 4H, H$_a$), 4.94 (s, 8H, OCH$_2$Ar), 2.06 and 2.01 (s, 24H, C[O]CH$_3$). ^{13}C NMR: δ 168.5 and 168.2 (s, C=O), 69.9 (t, OCH$_2$Ar), 43.9 (d, CH$_a$), 20.6 and 20.5 (q, C[O]CH$_3$).

Synthesis of the Högberg compound with 4-hydroxyphenyl substituents (**Ie**)

To a solution of **Id** (0.90 g, 0.58 mmol) in a mixture of benzene (25 mL, thiophene-free) and methanol (10 mL) was added 10% Pd on C (20 mg) and the mixture was stirred for 18 h at room temperature under a hydrogen atmosphere. Filtration and subsequent evaporation of the solvent afforded a nearly quantitative yield of **Ie**. mp 271–74°C (CH$_2$Cl$_2$). Mass spectrum (EI): (M$^+$) 1192 (*Calc.* 1192). ^{1}H NMR (DMSO-d_6): δ 6.86 and 6.70 (s, 4H, H$_c$), 6.56 (d, 8H, J = 8.8 Hz, aryl-H), 6.47 (d, 8H, J = 8.8 Hz, aryl-H), 6.15 and 6.03 (s, 4H, H$_b$), 5.17 (s, 4H, H$_a$), 1.94 (s, 24H, C[O]CH$_3$). ^{13}C NMR: δ 168.0 (s, C=O), 44.1 (d, CH$_a$), 20.5 (q, C[O]CH$_3$).

3. Results and Discussion

Thiophene sulfur atoms are not commonly used as donor sites in macrocyclic chemistry. However, Lucas *et al.* [12] showed that the thiophene sulfur atom can be used as a binding site for copper(II) ions. CPK model studies indicated that the ccc isomer of a Högberg compound with four 2-thienyl substituents (**Ia**) could form an almost square plane of sulfur atoms (diametrical S—S distance 5.5–6.0 Å) for complexation of cations like silver and copper(II). Condensation of 2-thiophenecar-boxaldehyde and resorcinol yielded a mixture of ccc and ctt isomers (**Ia** and **IIa**) which were isolated as the corresponding octaacetates in a total yield of 34%. The ratio between ccc and ctt was approximately 1:2, as followed from the integrals of the H$_a$ absorptions (5.68 and 5.73 ppm, respectively) in the ^{1}H NMR spectrum (Figure 2). After separation of the isomers by chromatography, the structure of the ccc isomer was unambiguously established by X-ray diffraction (Figure 3). The X-ray diffraction experiment showed that in the solid state the thiophene rings
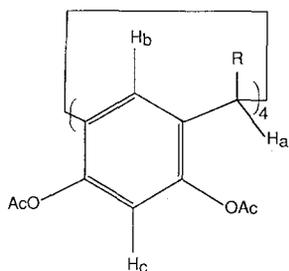
Fig. 2. Schematic drawing of a Högberg compound.
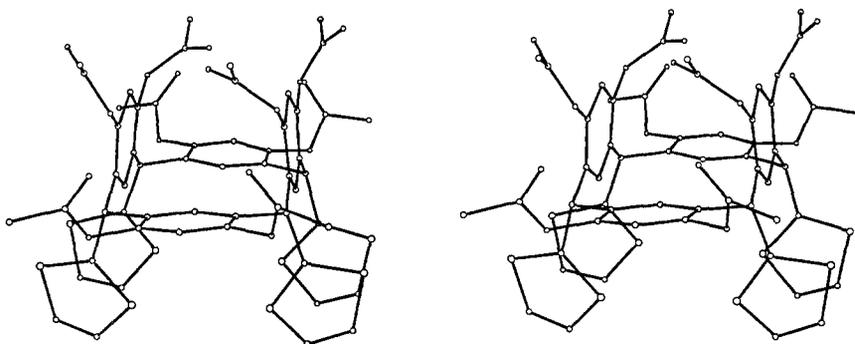
Fig. 3. Stereo view of **1a**.

occupy two positions related by a rotation of 180° around the 'exocyclic' bond. The occupancy of both positions is not the same. For one of the two crystallographically independent sulfur atoms the probability of being inside the cavity is approximately 50%, for the other this number is 30%. The distances between the partially occupied adjacent S-positions within the cavity are 3.949(7) and 4.963(5) Å.

From CPK models we concluded that the ccc isomer **Ib** of a Högberg compound derived from 3-(methylthio)benzaldehyde would have a plane of sulfur atoms with a diametrical S—S distance of about 4.0–4.5 Å. The condensation of 3-(methylthio)benzaldehyde and resorcinol gave (after acylation and purification by chromatography) **Ib** and **IIb** in a yield of 77% with a ccc:ctt ratio of 1:2. The structures of the isomers were proven by dynamic NMR spectroscopy. Previously, Högberg has shown that at elevated temperatures, in general a ccc isomer **I** can equilibrate with the two C_{2v} structures, which results on the NMR time scale in the formation of a C_{4v} isomer [1]. This C_{4v} isomer shows one singlet for the H_b protons (Figure 2), whereas the C_{2v} isomer exhibits two singlets of equal intensity for these protons. The ctt isomer **II** cannot equilibrate because it is much more rigid. Therefore compounds **II** exhibit, even at elevated temperatures, two singlets of equal intensity for H_b. Compound **Ib** shows two singlets (6.05 and 5.90 ppm) for H_b at room temperature in DMSO-d_6; at approximately 100°C these change into one broad singlet. The ctt isomer **IIb** exhibits two singlets at room temperature for H_b (6.20 and 5.85 ppm) which showed no coalescence upon heating to 105°C.

The corresponding oxygen derivative, synthesized from 3-methoxybenzaldehyde, also gave a 1:2 mixture of ccc and ctt isomers **Ic** and **IIc**, respectively, isolated as their acetates in a total yield of 74%. Characterization of the isomers was performed in the same way as for the 3-methylthio derivatives (**Ib** and **IIb**). Compound **Ic** at room temperature in DMSO-d_6 exhibits two singlets for H_b (6.06 and 5.95 ppm) that change into one broad singlet at 100°C. Compound **IIc** even at 100°C in DMSO-d_6, shows two singlets of equal intensity for H_b at 6.23 and 5.95 ppm. Condensation of 3-bromobenzaldehyde or 3-(benzyloxy)benzaldehyde with resorcinol, which would give macrocycles with cavities which could more easily be modified by standard methods, in our hands gave only polymeric material, from which no Högberg compound could be isolated. This may be caused by the fact that the bromo- and the benzyloxy-substituents are too large, thus favoring linear polymerization.

Condensation of 4-(benzyloxy)benzaldehyde and resorcinol followed by acylation with acetic anhydride yielded 76% of a 1:2 mixture of the ccc and ctt acetates **Id** and **IId**, respectively. After isolation of the ccc isomer **Id** via column chromatography, this compound was debenzylated with hydrogen on Pd/C (10%) in a nearly quantitative yield. The product still had the ccc configuration as followed from the ^{1}H NMR spectrum which, at room temperature in DMSO-d_6, exhibits two singlets for H_b at 6.15 and 6.03 ppm, which show coalescense upon heating up to 100°C. Compound **Ie** can be further modified by choosing the appropriate alkylating or acylating agents to give macrocycles with different cavities.

In the present paper we have discussed that Högberg compounds with a functionalized box-like cavity are easily accessible. In the near future, we will investigate the further modification of this cavity and its complexation properties.

Acknowledgement

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