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# 1,2,4,5-*Bis*-(1,4,7,10,13,16-Hexaoxahexadecamethylene)Benzene: Benzo-*Bis*-(18-Crown-6)

Jacobus J.H. Schlotter,[a] Ingrid J.A. Mertens,[a] Andre M.A. van Wageningen,[a] Frederik P.J. Mulders,[a] Jan W. Zwikker,[a] Hans-Jürgen Buschmann[b] and Leonardus W. Jenneskens[a]*

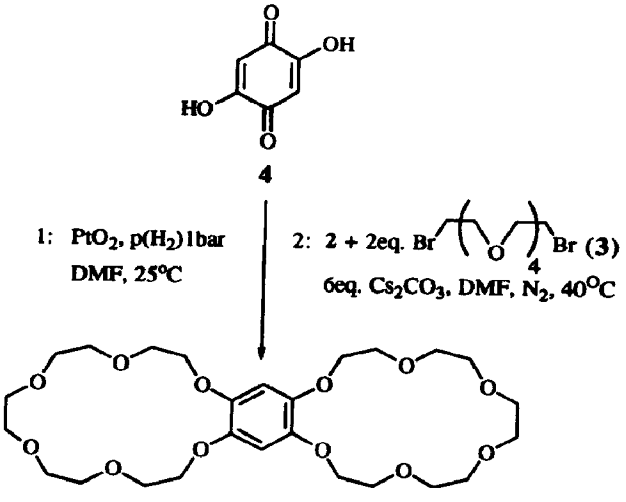
[a]Debye Institute, Department of Physical Organic Chemistry, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands.
[b]Deutsches Textilforschungszentrum Nord-West e.V., Frankenring 2, D-47798 Krefeld Germany.

***Abstract*:** 1,2,4,5-*Bis*-(1,4,7,10,13,16-hexaoxahexadecamethylene)benzene (**1**) is prepared in an one-pot synthesis from 2,5-dihydroxy-1,4-benzoquinone (**4**) and 1,14-dibromo-3,6,9,12-tetraoxatetradecane (**3**) in 35% yield. A study of its host-guest *1:1* and *1:2* alkali metal cation complexation reveals that the cations only interact with the *aliphatic* oxygen lone pairs, hence, leaving the $\pi$-electron system intact.

Since the first report on crown ethers,[1] numerous derivatives have been prepared and found application in host-guest chemistry and the construction of supramolecular ensembles.[2] However, only recently the synthesis of *bis*-(crown ether) derivatives, *i.e. bis-ortho-* and *bis-meta*-xylyl (crown ethers), has been reported in which the macrocycles are connected to the benzene core *via* Ar-$CH_2$-O linkages.[3] Hitherto, no *bis*-crown ethers are known with *two* crown ether rings directly coupled to *one* benzene core *via* Ar-O- linkages. Nevertheless, the latter are of interest to assess host-guest *1:1* and *1:2* complex formation selectivity concomitant with the presence of a second crown ether ligand site which modifies the electronic properties of both the benzene core and the available alkali metal cation binding sites.[2] Note that substitution of the benzene ring of benzo-(15-crown-5) markedly affects its alkali metal cation complexation properties, while this is not the case for the related benzo-(18-crown-6) analogues.[4]

Here we report the synthesis of the first macrocycle containing *two* crown ether rings directly coupled to *one* benzene core, *i.e.* 1,2,4,5-*bis*-(1,4,7,10,13,16-hexaoxahexadecamethylene)benzene (benzo-*bis*-(18-crown-6) (**1**)). Its alkali metal cation complexation behaviour (host-guest ratios *1:1* and *1:2*) is compared with that of benzo-(18-crown-6) (**5**). Compound **1** was prepared in an one-pot synthesis by etherification of 1,2,4,5-tetrahydroxybenzene (**2**) generated quantitatively by *in situ* hydrogenation of 2,5-dihydroxy-1,4-benzoquinone (**4**; $PtO_2$, $p(H_2)$ 1 bar, DMF 25 $^{o}C$)[5] with 2 eq. of 1,14-dibromo-3,6,9,12-tetraoxatetradecane (**3**; 6 eq. $Cs_2CO_3$, DMF 40 $^{o}C$)[6] in 35% yield after recrystallization (Scheme).[7,8] Although both the *ortho-* (**1**), its *meta-* and *para*-isomer can be formed, a comparison of the $^1H$- and $^{13}C$ NMR spectra of **1** and **5** unambiguously shows that, apparently due to the $Cs^+$ template effect,[6] the *ortho*-isomer **1** is the only product.[9] In line with related methoxy-benzenes, the second crown ether ring in **1** induces a shift of $E^{ox\cdot}$ ($E_{pa}$, peak anodic potential; **1**/**1**$^{+\cdot}$, 0.71 V and **5**/**5**$^{+\cdot}$, 1.33 V) indicating enhanced electron donation to the $\pi$-electron

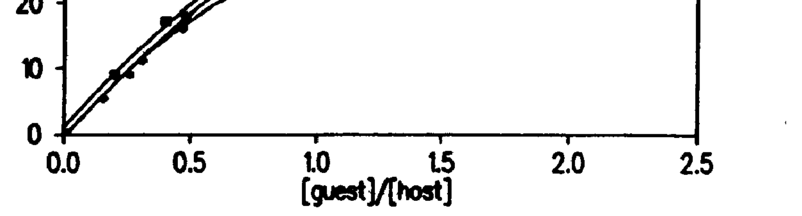
**Scheme**



system.[10] Hence, 1 will be a good probe molecule to study electron density modification of the crown ether oxygen binding sites due to the aryl bound oxygens of the additional crown ether ring.[4]

Qualitative insight in the metal cation complexation properties of 1 was derived from $^1H$ NMR titrations (DMSO-$d_6$, 25 °C) using KSCN and Kpicrate, respectively (Figure). The similar $\Delta\delta$ (Hz) values found for corresponding protons of 1 and 5 suggest that they possess an identical complexation behaviour for molar host-guest ratios up to *1:1*. Thus, the additional macrocycle does not appear to exert an influence on *1:1* complex formation.[11] The increase of $\Delta\delta$ (Hz) for 1 in going to host-guest ratios *1:2* provides evidence that *1:2* complex formation actually takes place. However, no inflection point is found in the curves at a ratio *1:1*. This

**Figure.** $\Delta\delta$ (Hz) values of the aromatic protons of 1 and 5, respectively, *vs*. molar guest/host ratios.[12]



can be rationalized by invoking a fast exchange of $K^+$ ions between ligand sites on the $^1H$ NMR timescale at 25 °C leading to a time-averaged NMR spectrum.[12] Analogous curves were also obtained using cyclic voltammetry and $KClO_4$ as titrant; only an averaged $E^{ox.}$ ($E_{pa}$(1/$1^{+\bullet}$)) was found up to host-guest *1:2* ratios. The moderate change of $E^{ox.}$ ($E_{pa}$) in going from **1**(0.71 V), **1**(*1:1*, 0.83 V) to **1**(*1:2*; 0.94 V), which differ from the $E_{pa}$ values of **5** (1.33 V), provides evidence that only the ***aliphatic*** oxygen lone pairs participate in alkali metal cation complexation.[10,11]

Quantitative insight in the alkali metal cation complexation properties of **1** with respect to **5** was derived from UV/Vis extraction experiments ($CHCl_3/H_2O$, 25 °C),[13] and by determination of enthalpies of complexation (ΔH: calorimetric titrations; anhydrous $CH_3OH$, 25 °C).[14] Although in the UV/Vis extraction experiments molar host-guest ratios of *1:1* and *1:2*, respectively, were used, the ΔG values represent a weighed average for *1:1* and *1:2* complex formation since both complexes cannot be distinguished.[13] Note that for all cations ΔG(**1**;*1:1*) and ΔG(**5**) are close in value and that ΔG(**1**;*1:2*) nearly equals twice ΔG(**1**;*1:1*), which supports the ultimate formation of *1:2* complexes (***vide supra***). The observation that ΔG(**1**;*1:2*) in the series is moderately smaller than twice the related ΔG(**1**;*1:1*) indicates that the equilibrium constant $K_2$ for *1:2* complex formation is smaller than $K_1$(*1:1*). Apparently, this is a consequence of coulombic repulsion due to the metal cation already present in the *1:1* complex. This is corroborated by the calorimetric titrations. Enthalpies of complexation for *1:1* complexes (ΔH(**1**;*1:1*)) were derived from titration experiments in which an excess of **1** was present. Conversely for the determination of ΔH(**1**;*1:2*), an excess of alkali metal cation was used. In the series ΔH(**1**;*1:1*) and ΔH(**5**) are again close in value and ΔH(**1**;*1:2*) equals 1.7-1.9 times the corresponding ΔH(**1**;*1:1*). These results confirm *1:2* complex formation invoked from the $^1H$ NMR titration- and UV/Vis extraction data and support our conjecture that *1:2* complex formation is only slightly influenced by the presence of one complexed cation. UV/Vis Spectroscopy ($CH_2Cl_2$) of host-guest complexes **1**(*1:2*) with picrate salts reveals that they are present in solution as separated ion-pairs. ($\lambda_{max.}$(picrate ion) 375-377 nm).[15]

In summary, the alkali metal cation complexes **1**(*1:1*) and **1**(*1:2*) can be obtained and $K^+$ is preferably accommodated (Table).[2,10,13] The absence of a remote substituent effect due to the aryl bound oxygens of the additional ligand site, suggests that upon complexation the cations only interact with the ***aliphatic*** oxygen lone pairs of the crown ether rings of **1** leaving the π-electron system of the benzene core essentially intact.

**Table.** Alkali metal cation complexation of **1** and **5** (UV/Vis extraction method[13]; ΔG(**1**;***host:guest***) and ΔG(**5**) and calorimetric titrations[14]; ΔH(**1**;***host:guest***) and ΔH(**5**) ($kJmol^{-1}$)).

| | **UV/Vis** | | | **Calorimetry** | | |
|---|---|---|---|---|---|---|
| **Cation** | -ΔG(**1**;*1:1*) | -ΔG(**1**;*1:2*) | -ΔG(**5**)[16] | -ΔH(**1**;*1:1*) | -ΔH(**1**;*1:2*) | -ΔH(**5**)[17] |
| $Li^+$ | 30.5 | 60.2 | 26.8 | -- | -- | -- |
| $Na^+$ | 35.2 | 70.4 | 33.1 | 29.9 | 56.8 | 36.8 (34.6) |
| $K^+$ | 46.9 | 90.4 | 41.8 | 49.7 | 83.0 | 50.7 (44.9) |
| $Rb^+$ | 46.9 | 87.8 | 38.5 | 42.9 | 73.2 | 44.5 (43.0) |
| $Cs^+$ | 40.6 | 76.2 | 35.2 | 40.4 | 70.6 | 43.5 (42.3) |

**References and notes.**

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4. For benzo-(15-crown-5) a Hammett relationship was found, while for **5** this was not the case; Ungaro, R.; El Haj, B.; Smid, J. *J. Am. Chem. Soc.*, **1976**, *98*, 5198.

5. Cf. also Dewaele, S. *US Patent* 3.780.114, 1973 for a similar reduction in THF.

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7. Etherification with 1,14-ditosyl-3,6,9,12-tetraoxatetradecane leads to extensive detosylation; cf. also Merz, A.; Rauschel, M. *Synthesis*, **1993**, 797.

8. Benzo-*bis*-(18-crown-6) (**1**): $^1$H NMR (300 MHz, $CDCl_3$, 25 °C) δ 6.59 (s, 2H), 4.10 (AA' part of AA'XX' pattern, 8H, 4x Ar-O-$CH_2$-$CH_2$-O) and 3.88 (XX' part of AA'XX' pattern, 8H, 4x Ar-O-$CH_2$-$CH_2$-O), 3.76-3.67 (AA'BB' pattern, 16H, 4x -$CH_2$-O-$CH_2$-$CH_2$-O-$CH_2$-), 3.66 (bs, 8H, 2x -$CH_2$-O-$CH_2$-$CH_2$-O-$CH_2$-) ppm; $^{13}$C NMR (75.5 MHz, $CD_2Cl_2$, 25 °C) δ 143.8, 106.1, 70.7, 70.6, 70.5, 70.0 and 69.8 ppm; FAB-MS, 546 ($M^{+\cdot}$); UV/Vis ($CH_3CN$; $\lambda_{max.}$ nm (log ε)) 233 (3.96), 297 (3.67); IR (KBr pellet) 3050, 2900-2880, 1220, 1100 $cm^{-1}$; M.p. 76.5-78.0 °C (recrystallization from $CH_3OH$); Elemental analysis: calc. C 57.13, H 7.74, O 35.12, found C 56.98, H 7.85, O 35.17.

9. $^1$H- and $^{13}$C resonances of **1** were assigned using selective $^1$H-decoupling $^1$H NMR experiments, CH correlation spectra, $^1$H NMR spectrum simulation and by comparison with $^1$H- and $^{13}$C NMR data of **5**; cf. Live, D.; Chan, S.I. *J. Am. Chem. Soc.*, **1976**, *98*, 3769. Note that the *meta*-analogue of **5**, *i.e.* 1,3-benzo-19-crown-6, possesses a different $^1$H NMR spectrum; $^1$H NMR (100 MHz, $CDCl_3$) δ 7.20-7.00 (m, 1H), 6.72-6.40 (m, 3H), 4.40-4.10 (m, 4H, 2x Ar-O-$CH_2$-$CH_2$-O) 4.00-3.70 (m, 4H, 2x Ar-O-$CH_2$-$CH_2$-O), 3.68 (m, 12H, 3x -$CH_2$-O-$CH_2$-$CH_2$-O-$CH_2$-).[6] The same applies for the *para*-analogue, *i.e. p*-phenylene-20-crown-6; $^1$H NMR (100 MHz, $CDCl_3$) δ 6.9 (s, 4H), 4.2-3.2 (m, 20H), cf. Helgeson, R.C.; Tarnowski, T.L.; Timko, J.M.; Cram, D.J. *J. Am. Chem. Soc.*, **1977**, *99*, 6411.

10. Cyclic voltammetry ($CH_3CN$/0.1 M. $Bu_4N^+PF_6^-$; $E^{ox.}$ ($E_{pa}$; peak anodic potential) *vs* SCE; reference ferrocene/ferrocenium). For methoxy-benzene derivatives; Zweig, A.; Hodgson, W.G.; Jara, W.H. *J. Am. Chem. Soc.*, **1964**, *86*, 4124. Enhanced electron donation to the π-system in going from **5** to **1** is also evident from the shift of δ $^{13}C_{Ar.}$-O ($^{13}$C NMR (75.5 MHz, $CD_2Cl_2$, 25 °C); **5**, 149.1 and **1**, 143.8 ppm).[8,9,11]

11. This is also supported by δ $^{13}C_{Ar.}$-O ($^{13}$C NMR (75.5 MHz, DMSO-$d_6$, 25 °C)) values of **1** and **5** and their KSCN complexes (**1** 142.6, **1**(*1:1*) 141.9 and **1**(*1:2*) 141.1 ppm, and **5** 148.5 and **5**(*1:1*) 147.4 ppm). The observed difference between **1** and **5**, and between their related complexes is in line with predictions using $^{13}C_{Ar.}$-$OCH_3$ group increments, *i.e.* Δδ($^{13}C_{Ar.}$-O)=δ(**1**)-δ(**5**) is *ca.* -5 to -6 ppm; cf. Breitmaier, E.; Voelter, W. *$^{13}$C NMR Spectroscopy*, VCH Thieme Verlag, **1978**.[10]

12. Similar titration curves were obtained for the *aliphatic* crown ether ring protons of **1** and **5**, respectively.

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17. ΔH(**5**) between parentheses; Izatt, R.M.; Clark, G.A.; Lamb, J.D.; King, J.E.; Christensen, J.J. *Thermochimica Acta*, **1986**, *97*, 115.

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