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A cage compound derived from cyclotriveratrylene and diphenylglycoluril sub-units

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Abstract. To diphenylglycoluril (**2**), four aliphatic chains were attached, each with a vanillyl alcohol group at the end. In an acid-catalyzed reaction, three of the vanillyl alcohol groups cyclize to form a cyclotriveratrylene unit. The resulting compound (**3**) has a well-defined cavity and a free, functionalized arm. Cyclization of four vanillyl alcohol groups (**5**) does not occur, probably for steric reasons.

Introduction

Organic molecules containing an intramolecular cavity, as well as a nearby catalytic centre, are currently receiving a great deal of attention as synthetic equivalents of enzymes (so called synzymes)[1]. Recently, we showed that such synthetic systems can be constructed from concave building blocks containing ligating arms[2]. Coordination of the arms to a metal centre results in the formation of a metallocage (Fig. 1). In this approach, the metal has a dual function: *(i)* it holds the framework of the cage and *(ii)* it is a potentially reactive site.

In this paper we describe a different approach to the synthesis of molecules containing a cavity as well as a catalytic centre. The approach is outlined in Fig. 2. If one starts from two concave sub-units with different numbers of reactive groups or functionalities (X and Y in Fig. 2,A), a cage molecule can be assembled in which one or more of these groups are unused. In a later stage, these groups can be converted into catalytic functions (Fig. 2,A). Alternatively, one can use a concave building block with reactive groups (P) and perform a cyclocondensation or cyclopolymerisation reaction. If this reaction is a controlled process, reactive groups will remain which can there be transformed into catalytic functions (Fig. 2,B). We have used procedure B to synthesize a cage compound which involves the concave building blocks cyclotriveratrylene (**1**) and diphenylglycoluril (**2**)[3,4]. This molecule has one functional group that can be transformed into a catalytic function.

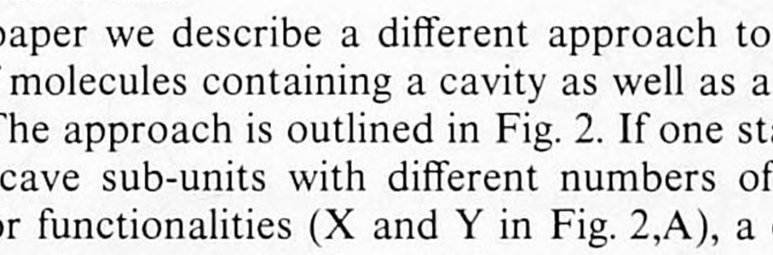


Fig. 1. Formation of a metallocage.

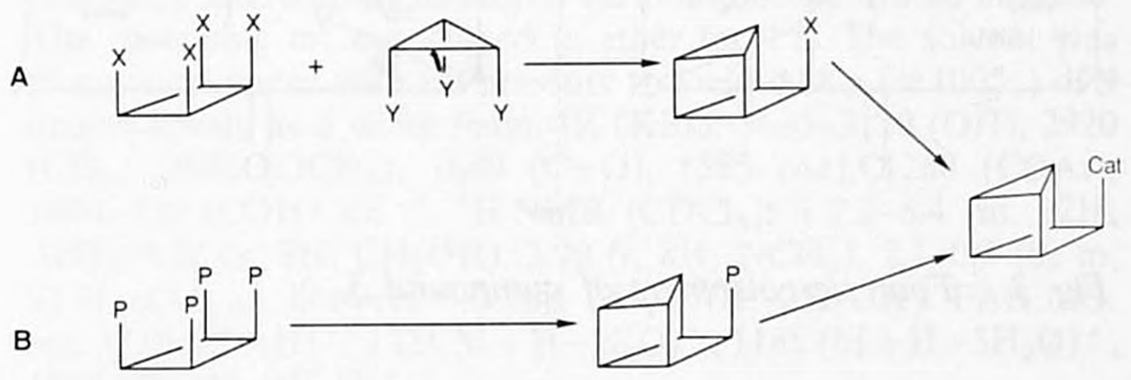


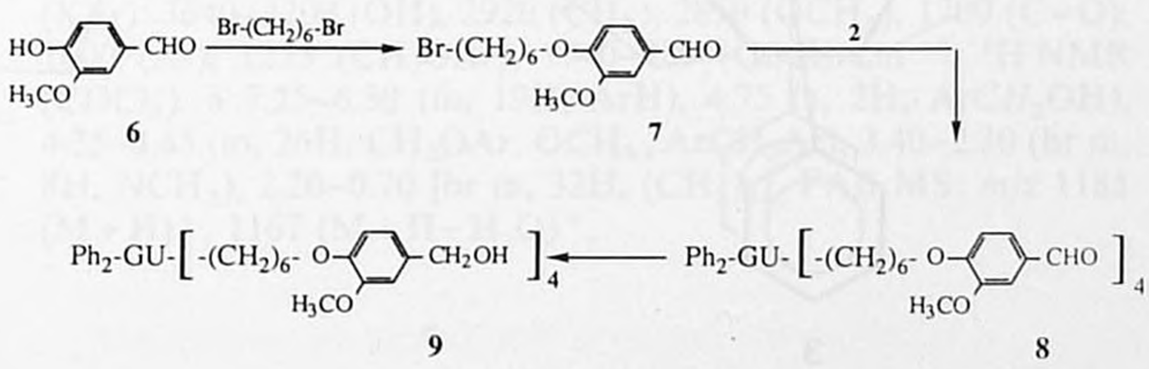
Fig. 2. Two strategies (A and B) to synthesize a compound possessing a cavity as well as a catalytically active centre.

Results and discussion[#]

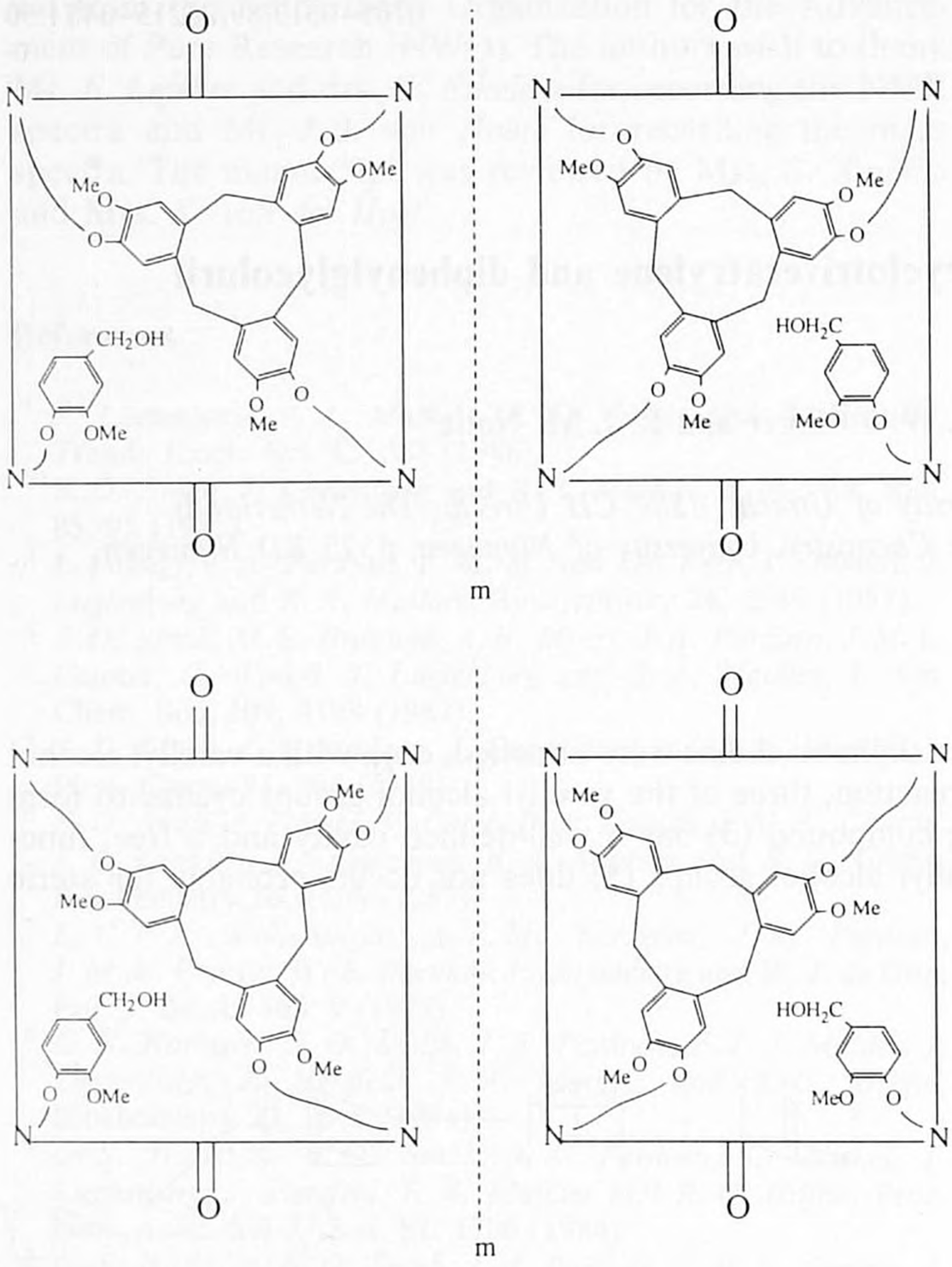
To diphenylglycoluril[5] (**2**), four $-(CH_2)_6-$ arms, terminated with vanillyl groups, were attached as shown in Scheme 1. Vanillin (**6**) was heated in aqueous base with 1,6-dibromohexane under phase-transfer conditions using methyltrioctylammonium chloride (Aliquat 336) as the phase-transfer catalyst to give compound **7** (81%). The latter compound was coupled (≈50%) to **2** in *N*,*N*-dimethylformamide using sodium hydride as base. The resulting product was quantitatively reduced to the corresponding benzylic alcohol **9** with $NaBH_4$ in dioxane. An alternative route, in which 1,6-dibromohexane is first attached to **2** and subsequently coupled to vanilin, was unsuccessful.

Intramolecular condensation of the vanillyl alcohol subunits in **9** was achieved by heating in formic acid under high-dilution conditions. Chromatographic work-up afford-

Scheme 1

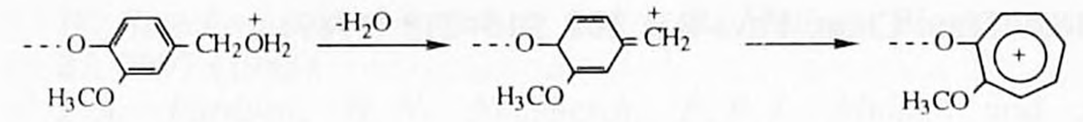


[#] IUPAC names of compounds: cyclotriveratrylene (**1**) = 10,15-dihydro-2,3,7,8,12,13-hexamethoxy-5*H*-tribenzo[*a*,d,*g*]cyclononene; vanillin (**6**) = 4-hydroxy-3-methoxybenzaldehyde; vanillyl alcohol = 4-hydroxy-3-methoxybenzyl alcohol; diphenylglycoluril, see Experimental.



m

Fig. 3. Four stereoisomers of compound **3**.



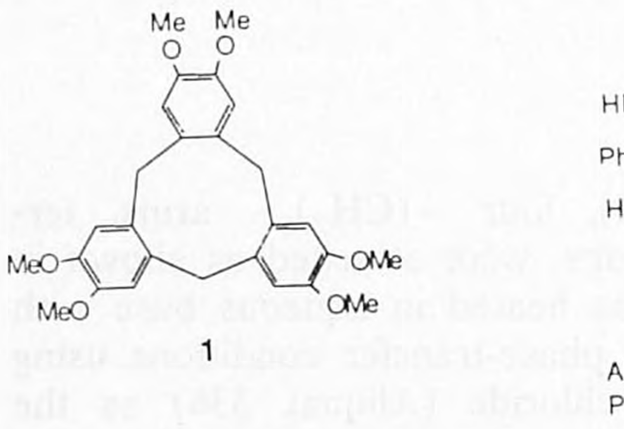
M = 1185 M = 1167

Scheme 2

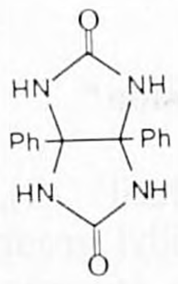
ed two solids, compounds **3** and **4**, in approximately 30% and 10% yield, respectively. Compound **3** contains a cyclotriveratrylene sub-unit and one free arm. It was fully characterized by elemental analysis and spectroscopic techniques (see Experimental). The cyclotrimerization reaction, by which **3** is formed, can proceed in two ways with respect to the diphenylglycoluril unit, leading to four stereoisomers (Fig. 3). The presence of these isomers can be seen in the ^{13}C NMR spectrum which shows more than one signal for each carbon atom of **3**. The benzylic carbon of the free arm gives only one signal in the ^{13}C NMR spectrum, indicating that the free arm is not influenced by the stereoisomers. So far, we have not been able to separate these isomers.

Based on the FAB MS and ^{1}H NMR spectra, we ascribe a non-cyclic, tetrameric structure to compound **4**. We found that the ratio **3**/**4** depends on the reaction conditions used. For instance, when a mixture of acetic acid and sulfuric acid (100:1, v/v) is substituted for formic acid, only compound **3** is formed. We ascribe this to the fact that the condensation of the vanillyl alcohol groups is a reversible process[3d,6]. In the presence of strong acid, **4** is converted into the thermodynamically more stable **3**.

The cyclic tetramer **5** could not be detected in our reaction mixtures. The FAB mass spectrum of **3** showed a signal at *m/z* 1167 which could correspond with $(M + H)^+$ of **5**. However, with the aid of MAIKE spectroscopy (Mass Analysed Ion Kinetic Energy) in combination with ^{1}H NMR, we were able to show that this signal is due to a rearrangement of the protonated side-arm of **3** (Scheme 2). Our result



1



2
Abbreviated as
Ph_2-GU-H_4

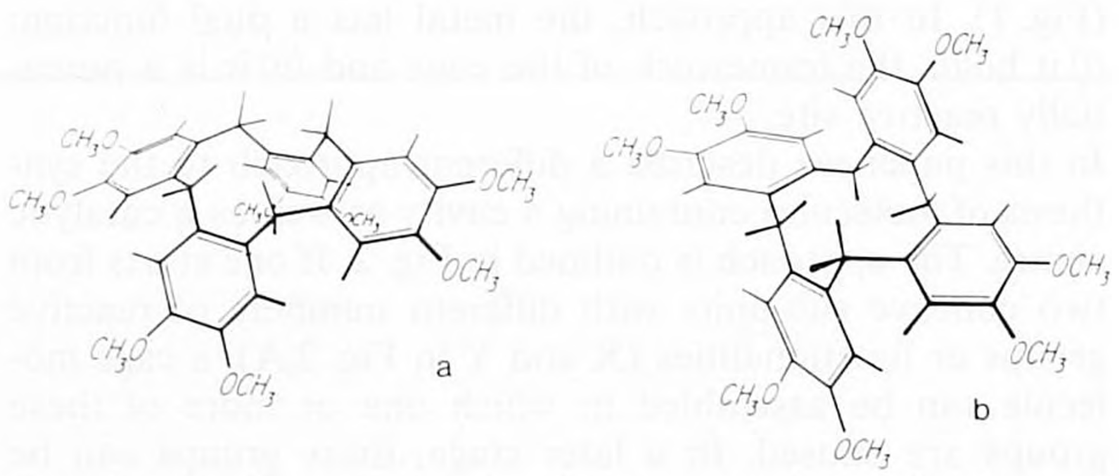
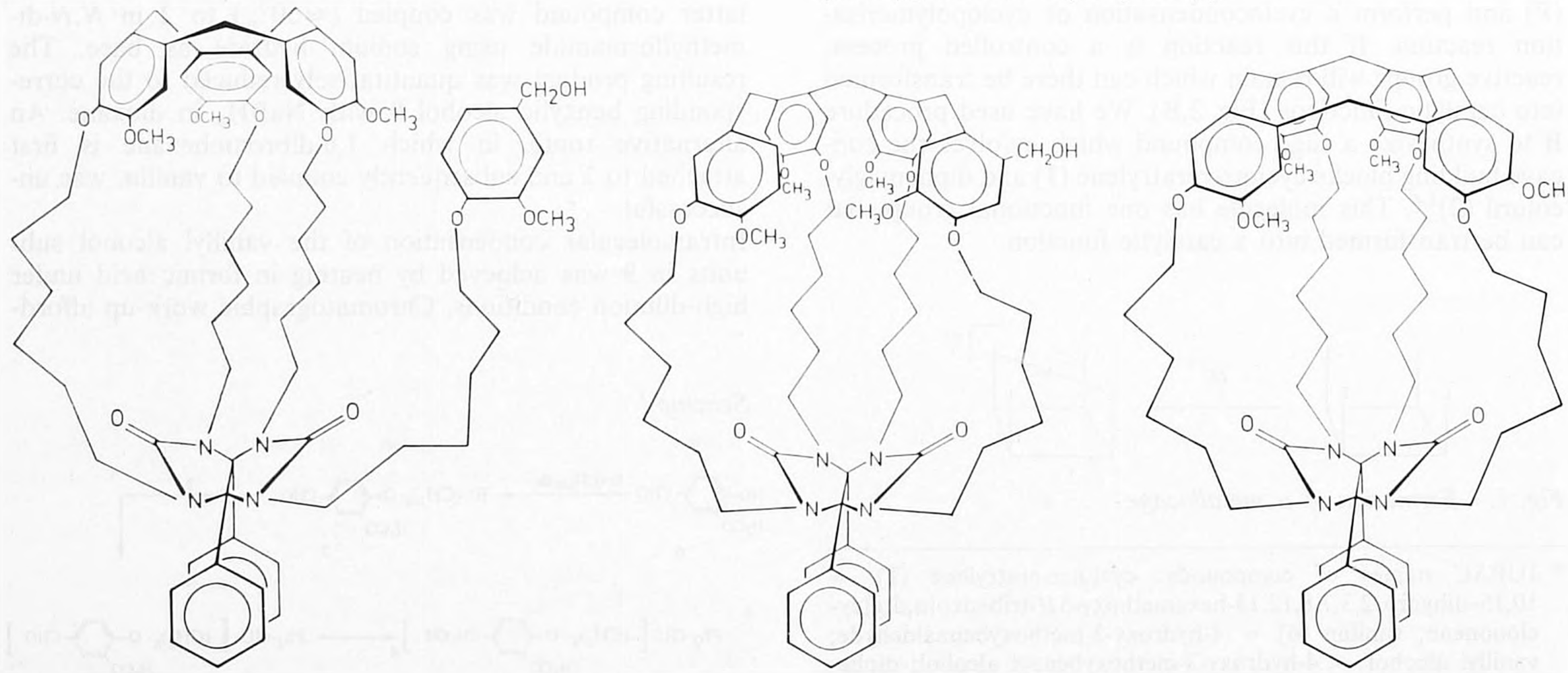


Fig. 4. Conformations of cyclotetraveratrylene: the "crown" form (a) and the "sofa" form (b).



3 4 5

suggests that ring closure of **4** to **5** is an unfavourable process. It is known from the literature[7] that cyclotetraveratrylene can have three conformations: two related "crown" forms (C_{4v} and C_{2v}, Fig. 4a) and a "sofa" form (C_{2h}, Fig. 4b). The latter is the most stable, since it has one of its veratryl units in a less strained upward position. CPK models suggest that a "sofa" form of the cyclotetraveratrylene sub-unit in **5** is not possible for steric reasons.
Preliminary experiments show that the CH_2OH function of the free arm in **3** can be easily modified. Our efforts are being directed towards the derivatization of **3** with imidazolyl functions. These functions can act as a nucleophilic catalyst on a substrate bound in the cavity of **3** or they can be used to coordinate a transition metal centre.

Experimental

General

Unless otherwise indicated, commercial materials were used as received. DMSO, dioxane and DMF were dried over 4 Å sieves and methanol over 3 Å sieves prior to use. Diethyl ether, toluene and hexane were distilled from sodium ketyl, while $CHCl_3$ was distilled from $CaCl_2$. FAB mass spectra were recorded on a VG ZAB 2F spectrometer (matrix: 3-nitrobenzyl alcohol). IR spectra were measured on a Perkin-Elmer Model 283 spectrometer. ^{1}H NMR spectra were recorded on Varian EM-360, Bruker AW-80 and Bruker WP-200 instruments. Chemical shifts (δ) are reported in ppm downfield from internal $(CH_3)_4Si$. Abbreviations used are s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Coupling constants are reported in Hz. Elemental analyses were carried out by the Elemental Analytical Section of the Institute for Applied Chemistry TNO, Zeist, The Netherlands. Melting points were determined on a Mettler FP5/FP51 photoelectric melting point apparatus. Silica gel 60 (Merck, particle size 0.040–0.063 mm, 230–400 mesh, ASTM), neutral alumina (Janssen, active, 50–200 micron, 70–290 mesh, ASTM) and Sephadex LH-20 (Pharmacia) were used in column chromatography. Thin-layer chromatography was performed using plates of silica gel 60 F254 (Merck) and alumina (Merck, neutral, type E).

Compounds

*Tetrahydro-3a,6a-diphenylimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)--dione (diphenylglycoluril)* (**2**)

This compound was synthesized according to a literature procedure[5].

4-(6-Bromohexyloxy)-3-methoxybenzaldehyde (**7**)

A solution of 6.08 g (40 mmol) of **6** and 1.6 g (40 mmol) of sodium hydroxide in 40 ml of water was vigorously stirred with 97.6 g (400 mmol, 61 ml) of 1,6-dibromohexane and 1.5 g of Aliquat 336 at 70 °C for *ca.* 5 h. The progress of the reaction was followed with TLC (silica, eluent $CHCl_3/CH_3OH$, 10:1 v/v). To this end, a sample of the water layer was acidified to pH 6 and extracted with $CHCl_3$. After TLC had indicated the disappearance of **6**, the organic layer was evaporated to dryness under reduced pressure. The remaining oil was dissolved in chloroform, washed with a 0.25 *M* aqueous sodium hydroxide solution, three times with a saturated aqueous sodium chloride solution and evaporated under reduced pressure. The crude product was crystallized from ether. Yield 10.17 g (80.7%) of **7** as white crystals; m.p. 53.1 °C. IR (KBr): 2920 (CH_2), 2850 (OCH_3), 2620 (CHO), 1670 (C=O), 1580 (Ar), 1260 (COAr), 550 (CBr) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.81 (s, 1H, ArCHO), 7.5–6.8 (m, 3H, ArH), 4.09 (t, 2H, CH_2OAr), 3.90 (s, 3H, OCH_3), 3.40 (t, 2H, CH_2Br), 2.2–1.2 [br m, 8H, $(CH_2)_4$].

*1,3,4,6-Tetrakis[6-(4-formyl-2-methoxyphenoxy)hexyl]tetrahydro--3a,6a-diphenylimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione* (**8**)

A mixture of 0.53 g (22 mmol) of NaH, 1.47 g 5 mmol) of **2** and 6.93 g (22 mmol) of **7** in 125 ml of DMF was stirred at 50 °C for 16 h under a nitrogen atmosphere. The reaction mixture was adjusted to pH 7 using 1 *M* hydrochloric acid with vigorous stirring. The solvent was evaporated under reduced pressure and the residue was dissolved in chloroform, washed three times with a saturated aqueous sodium chloride solution, dried ($MgSO_4$), filtered over infusorial earth and evaporated under reduced pressure. The remaining yellow oil was purified by column chromatography (silica, eluent $CHCl_3/CH_3OH$, 30:1 v/v). The product fractions were collected, stirred in diethyl ether for 1 h and then evaporated under reduced pressure to yield 3.08 g (50%) of **8** as a white foam; m.p. 52.6 °C. IR (KBr): 2920 (CH_2), 2850 (OCH_3), 2605 (CHO), 1720–1670 (C=O), 1580 (Ar), 1260 (COAr) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.78 (s, 4H, ArCHO), 7.5–6.5 (m, 22H, ArH), 4.03 (t, 8H, CH_2OAr), 3.89 (s, 12H, OCH_3), 3.5–2.8 (br m, 8H, NCH_2), 2.3–1.0 [br m, 32H, $(CH_2)_4$]. FAB MS: *m/z* 1231 $(M+H)^+$; other signals were observed at *m/z* values corresponding to the equation: 1231 − $k \times 82$ (alkyl chain) − $l \times 152$ (vanillyl group), $k = 1, 2, 3$, $l = k, \ldots, 3$.

*1,3,4,6-Tetrakis[6-[4-(hydroxymethyl)-2-methoxyphenoxy]hexyl]tetrahydro-3a,6a-diphenylimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione* (**9**)

To a mixture of 0.88 g (0.72 mmol) of **8** and 0.45 g (11.9 mmol) of finely powdered $NaBH_4$ in 100 ml of dioxane, 15–20 ml of 1 *M* aqueous sodium hydroxide was added dropwise with stirring. During this addition, the temperature rose to approximately 30 °C. The resulting mixture was stirred for 1 h, brought to pH 6 with concentrated hydrochloric acid and evaporated under reduced pressure. The resulting oil was dissolved in $CHCl_3$, washed three times with a saturated aqueous sodium chloride solution, dried ($MgSO_4$), filtered over infusorial earth and concentrated *in vacuo*. The remaining oil was stirred in ether for 1 h. The solvent was evaporated under reduced pressure to yield 0.88 g (≈100%) of **9** quantitatively as a white foam. IR (KBr): 3640–3120 (OH), 2920 (CH_2), 2850 (OCH_3), 1680 (C=O), 1585 (Ar), 1260 (COAr), 1090–950 (COH) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.2–6.4 (m, 22H, ArH), 4.52 (s, 2H, CH_2OH), 3.90 (t, 8H, NCH_2), 2.1–0.9 [br m, 32 H, $(CH_2)_4$], between 3.0 and 1.5 (s, 4H, CH_2OH). FAB MS: *m/z* 1239 $(M+H)^+$, 1221 $M+H-H_2O)^+$, 1185 $(M+H-3H_2O)^+$, 1167 $(M+H-4H_2O)^+$.

Ring closure to compounds **3** *and* **4**

To 200 ml of formic acid, a solution of 200 mg (0.16 mmol) of **9** in 1 ml of DMF was added dropwise with vigorous stirring at ambient temperature. Thereafter, the mixture was heated to 60 °C during which time a green colour developed. Within $2\frac{1}{2}$ h, the solution had become colourless again and the solvent was evaporated under reduced pressure. Traces of formic acid were removed by codistillation with toluene. The residue was first purified by gel-permeation chromatography (Sephadex LH-20, eluent $CHCl_3$). The product fractions were collected and refluxed in methanol for 15 min. After evaporation under reduced pressure, the residue was further purified by chromatography over silica (eluent ethyl acetate/chloroform/methanol, 10:10:1 v/v/v); yield ≈ 59 mg (31%) of white **3**; m.p. > 125 °C (decomp.). IR (KBr): 3640–3200 (OH), 2920 (CH_2), 2850 (OCH_3), 1700 (C=O), 1600 (Ar), 1255 (CH_2OAr), 1040–980 (COH) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.5–6.2 (m, 19H, ArH), 4.8 (d, 3H, ArC*H*HAr, *J* 14 Hz), 4.6 (s, 2H, ArCH_2OH), 4.4–3.3 (m, 23H, CH_2OAr, OCH_3, ArCH*H*Ar, *J* 14 Hz), 3.3–2.2 (br m, 8H, NCH_2), 2.2–0.7 [br m, 32H, $(CH_2)_4$]. ^{13}C NMR ($CDCl_3$): δ 159.9–160.4 (C=O), 150.7–146.1 (Ar), 134.3–130.2 (Ar), 128.9–127.3 (Ar), 122.1–110.9 (Ar), 88.8–88.5 [NC(N)Ar], 70.3–68.8 (CH_2OAr), 65.2 (CH_2OH), 56.2–55.7 (OCH_3), 44.9–41.9 (NCH_2), 36.5–36.2 ($ArCH_2Ar$), 32.4–24.2 $[(CH_2)_4]$.FAB MS: *m/z* 1185 $(M+H)^+$, 1167 $M+H-H_2O)^+$, 1032 (M + H–vanillyl alcohol $(C_8H_9O_3))^+$, 950 $M+H-CH_2$ chain)$^+$. Anal. calcd. for $C_{72}H_{88}O_{11}N_4$: C 72.97, H 7.43, N 4.73, O 14.86; found: C 73.13, H 7.58, N 4.45, O 14.84%.
Yield ≈19 mg (10%) of white **4**; m.p. > 120 °C (decomp.). IR (KBr): 3640–3200 (OH), 2920 (CH_2), 2850 (OCH_3), 1700 (C=O), 1600 (Ar), 1255 (CH_2OAr), 1040–980 (COH) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.25–6.30 (m, 19H, ArH), 4.75 (s, 2H, ArCH_2OH), 4.25–3.45 (m, 26H, CH_2OAr, OCH_3, $ArCH_2Ar$), 3.40–2.30 (br m, 8H, NCH_2), 2.20–0.70 [br m, 32H, $(CH_2)_4$]. FAB MS: *m/z* 1185 $(M+H)^+$, 1167 $(M+H-H_2O)^+$.

Acknowledgements

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